

Spatial orientation and postural control under vestibular guidance in patients with central dysfunction of the nervous system

Ms. Mariya Krasenova Chepischeva, MSc, MPhil
(PhD Candidate)

Imperial College London
Faculty of Medicine, Department of Brain Sciences

This thesis is submitted for the degree of Doctor of Philosophy
London, 2023

Abstract

The brain processing of the vestibular signals of self-motion is used for guiding spatial orientation as well as postural control, two faculties simultaneously engaged in ecological behaviour such as foraging. It follows that brain disease affecting the processing of vestibular signals will manifest with spatial disorientation and postural imbalance. Research investigating the neural control of these two vestibular-dependent functions is sparse, particularly in patients with central dysfunction of the nervous system. This thesis attempts to assess how the spatial and postural modalities are affected in patients with brain disease by using clinical and non-clinical behavioural tests and linking these with neuro-imaging data, where available.

I investigated vestibular-guided spatial and postural control in:

(1) *acute traumatic brain injury* - linking behavioural tests of vestibular-spatial orientation and posture with structural brain imaging, I found that (1) postural imbalance is linked to widespread bi-hemispheric WM microstructural abnormalities, whereas spatial impairment is not as widespread and predominantly but not exclusively right-hemispheric including also some left-hemispheric regions, as assessed by whole-brain and ROI DTI, (2) imbalanced patients' right inferior longitudinal fasciculus correlates with vestibular perceptual thresholds and represents a circuit whose damage might be linked to loss of vestibular motion perception and imbalance.

(2) *patients with memory and (balance) complaints* – using vestibular-based posturography and specifically designed vestibular system-based spatial tests of self-motion perception, egocentric and allocentric (egocentric+) performance, I found that (1) patients with worse cognition show impaired balance and abnormal performance for all three vestibular spatial tasks, (2) the allocentric (egocentric+) task discriminated better between patients and controls than the pure egocentric task, and (3) cognitive tests correlate better with the allocentric than egocentric navigation.

These findings suggest that vestibular-dependent spatial orientation and postural control are deficient in brain disease patients, some of whom with cognitive impairment. Understanding how posture, navigation, and cognition are linked from a vestibular system perspective and how they are affected during disease may allow the development of targeted treatment of these ecologically important functions.

Acknowledgements

I would like to thank my amazing mentor **Prof. Amin Hajitou** for all his time, for his encouragement, and constant support throughout my PhD study! He has been an invaluable support, and I am honoured to have met such a distinguished scientist and a great person!

I would like to thank **Dr Elena Calzolari**, who is not only an excellent scientist but also a very dear friend to me! She has been my senior during this PhD journey! I want to thank her for all the time she shared with me and for giving me her invaluable advice on how to improve as a scientist!

I would like to thank **Dr Amy Jolly** for her fantastic support and for teaching me the mysteries of DTI!

I would like to thank **Mr Dave Buckwell** for his never-ending support and help with all the equipment in the Neuro-Otology Lab!

I would like to thank three amazing colleagues and friends of mine – **Ms Rebecca Smith, Dr Min Xiang and Dr Qadeer Arshad!**

I would like to thank **my amazing mother, Vera (my hero and model in life)** and **my wonderful sister, Lyubomira** for all their love, never stopping support, encouragement and faith in me during all this time! There will never be enough words to thank them for everything they did for me on my way to “science”! I hope I have accomplished something that makes them proud!

This work involves the help of more than 30 memory and (balance) patients (and their spouses, carers, support staff from the Alzheimer’s Society UK), 40 traumatic brain injury patients and 90 healthy participants! All of them and their tremendous desire to help are the reason for this PhD project to be possible. They not only gave me their support and energy by taking part in my study but also showed me some great kindness! I want to thank all my participants for their kind and encouraging words, for their smiles and hugs that kept me going and feeling tireless when the hours of work were already crushing! I will be forever grateful for having had the chance to know every one of these wonderful people!

Thank you, a million times!

Table of Content

Literature Review and Hypotheses – CHAPTER I	19
1. Spatial orientation	20
2. Postural control	22
3. Vestibular system	23
3.1. Vestibular processing	24
3.1.1. Peripheral vestibular system	24
3.1.2. Central vestibular processing in the medulla of the brainstem	25
3.1.3. Central vestibular processing – from VN complex to the cerebral cortex	27
3.1.4. Cerebral cortical regions implicated in vestibular processing	28
3.2. Special aspects of vestibular processing with regard to spatial orientation and postural control	30
3.2.1. Acceleration – Velocity – Position	30
3.2.2. Self-motion	30
3.2.3. Tilt – Translation ambiguity	32
3.2.4. Passive vs active motion	33
3.2.5. Velocity storage	34
3.2.6. Cognitive function	35
4. Introduction of the study populations for this thesis	36
4.1. Traumatic brain injury (TBI) patients – non-vestibular research evidence	36
4.2. Patients with memory and (balance) impairment – non-vestibular research evidence	38
5. Current limitations	39
6. Aim/Hypotheses/Objectives	39
I. HYPOTHESIS	40
II. HYPOTHESIS	42
III. HYPOTHESIS	43
Materials and Methods – CHAPTER II	45
1. Summary of methods	46
2. Recruitment of participants	46
2.1. Acute Traumatic Brain Injury study	46
2.2. Memory and (balance) patients - a pilot study	48
3. Laboratory Testing	49
3.1. Vestibular system testing – neurophysiology	49
3.1.1. Video Head Impulse Test (vHiT)	49
3.1.2. Vemps (cVemps and oVemps)	50
3.2. Vestibular system and Cognition alongside Dizziness/Anxiety/Depression questionnaires	50
3.2.1. MMSE and ACE III -R	50
3.2.2. Trail Making (A, B)	51
3.2.3. Dizziness Handicap Inventory (DIH)	51

3.2.4. Generalized Anxiety Disorder 7-item (GAD-7)	51
3.2.5. The Patient Health Questionnaire (PHQ-9).....	51
3.3. Vestibular system and Postural control testing.....	51
3.3.1. Posturography test	51
3.3.2. Activities-specific Balance Confidence (ABC) questionnaire.....	53
3.4. Vestibular system and Spatial Orientation testing.....	53
3.4.1. Vestibular motion perception (VMP) task.....	53
3.4.2. Visual Reaction Time test	54
3.4.3. Egocentric task – JOYSTICK task	55
3.4.4. Allocentric (egocentric ⁺) task – MOUNTAIN task	57
3.5. Vestibular system and Imaging	59
3.5.1. Voxel-based morphometry (VBM)	59
3.5.2. Diffusion Tensor Imaging (DTI)	61
 Psychophysics, behaviour, neuropsychology and neurophysiology - TBI study – CHAPTER III.....	64
1. Introduction	65
2. Materials and Methods.....	66
2.1. Recruitment of Acute Traumatic Brain Injury patients	66
2.2. Methodology	67
2.3. Statistical analysis	67
3. Psychophysics, behaviour, neuropsychology, neurophysiology - Results	69
3.1. The peripheral vestibular system.....	69
3.1.1. Video Head Impulse Test (vHiT) - (high-frequency semicircular canal testing).....	69
3.1.2. Vestibular-evoked myogenic potentials (cervical/ocular) – otolith testing.....	70
3.1.3. Electrooculography (EOG) – (low-frequency semicircular canal testing).....	70
3.2. Cognitive skills and Dizziness/Anxiety/Depression - questionnaires.....	70
3.2.1. Addenbrooke’s Cognitive Examination (ACE).....	70
3.2.2. Trail-making test - A and B.....	71
3.2.3. DHI, PHQ-9 and GAD-7.....	72
3.3. Postural control	72
3.3.1. SWAY test/ Posturography	72
3.3.2. ABC balance questionnaire	73
3.4. Spatial navigation.....	74
3.4.1. Vestibular motion perception test.....	74
3.4.3. Visual Reaction time test.....	76
3.5. Vestibular mediated balance and Vestibular Motion Perception.....	76
4. Summary/Conclusion	77
 Psychophysics, behaviour, neuropsychology and neurophysiology - Memory and (balance) patients - a pilot study – CHAPTER IV	79
1. Introduction	80
2. Materials and Methods.....	82
2.1. Recruitment of Memory and (balance) patients	82

2.2. Methodology	83
2.3. Statistical analysis	82
3. Results	85
3.1. The peripheral vestibular system.....	85
3.1.1. Video Head Impulse Test (vHiT) - (high-frequency semicircular canal testing).....	86
3.1.2. Electrooculography (EOG) - (low-frequency semicircular canal testing)	86
3.2. Cognitive skills	86
3.2.1. MMSE.....	86
3.2.2. Addenbrooke's Cognitive Examination (ACE).....	86
3.3. Postural control	88
3.4. Spatial navigation.....	89
3.4.1. Vestibular self-motion perception test.....	89
3.4.2. Visual Reaction Time test	92
3.5. Vestibular mediated Balance and Vestibular Motion Perception	92
4. Discussion/Conclusion.....	93
 Vestibular spatial navigation -Memory and (balance) patients - a pilot study – CHAPTER V	96
A. HEALTHY CONTROLS.....	97
1. Introduction	97
2. Materials and Methods.....	98
2.1. Healthy controls – Recruitment.....	98
2.2. Methodology	98
2.3. Statistical analysis	100
3. Results	101
3.1. JOYSTICK task	101
3.2. MOUNTAIN task	103
4. Discussion.....	104
 B. MEMORY and (BALANCE) PATIENTS	109
1. Introduction	109
2. Materials and Methods.....	111
2.1. Recruitment of memory and (balance) patients.....	111
2.2. Methodology	111
2.3. Statistical analysis	111
3. Results	113
3.1. Vestibular motion perception task.....	113
3.2. MAIN JOYSTICK analysis	114
3.3. MOUNTAIN task	117
4. Discussion.....	120
4.1. INITIAL JOYSTICK analysis	120
4.2. MAIN analysis (VMP, JOYSTICK and MOUNTAIN task).....	121
1. The Vestibular Motion Perception test.....	121

2. JOYSTICK (egocentric) task	124
3. MOUNTAIN (allocentric (egocentric+)) task	126
5. Extended Discussion	129
5.1. Vestibular-guided Spatial performance prediction based on a continuous three-step model	129
5.2. The continuous three-step model - performance prediction based on the results achieved in this study.....	131
5.3. VMP is not an accepted way to divide patients in groups but shows its potential.....	135
5.4. The anatomical correlates of vestibular-guided spatial disorientation in Alzheimer's disease.....	135
IV. Conclusion (section A and B).....	136
 Diffusion tensor imaging - TBI study – CHAPTER VI.....	137
A. DTI WHOLE-BRAIN ANALYSIS	138
1. Introduction	138
2. Materials and Methods.....	139
2.1. Recruitment of patients	139
2.2. Methodology	139
2.3. Statistical analysis	140
3. Results	142
I. DTI MEAN WHOLE-BRAIN VALUE ANALYSIS.....	142
3.1. Analysis of variance.....	142
II. DTI WHOLE-BRAIN VOXELWISE ANALYSIS.....	145
A. FRACTIONAL ANISOTROPY (FA).....	145
1) FA - Vestibular motion perception division	145
2) FA - Sway 95% confidence ellipse SC (Soft Closed) division	146
B. MEAN DIFFUSIVITY (MD).....	146
1) MD - Vestibular motion perception division	146
2) MD – Sway 95% confidence ellipse SC (Soft Closed) division	147
C. AXIAL DIFFUSIVITY (AD).....	147
D. RADIAL DIFFUSIVITY (RD).....	151
1) RD - Vestibular motion perception division	151
2) RD - Sway 95% confidence ellipse SC (Soft Closed) division	151
4. Summary/ Discussion	151
A. Mean Whole-Brain value analysis	151
B. Whole-Brain Voxelwise analysis	153
4.1. Fractional anisotropy (FA).....	153
VMP division	153
Sway division.....	154
4.2. Mean diffusivity (MD).....	154
VMP division	154
Sway division.....	154
4.3. Axial diffusivity (AD).....	155
VMP division	155
Sway division.....	155
4.4. Radial diffusivity (RD)	155

VMP division	155
Sway division.....	156
4.5. EOG (all parameters/all divisions).....	156
5. Discussion/Conclusion.....	156
 B. DTI WHITE MATTER TRACTS with VESTIBULAR INPUT.....	159
1. Introduction	159
2.1. Recruitment of patients	160
2.2. Methodology	160
2.3. Statistical analysis	67
3. Results	161
4. Discussion/Conclusion.....	163
 Vestibular regions and CC - TBI study – CHAPTER VII	166
I. CORPUS CALLOSUM (CC).....	167
1. Introduction	167
2. Materials and Methods.....	168
2.1. Recruitment of patients	168
2.2. Methodology	168
2.3. Statistical analysis	1678
3. Results	170
A. DTI MEAN VALUE ANALYSIS	170
3.1. Vestibular Motion Perception (VMP) division.....	170
3.2. Vestibular Sway division	171
B. VOXELWISE ANALYSIS – DTI	172
4. Summary/Discussion	174
A. Mean value analysis	174
B. DTI Voxelwise analysis – Corpus Callosum.....	176
5. Conclusion	178
 II. VESTIBULAR REGIONS.....	180
1. Introduction	180
2. Materials and Methods.....	180
2.1. Recruitment of patients	181
2.2. Methodology	181
2.3. Statistical analysis	180
3. Results	182
A. MEAN VALUE ANALYSIS.....	182
3.1. Vestibular Motion Perception (VMP) division.....	183
3.2. Vestibular Sway division	184
B. VOXELWISE ANALYSIS – DTI	185
4. Summary/Discussion	191

A. Mean value analysis – DTI analysis.....	191
B. DTI – voxelwise analysis	192
C. DTI ROI voxelwise analysis – vestibular spatial and postural processing - Summary.....	199
E. EOG – Vestibular Ocular reflex (VOR)	202
6. Conclusions – TBI study.....	202
 Summary of Findings and Future Work – CHAPTER VIII.....	 203
Appendix – CHAPTER IX	219
References – CHAPTER X.....	231

List of Figures

Chapter I

- Figure. 1. Strategies in spatial navigation.
- Figure. 2. Inverted pendulum as a model for human sway. Posturography test.
- Figure. 3. The peripheral vestibular system.
- Figure. 4. Vestibular processing.
- Figure. 5. Vestibular Thalamocortical pathway.
- Figure. 6. Head movements in six dimensions.
- Figure. 7. Vestibular pathways sending vestibular information to the “vestibular cortex”.
- Figure. 8. Schematic presentation of Hypothesis I.
- Figure. 9. Schematic presentation of Hypothesis II.
- Figure. 10. Schematic presentation of Hypothesis III.

Chapter II

- Figure. 11. Program ANALYSIS (Inhouse Software) used to calculate the stabilogram/posturography test.
- Figure. 12. Vestibular motion perception task.
- Figure. 13. JOYSTICK task (i.e. egocentric task) – procedure of the task.
- Figure. 14. Analysis of JOYSTICK data.
- Figure. 15. Allocentric (egocentric+) task, i.e. the MOUNTAIN task.
- Figure. 16. MOUNTAIN task (i.e. allocentric (egocentric+) task) – procedure.
- Figure. 17. DTI tensor and calculation of FA, MD, AD and RD.
- Figure. 18. DTI pipeline and statistical analysis (mean value and voxelwise analysis).

Chapter III

- Figure. 19. ACE performance in acute TBI patients based on Vestibular Motion Perception (patients only).
- Figure. 20. Correlation between ACE TOTAL and VMP (left) and Sway 95% confidence ellipse SC (right).
- Figure. 21. Trail-making test performance in acute TBI (patients only) based on VMP division.
- Figure. 22. Sway area 95% confidence ellipse – acute TBI and healthy controls performance.
- Figure. 23. Vestibular Motion Perception performance – patient/control division.
- Figure. 24. Vestibular Motion Perception performance – acute TBI and controls.
- Figure. 25. Vestibular-mediated balance (Sway area 95% confidence ellipse) and VMP thresholds in acute TBI.

Chapter IV

- Figure. 26. Memory and (balance) patients - MMSE vs Vestibular Motion Perception (VMP).
- Figure. 27. Memory and (balance) patients - ACE components.
- Figure. 28. Sway performance of healthy controls >60yrs versus memory and (balance) patients.

Figure. 29. Sway performance (area 95% confidence ellipse, RMS AP and RMS L).

Figure. 30. Memory and (balance) patients – VMP performance.

Figure. 31. Memory and (balance) patients – Mean VMP test.

Figure. 32. Vestibular-mediated balance and Vestibular-perceptual thresholds in memory and (balance) patients.

Chapter V

Figure. 33. The three-step spatial model.

Figure. 34. Healthy controls age groups (<40yrs, <(40-60)>yrs, >60yrs) – Individual and Group JOYSTICK performance.

Figure. 35. Healthy controls age groups (<40yrs, <(40-60)>yrs, >60yrs) - Group JOYSTICK performance - %Error.

Figure. 36. Healthy controls age groups (<40yrs, <(40-60)>yrs, >60yrs) – Individual and Group MOUNTAIN performance.

Figure. 37. Healthy controls age groups (<40yrs, <(40-60)>yrs, >60yrs) – Group MOUNTAIN performance - % Error.

Figure. 31. (Duplicate from Chapter IV) Memory and (balance) patients – Mean VMP test.

Figure. 38. Memory and (balance) patients – Individual JOYSTICK task performance.

Figure. 39. Memory and (balance) patients and HC > 60yrs – Individual and Group JOYSTICK task performance.

Figure. 40. Memory and (balance) patients and HC > 60yrs – Group JOYSTICK task performance (SLOPE and R²).

Figure. 41. Memory and (balance) patients and HC > 60yrs - Group JOYSTICK task performance based on %Error.

Figure. 42. Memory and (balance) patients – Individual MOUNTAIN task performance.

Figure. 43. Memory and (balance) patients and HC > 60yrs – Individual and Group MOUNTAIN task performance.

Figure. 44. Memory and (balance) patients and HC > 60yrs – Group MOUNTAIN performance (SLOPE and R²).

Figure. 45. Memory and (balance) patients and HC > 60yrs – Group MOUNTAIN task performance based on %Error.

Figure. 46. The continuous three-step model.

Figure. 47. Spatial performance prediction based on a continuous three-step model.

Figure. 48. Spatial performance prediction based on the results from the three-step model.

Chapter VI

Figure. 49. Comparison between patient/controls for FA, MD, AD and RD.

Figure. 50. DTI Mean whole-brain analysis for Fractional anisotropy (FA) based on VMP and Sway division.

Figure. 51. DTI Mean whole-brain analysis for Mean Diffusivity (MD) based on VMP and Sway division.

Figure. 52. DTI Mean whole-brain analysis for Axial Diffusivity (AD) based on VMP and Sway division.

Figure. 53. DTI Mean whole-brain analysis for Radial Diffusivity (RD) based on VMP and Sway division.

Figure. 54. Fractional Anisotropy (FA) Voxelwise Correlation based on VESTIBULAR MOTION perception division.

Figure. 55. Fractional Anisotropy (FA) Voxelwise Comparison based on VESTIBULAR MOTION perception division.

Figure. 56. Fractional Anisotropy (FA) Voxelwise Correlation based on SWAY 95% confidence ellipse division.

Figure. 57. Fractional Anisotropy (FA) Voxelwise Comparison based on SWAY 95% confidence ellipse division.

Figure. 58. Mean Diffusivity (MD) Voxelwise Correlation based on VESTIBULAR MOTION perception division.

Figure. 59. Mean Diffusivity (MD) Voxelwise Comparison based on VESTIBULAR MOTION perception division.

Figure. 60. Mean Diffusivity (MD) Voxelwise Correlation based on SWAY 95% confidence ellipse division.

Figure. 61. Mean diffusivity (MD) Voxelwise Comparison based on SWAY 95% confidence ellipse division.

Figure. 62. Radial Diffusivity (RD) Voxelwise Correlation based on VESTIBULAR MOTION perception division.

Figure. 63. Radial Diffusivity (RD) Voxelwise Comparison based on VESTIBULAR MOTION perception division.

Figure. 64. Radial Diffusivity (RD) Voxelwise Correlation based on SWAY 95% confidence ellipse division.

Figure. 65. Radial Diffusivity (RD) Voxelwise Comparison based on SWAY 95% confidence ellipse division.

Figure. 66. Correlation between abnormal Sway patients and VMP (MD parameter).

Figure. 67. Most common White Matter Tracts present in the DTI Whole-Brain voxelwise analysis.

Figure. 68. DTI WM Tracts – VMP division.

Figure. 69. DTI WM Tracts – Sway division.

Chapter VII

Figure. 70. Corpus Callosum in 3D view.

Figure. 71. DTI analysis – Corpus Callosum (CC) – VMP division.

Figure. 72. DTI analysis – Corpus Callosum (CC) – Sway 95% confidence ellipse division.

Figure. 73. DTI voxelwise analysis – SPLENIUM of Corpus Callosum.

Figure. 74. DTI voxelwise analysis – BODY of Corpus Callosum.

Figure. 75. DTI voxelwise analysis – GENU of Corpus Callosum.

Figure. 76. Eleven brain regions known for their link to the Vestibular system.

Figure. 77. DTI analysis – Mean values for Vestibular regions – Vestibular Motion Perception (VMP) division.

Figure. 78. DTI analysis Mean-values for Vestibular regions – Vestibular Sway 95% confidence ellipse division.

Figure. 79. DTI voxelwise analysis – AMYGDALA.

Figure. 80. DTI voxelwise analysis – CAUDATE.

Figure. 81. DTI voxelwise analysis – ETC.

Figure. 82. DTI voxelwise analysis – HIPPOCAMPUS.

Figure. 83. DTI voxelwise analysis – INSULA.

Figure. 84. DTI voxelwise analysis – THALAMUS (left).

Figure. 85. DTI voxelwise analysis – OP2.

Figure. 86. DTI voxelwise analysis – PUTAMEN.

Figure. 87. DTI voxelwise analysis – THALAMUS (right).

Figure. 88. DTI voxelwise analysis – TPJ (ant).

Figure. 89. DTI voxelwise analysis – TPJ (post).

Figure. 90. Overview of vestibular-guided spatial orientation for a suggested three-step model.

Figure. 91. DTI voxelwise analysis results – summary of brain regions and their links to VMP and vestibular Sway.

Appendix

Figure. A1. VBM pipeline.

Figure. A2. Memory and (balance) patients – Number of JOYSTICK task errors completed during the task.

Figure. A3. Memory and (balance) patients – Group JOYSTICK – the difference in performance based on a R/L rotation.

Figure. A6. VBM whole-brain voxelwise analysis – summary of statistically notable findings (axial view).

Figure. A7. Axial Diffusivity analysis.

Figure. A9. DTI WM Tracts – patient/control.

Figure A8. DTI voxelwise analysis.

Figure. A10. DTI analysis – Corpus Callosum with its three regions SPLENIUM, BODY and GENU – patient/control.

Figure. A11. DTI analysis - Vestibular regions - mean values (patient/control).

List of Tables

Chapter II

Table.1. Mayo classification system for TBI.

Chapter III

Table. 2. Acute TBI patients - demographics.

Table. 3. TBI - Vestibular Neurophysiology - descriptive statistics.

Table. 4. TBI questionnaires.

Chapter IV

Table. 5. Demographics and clinical condition of the patients recruited.

Table. 6. MMSE criteria.

Table. 7. Memory and (balance) patients - Vestibular Neurophysiology.

Table. 8. Memory and (balance) patients - detailed VMP performance based on division method.

Chapter V

Table. 9. Spatial performance of PATIENTS from the three-step model.

Chapter VI

Table. 10. Voxelwise correlations and Voxelwise t-tests for Fractional anisotropy (FA).

Table. 11. Voxelwise correlations and Voxelwise t-tests for Mean Diffusivity (MD).

Table. 12. Summary of DTI whole-brain voxelwise analysis for VMP, Sway and patient-control division methods.

Chapter VII

Table. 13. Corpus Callosum DTI mean value analysis.

Table. 14. Summary for CC voxelwise DTI analysis – FA and MD (1/2).

Table. 14. Summary for CC voxelwise DTI analysis – AD and RD (2/2).

Table. 15. ROI DTI mean values analysis – summary of t-tests /ANOVA for patient/control and VMP/Sway division.

Table. 16. Summary for ROI voxelwise analysis – FA and MD (1/2).

Table. 16. Summary for ROI voxelwise analysis – FA and MD (2/2).

Table. 17. Summary for ROI voxelwise analysis – AD and RD (1/2).

Table. 17. Summary for ROI voxelwise analysis – AD and RD (2/2).

Appendix

Table. A4. A direct comparison between the functions affected by AD pathology and the skills needed for the three tasks.

Table. A5. Voxelwise VBM analysis – summary of significant GM and WM correlation and comparison (t-test) contrasts.

Table. A12. Summary for CC voxelwise VBM analysis.

Table. A13. Summary for VBM ROI voxelwise analysis – GM and WM.

Table. A14. Summary for VBM ROI voxelwise analysis – GM and WM.

List of Live Links

Expert Diagnostics in Acute stroke with Vertigo – EnDeAVOr

https://drive.google.com/file/d/1jKndSLDb640qI5LU_3lIR96rWboyZnQ9/view?usp=sharing

Chapter V

Mountain task

<https://drive.google.com/file/d/1aQYJalon9myia4bsTFGhPwsajlTKIdZQ/view?usp=sharing>

Statement of Publications/Posters

I) The data in this thesis have been presented in several seminars, conferences and scientific meetings (UK and worldwide).

II) Some parts of the TBI study (MRC-funded study) have already been published:

1. *Calzolari E and *Chepishева M (shared first authorship), Smith RM, Mahmud M, Hellyer PJ, Tahtis V, Arshad Q, Jolly A, Wilson M, Rust H, Sharp DJ, Seemungal BM. Vestibular agnosia in traumatic brain injury and its link to imbalance. *Brain*. 2021 Feb 12;144(1):128-143. doi: 10.1093/brain/awaa386. PMID: 33367536; PMCID: PMC7880674.

III) The literature Review from this PhD thesis gave rise to some review articles.

Consequently, parts of the reviews that are available online under the CC BY-NC 4.0/CC BY 4.0 have also been *literally* used in the thesis. They will not be cited every time to avoid over-citation of personal work (statement discussed with Imperial College London, Library and Open Access Team).

1. Chepishева, M. K. (2022). Spatial Orientation, Postural Control and the Vestibular System in Healthy Elderly and Alzheimer's Dementia. SSRN Neurodegeneration & Nervous System Aging EJournal. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4007515(pre-print).
2. Chepishева, M. K. (2021). The Vestibular system and its implications in spatial orientation and postural control. SSRN Neuroscience, Sensory & Motor Neurobiology EJournal. <https://doi.org/http://dx.doi.org/10.2139/ssrn.3988338> (current version available as pre-print, under revision) (pre-print).
3. Chepishева, M. K. (2023). Spatial Orientation, Postural Control and the Vestibular System in Healthy Elderly and Alzheimer's Dementia. *PeerJ*, May 2 (11:e15040). <https://doi.org/10.7717/peerj.15040>.

IV) Other projects:

1. Book Chapter on TBI:

*Rebecca Smith, *Mariya Chepishева, *Thomas Cronin (*all first authors), Barry M. Seemungal, Chapter 16 - Diagnostic Approaches Techniques in Concussion/Mild Traumatic Brain Injury: Where are we? (Book Chapter) Editor(s): Michael E. Hoffer, Carey D. Balaban, *Neurosensory Disorders in Mild Traumatic Brain Injury*, Academic Press, 2019, Pages 247-277(Mariya's section on BIOMARKERS, pages 253-263) (not part of the PhD thesis).

2. BRC final report on a Stroke project available in Appendix:

*Chepishева M, *Xiang M, Rust H, Bharath A, Mandic D, Seemungal BM, Expert Diagnostics in Acute stroke with Vertigo – EnDeAVOr (not part of the PhD thesis).

https://drive.google.com/file/d/1jKndSLDb640qI5LU_3lIR96rWboyZNQ9/view?usp=sharing

Declarations of Originality

The work within this thesis is my own except where otherwise referenced.

- 1) Acute TBI study (Chapters III, VI, VII) – the data were collected as part of a broader research collaboration (MRC-funded study) - Dr Elena Calzolari, Ms Mariya Chepishcheva (myself), Ms Rebecca Smith, Dr Heiko Rust and Dr Barry Seemungal.

Additional collaborators for the publication in Brain Journal - Dr M. Mahmud, Dr Peter Hellyer, Dr Tahtis, Dr Qadeer Arshad, Dr Amy Jolly, Dr M Wilson and Prof. David Sharp.

- 2) Memory and (balance) patients (Chapter IV, V) – ideas about possible projects discussed with Dr Barry Seemungal, Dr Elena Calzolari and Dr Heiko Rust. In addition, Dr Rust examined all patients clinically.

Additional collaborators – Dr Paul Edison, Ms Emily Blunt, Ms Merel van der Thiel and Prof. James Rowe.

Ms Rebecca Smith helped me look up the patients' medical records while I did not have access to the NHS database/system.

Tasks used for this PhD thesis:

- 1) Vestibular Motion Perception task (Chapters III, IV, V, VI, VII) – as per (Seemungal et al., 2008).
- 2) Joystick task (Chapter V) – task adapted from (Brevern et al., 1997) and further developed to address this current study and its hypotheses (i.e. the task went through several improvement stages).
- 3) VR Mountain Task (Chapter V) (inspired by the “Curtain task” (Seemungal, 2006)) – I developed this task for my PhD study and it went through several developmental stages.
- 4) Passive rotation Adaptation task, Passive rotation Mental transformation task, Active locomotion Human MWM VR task and further/future suggestions for vestibular-guided spatial tasks (all of which are available in Appendix) – I developed these tasks as additional testing batteries.

The following collaborations were established:

- 1) Alzheimer's Society UK.
- 2) Join Dementia Research UK.

Copyright declaration

The copyright of this PhD thesis rests with the author,

Ms. Mariya Krasenova Chepisheva, MSc, MPhil.

Unless otherwise indicated, its contents are licensed under a Creative Commons Attribution-NonCommercial 4.0 International Licence (CC BY-NC 4.0).

Under this licence, you may copy and redistribute the material in any medium or format. You may also create and distribute modified versions of the work. This is on the condition that: you credit the author and do not use it, or any derivative works, for a commercial purpose.

When reusing or sharing this work, ensure you make the licence terms clear to others by naming the licence and linking to the licence text. Where a work has been adapted, you should indicate that the work has been changed and describe those changes.

Please seek permission from the copyright holder for uses of this work that are not included in this licence or permitted under UK Copyright Law.

Chapter I

Literature Review and Hypotheses

1. Spatial orientation

Spatial navigation is the ability to orient ourselves in space and is essential for the survival of the species and the successful execution of our daily activities. It is a multifaceted process that requires dynamic updating of the relationship “between the body and the environment” (Berthoz & Viaud-Delmon, 1999) and uses various spatial strategies owing to the recruitment of multiple brain regions (Vlček & Laczó, 2014). Spatial navigation incorporates, among others, spatial orientation, vision, proprioception, postural control, balance, decision-making, processing speed, general cognitive control, attention to landmarks and short-term memory for keeping our final position goal in mind (Montello, 1998), (Wolbers & Wiener, 2014), (Spiers & Gilbert, 2015), (Ekstrom et al., 2017). **Spatial orientation** is a crucial part of spatial navigation and presents the ability to determine the position or direction of objects to their surrounding environment. This way, it helps us identify our body position in space with respect to our current and previous locations (Benton & Tranel, 1993). In this thesis, both spatial navigation and spatial orientation are used interchangeably.

When we move, we face multiple challenges concerning the environment in which we navigate. Therefore, our navigational strategies in different cases vary depending on the size of the environment in which we navigate, our knowledge of the space, the availability of environmental cues, the location of the destination and the path we take to reach it (Montello, 1998), (Wiener et al., 2009), (Meilinger et al., 2013), (Wolbers & Wiener, 2014), (Lester et al., 2017). There are two main categories of spatial strategies we use (Fig.1): (1) **egocentric** - referenced to the body, which typically uses self-motion and (2) **allocentric** - concerning unchanging landmarks in the environment (O’Keefe & Nadel, 1978).

Egocentric navigation is based on information from the vestibular, visual (optic flow) and proprioceptive systems. Research evidence supports the critical role of the posterior parietal cortex (PPC) in egocentric orientation (Stein, 1989), but the role of the PPC in vestibular-guided egocentric orientation is less clear. Still, it was shown that repetitive transcranial magnetic stimulation (rTMS) of the PPC in healthy humans disrupts aspects of their contralateral vestibular egocentric navigation (i.e. angular position and motion duration) but not angular velocity perception (i.e. vestibular self-motion perception) (Seemungal et al., 2008), (Seemungal et al., 2009). This implied a central role of the PPC in vestibular egocentric navigation and, specifically also in human path integration.

Importantly, during egocentric navigation, we use our long-term memory for skills and actions (i.e. procedural memory) via the caudate nucleus region of the striatum to exhibit fairly automatic navigation ‘by following habitual paths’ (Hartley et al., 2003), (Iaria et al., 2003), that we are used to take.

Allocentric navigation is based on information coming from external sources such as visual, auditory, olfactory and tactile stimuli. These cues are usually static and retain a constant relationship among each other that helps us orientate. We take advantage of these environmental cues by using our spatial memory, which is mainly processed by the hippocampus and parahippocampal structures (E. Maguire et al., 1996), (Burgess et al., 2001), (Tu et al., 2015), (Lester et al., 2017). The hippocampus is a crucial brain structure responsible for long-term memory and spatial navigation (E. Maguire et al., 1996).

While allocentric and egocentric processing networks are centred on different “hubs”, they engage many mutual regions – the prefrontal cortex, visual cortex, hippocampus, retrosplenial cortex, inferotemporal cortex, entorhinal cortex, parahippocampal cortex and thalamus (Ekstrom et al., 2017). Still, the retrosplenial cortex, which is responsible for memory and navigation, is believed to play a central role in linking the PPC and the hippocampus (O’Keefe & Nadel, 1978), (Vann et al., 2009). This way, it assists in the bidirectional translation between egocentric and allocentric strategies and helps the network to work as a whole (E. A. Maguire, 2001), (Burgess et al., 2001), (Byrne et al., 2007).

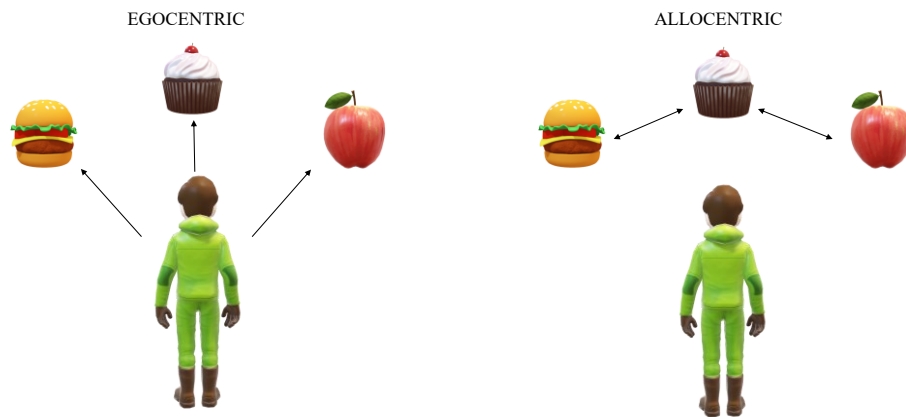


Figure. 1. Strategies in spatial navigation. Egocentric is referenced to the self, and Allocentric is referenced to stable landmarks from the environment.

The discovery of the spatial navigational cells in animals and sometimes also in humans has provided a crucial understanding of the neural mechanisms underlying spatial navigation and has contributed significantly to our understanding of the “spatial cognitive map” suggested by Edward C. Tolman in 1948. The variety of these spatial cells is enormous: place cells (they let us know ‘where we are in the space’), HD cells (they help us ‘know our direction in space’), grid cells (they help to ‘keep track of where we are during a movement as we update our location’), border/boundary cells, speed cells, time cells, odour cells, soundwave cells, goal cells, object cells, conjunctive cells, movement or action sensitive cells (Moser et al., 2008), (Hartley et al., 2014), (Moser et al., 2015), (Epstein et al., 2017). Importantly, none of these cells works in isolation, but in concordance with other spatial cells to ensure a comprehensive reconstruction of the “spatial cognitive map” (Brandt et al., 2017), (G. Chen et al., 2019).

Throughout the years, human-based spatial research has shown a variety of tasks and has continuously built upon existing tests to nowadays offer a great range of ‘pencil and paper’, ‘computer screen-based’, ‘virtual reality’, ‘immersive reality’ and ‘real world activities’ behavioural batteries. As discussed later in the thesis, these behavioural tests are often combined with neuroimaging techniques to show how navigational deterioration affects all aspects of life. All this stresses the crucial need for a better understanding of the underlying mechanisms of spatial disorientation.

2. Postural control

When moving in our environment, many of the issues we face are connected not only to the processing of information about the space around us, i.e. spatial information but also to maintaining our balance. Balance and postural control are two functions that, although separate, are an integral part of spatial navigation. **Balance** is the ability to retain a state of equilibrium, e.g. remain in an upright and/or stable position without falling when standing or also when e.g. leaning over a rail. **Postural control** is defined as “the act of maintaining, achieving or restoring a state of balance during any posture or activity” (Pollock et al., 2000). In this thesis, I use these two terms interchangeably as my goal is not to delineate the difference between them but to explore postural performance (i.e. balance or postural control) through the lens of the vestibular system in pathological individuals.

The ability to control our posture based on the demands of simultaneously occurring tasks, such as manipulating objects, leading a conversation with someone or simply walking, starts to develop in infancy. In contrast to quadrupeds, which may take a few hours to run, humans take several years to learn to balance, given the inherent instability of the bipedal stance (Haddad et al., 2013).

A comprehensive review of the balance literature showed that similar to spatial navigation, balance is a “whole brain phenomenon” (Surgent et al., 2019). It implicates multiple brain structures - the cerebellum, brainstem, basal ganglia, thalamus, as well as cortical regions - primarily fronto-temporo-parietal regions (Surgent et al., 2019). Thus, balance presents common structures with spatial orientation and might show some anatomical and possibly even functional link to it.

Interestingly, similarly to a “spatial map”, a “posture map” has been suggested to exist in animals after researchers recorded neural signals in the PPC and motor cortex of freely moving rats (Mimica et al., 2018). Although PPC and the motor cortex are known to be implicated in movement planning and navigation, there was strong tuning to the posture of the head, neck and back but less tuning to the movement (Mimica et al., 2018). However, much research is still needed to answer multiple questions arising from this “posture map” discovery: (1) can such activity in PPC be triggered during static or only during dynamic posture, i.e. moving or walking (G. Chen, 2018). Further, (2) how do the PPC and motor area signals translate to angular movement signals in the superior colliculus, which is believed to be implicated in the rotational movements of the head (G. Chen, 2018). Lastly, (3) considering the link between the hippocampus, PPC and the retrosplenial cortex, it is intriguing whether the posture cells of the PPC also take part in navigation and translation from egocentric to allocentric strategy (G. Chen, 2018). At all events, at this point, there is no study discussing “posture maps” in humans.

In clinical practice, postural control can be quantified by measuring body sway during steady standing. Body sway occurring when standing still can be most simply modelled as an inverted pendulum (Winter, 1995) with the ankle acting as a pivot (Fig. 2, left). A well-established clinical test, providing the possibility to test patients’ sway under different conditions (e.g. eyes-open or closed/stable or unstable surface) is the posturography test (Fig. 2, right). For instance, the visual system helps to monitor and adjust our position in space while we are in the light, but in the dark, we need to rely on a

combination of proprioceptive and vestibular signals. Proprioception is part of the somatosensory signal and is considered the ability to know one's body position in space, whereas the vestibular system gives the ability to know one's head position in space. However, when one is not only in the dark but also on an unstable surface, one must rely mainly on their vestibular system, as the proprioceptive and visual signals are not reliable/available, respectively.

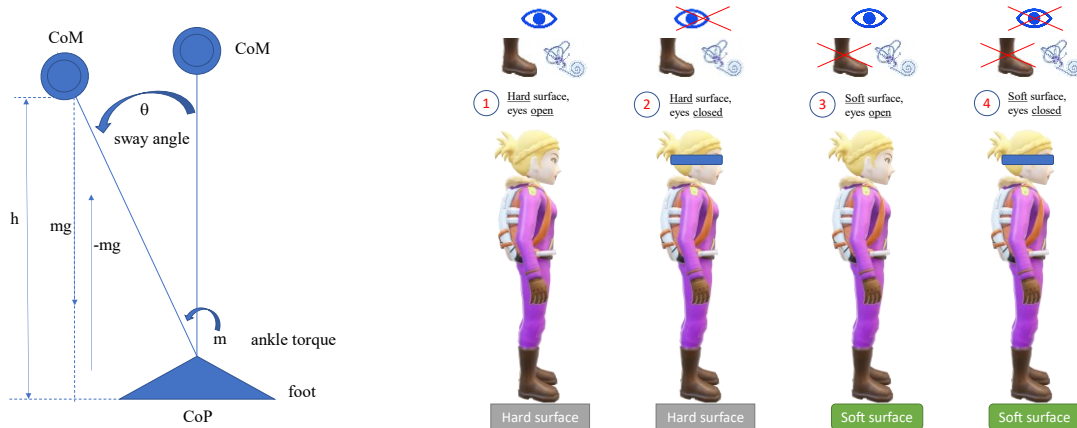


Figure. 2. Inverted pendulum as a model for human sway (left panel) [CoM – centre of Mass, CoP – centre of Pressure, θ – sway angle, m – ankle torque, h – height, mg – gravitation force]. **Posturography test** (right panel) representing four conditions (1)hard surface, eyes-open, (2) hard surface, eyes-closed, (3) soft surface, eyes-open and (4) soft surface, eyes-closed).

Research in postural analysis has remained relatively unchanged for years. When in 1995, it was noted that “postural analysis of upright stance was often restricted to studying the trajectory of the Centre of Pressure (CoP)” (Crétual, 2015), it was hardly expected that even today, this has not largely changed with CoP model accounting for 2/3 of the articles discussing postural analysis (Crétual, 2015). The posturography test mentioned above is a good example of such a test. Still, other biomechanical models addressing linear and non-linear assessment methods start finding their way in standing posture analysis. Thus, a step towards a more sensitive identification of abnormal posture is constantly made.

3. Vestibular system

The vestibular system is essential for maintaining our sense of balance and equilibrium, and the stability of our gaze (Bronstein et al., 2015), (Bear et al., 2016), (Brandt & Dieterich, 2017). It is also a vital contributor to our perception of self-motion and spatial orientation. Being involved in many multimodal collaborations with other sensory and motor signals (Angelaki & Cullen, 2008), (Besnard et al., 2015), (Cheng & Gu, 2018), (K. E. Cullen, 2019), the vestibular system does not provide a singular conscious sensation, and we are rarely aware of it until it fails and starts to act abnormally (Guedry, 1974). Yet, it contributes to a variety of functions from crucial reflexes (e.g. vestibulo-ocular reflex (VOR), vestibulospinal reflex (VSR), vestibulocollic reflex (VCR)) to the high-level perception of space and

motor coordination (Angelaki & Cullen, 2008), (Seemungal, 2014). In the dark, the vestibular system helps us orientate during angular movements such as turns and rotations and contributes to our perception of self-motion and position in space (Seemungal et al., 2004), (Grabherr et al., 2008), (K. E. Cullen, 2019).

3.1. Vestibular processing

3.1.1. Peripheral vestibular system

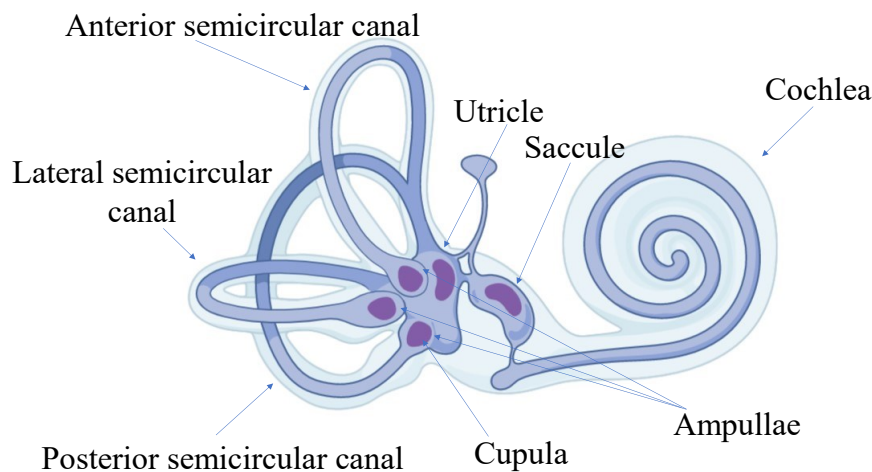


Figure. 3. The peripheral vestibular system (Inner ear was created with [BioRender.com](https://www.biorender.com)).

The vestibular system consists of a peripheral and a central part. The peripheral vestibular system is located in the inner ear, next to the auditory sensory organs, and consists of two groups of organs: (a) the three semicircular canals (SCCs) and (b) the two otolith organs (Fig.3).

The *semicircular canals* (*lateral*, *anterior* and *posterior*) are located approximately orthogonally to each other and sense angular acceleration and head rotations in three axes: yaw, pitch and roll (Fernandez & Goldberg, 1971). This is achieved with the help of a unique sensory detector for rotation called *crista ampullaris* (Leigh & Zee, 2015).

The *otoliths*, i.e. the *utricle* and the *saccule*, respond to linear acceleration and sense head horizontal and head vertical linear acceleration, respectively and gravity (i.e. gravitational acceleration) also during a static head tilt (Fernandez & Goldberg, 1976), (Leigh & Zee, 2015). More precisely, the utricle responds best to “lateral (ear to shoulder) tilts and side-to-side or fore-and-aft translations of the head”, whereas the saccule – to “up-and-down translations and pitch (nose up or nose down) tilts of the head” (Leigh & Zee, 2015). The otoliths’ specialised sensory detector is called *macula* (Leigh & Zee, 2015). Both *cristae* and *maculae* have their own receptor cells (i.e. hair cells type I and II) sending afferent fibres that are very sensitive to motion acceleration, even when we are at rest and/or motionless (Angelaki & Cullen, 2008). The vestibular afferents that form the vestibular part of the

vestibulocochlear nerve (CN VIII) go via the acoustic meatus and reach the vestibular nucleus (VN) complex in the medulla of the brainstem (Purves et al., 2017).

Thus, generally, after having left the inner ear, they “exit” the peripheral vestibular system and “enter” the central part of the vestibular system.

3.1.2. Central vestibular processing in the medulla of the brainstem

The vestibulocochlear nerve (CN VIII) gives projections containing between 14,000 and 18,000 axons (Leigh & Zee, 2015) to the vestibular nuclei (VN) complex. This VN complex consists of four major nuclei – *Medial* (with the biggest volume and length), *Lateral*, *Superior* and *Inferior* (also called descending) (Leigh & Zee, 2015).

Many afferents towards the vestibular nuclei (VN) complex bifurcate, giving ascending and descending pathways within the VN complex. “Some projections from the utricle overlap with those from the lateral SCC, presumably reflecting their common roles in detecting horizontal motion; and some projections from the saccule, which is involved in detecting vertical motion, overlap with those from the vertical SCCs” (Leigh & Zee, 2015). All this has a clinical consequence in case of damage to any of these afferents.

The vestibular afferents coming from the semicircular canals and otoliths are classified as **regular** and **irregular** based on their resting state discharge. Irregular afferents are longer and transfer information from hair cells type I or from type I and II together, whereas the regular afferents – only from hair cells type II (Eatock & Songer, 2011), (K. Cullen, 2012).

For a long time, it has been assumed that both types of afferents and the four vestibular nuclei located in the VN complex (*Inferior*, *Lateral*, *Medial*, *Superior*) in the medulla of the brainstem code the head movement information in a linear manner. Recently, it was shown that this is rather a nonlinear encoding, especially for frequencies > 1 Hz and head rotational velocity > 50 deg/sec (K. E. Cullen, 2019), which are often the conditions we face outside the research laboratory, i.e. in real life. Thus, considering our self-motion is not limited to a single dimension but incorporates in itself linear and angular movements, “linear-nonlinear cascade models” are needed (K. E. Cullen, 2019) to explain the full complexity of natural self-motion. In such a model, both types of afferents (i.e. regular and irregular) have their essential role. While **regular afferents** transmit twice as much information and have lower thresholds of detection (Sadeghi et al., 2007), **irregular afferents** are more suited to match the dynamics of the natural stimulus distribution and distinguish between different stimuli waveforms (Roy & Cullen, 2001). However, more research is needed about the exact way these two types of models switch between each other, the conditions they require and how they are supposed to function, especially in humans.

In contrast to other systems, many of the vestibular system second-order neurons (more precisely, the neurons in the vestibular nuclei (VN) complex of the medulla) are both sensory and premotor neurons

(K. E. Cullen & Roy, 2004). This, in turn, contributes to very short latencies (Angelaki & Cullen, 2008) and, thus – quick responses, both while we are in the light and in the darkness. Importantly, in the dark, the vestibular cues guide our head orientation (Leigh & Zee, 2015) and let us discriminate between directions (right or left) of whole-body angular movements via the perception of self-motion, helping us to calculate our final position in space, i.e. our location (Seemungal et al., 2004), (Grabherr et al., 2008), (K. E. Cullen, 2019).

From the vestibular nuclei (VN) complex, three classes of neurons play an essential role – vestibular only (VO), position-vestibular-pause (PVP) and eye-head (EH) neurons (Leigh & Zee, 2015).

Vestibular-only (VO) neurons are insensitive to eye movements. These neurons receive direct input from the semicircular canals and are less responsive to self-generated (active) movements than externally applied (passive) head rotations. They generate head-stabilisation responses (via the VCR) and handle vestibular information used for spatial navigation (K. E. Cullen & Roy, 2004).

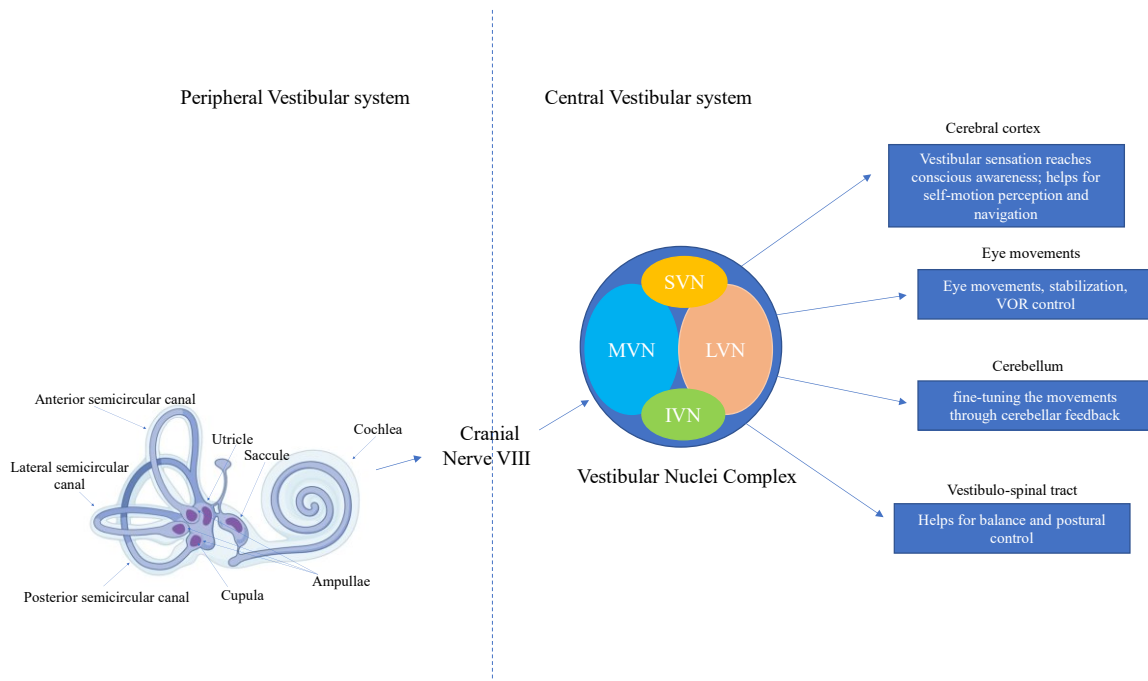


Figure. 4. Vestibular processing (text adapted from (Leigh & Zee, 2015), (Bear et al., 2016), (Purves et al., 2017), (K. E. Cullen, 2019)). (Inner ear was created with [BioRender.com](https://www.biorender.com)).

The second type of neurons are the **position-vestibular-pause (PVP) neurons** that contribute to the stabilising of the gaze via the VOR and optokinetic reflexes. Being involved in gaze, the PVP neurons are equally sensitive to active and passive head movements during gaze stabilisation (Roy & Cullen, 1998), (Angelaki & Cullen, 2008). However, during gaze redirection, they suppress active movements more than they suppress passive movements (Roy & Cullen, 1998), (Angelaki & Cullen, 2008) and attenuate the VOR gain (Roy & Cullen, 1998), (K. E. Cullen & Roy, 2004). This behaviour seems logical, as the neurons should continue to generate the VOR, irrespective of whether we are moving actively or passively (K. E. Cullen et al., 2011).

The third and last group of neurons are the *eye-head (EH) neurons* that are important for the stabilisation of gaze during smooth pursuit. The EH neurons are the main premotor input during smooth pursuit and also show some small contributions to VOR and VCR pathways. They are essential for generating both head-restrained and head-unrestrained gaze pursuit (K. E. Cullen & Roy, 2004).

These three classes of neurons are briefly mentioned once more in the section where I stress the importance of the discrimination between “active vs passive movements”.

The Vestibular nuclei (VN) complex gives rise to four main vestibular pathways that, after exiting the complex, engage in ascending or descending projections crucial for our vestibular-guided spatial orientation and postural control (Fig.4): (1) an ascending path through the thalamus where the vestibular signal reaches conscious awareness by entering the cerebral cortex, (2) an ascending path responsible for eye movements and VOR control, stabilising our gaze, (3) a path going to the cerebellum and back, fine-tuning motor movements, and (4) a descending vestibulospinal tract, responsible for balance and postural control of our active and passive movements. This tract can be divided into two pathways – one for limb control and one for neck muscle control (Bear et al., 2016), (Purves et al., 2017).

3.1.3. Central vestibular processing – from VN complex to the cerebral cortex

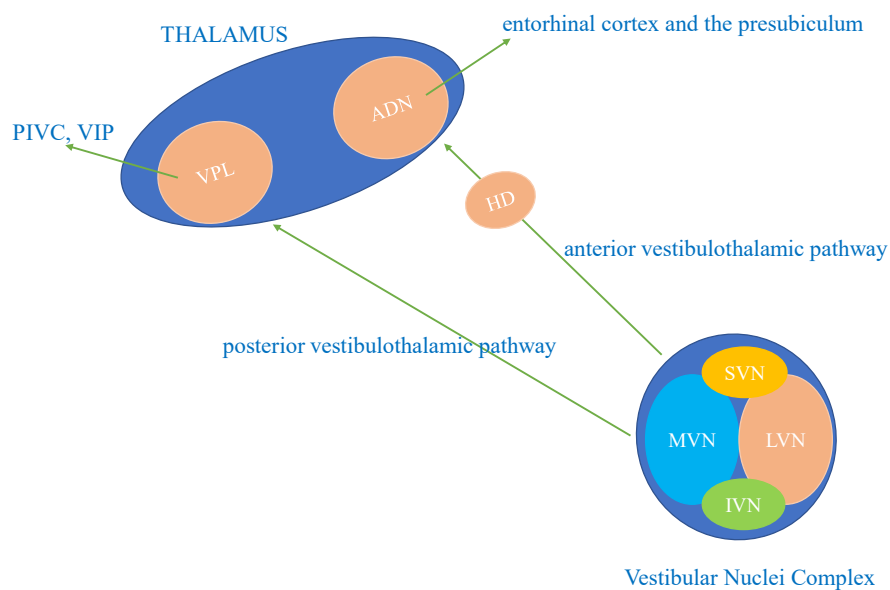


Figure. 5. Vestibular Thalamocortical pathway (inspired by (Wijesinghe et al., 2015) and (K. E. Cullen, 2019)). *legend - anterior dorsal nuclei of the thalamus (ADN), the ventral posterior lateral nucleus of the thalamus (VPL), The parieto-insular vestibular cortex (PIVC) and ventral intraparietal area (VIP), medial vestibular nucleus (MVN), lateral vestibular nucleus (LVN), superior vestibular nucleus (SVN) and inferior vestibular nucleus (IVN).

Unlike other sensory modalities, the ‘vestibular cortex’ appears distributed without a primary sensory area and an association cortex, as found in other sensory modalities such as vision or touch (Guldin & Grüsser, 1998).

The processing of central vestibular information is “highly convergent and strongly multimodal” (Angelaki & Cullen, 2008). Interactions between the vestibular and visual (through the VOR and eye movements), proprioceptive and motor signals (via the VSR and the VCR and the cerebellum sending signals to premotor, sensory-motor, brainstem and spinal cortex areas) take place throughout the central vestibular pathways (Angelaki & Cullen, 2008).

To reach the cerebral cortex, the vestibular information travels from the vestibular nuclei (VN) complex further through the anterior and posterior thalamocortical pathways to reach the anterior dorsal nuclei of the thalamus (ADN) and the ventral posterior lateral nucleus of the thalamus (VPL), respectively (K. E. Cullen, 2019) (Fig. 5). The thalamus plays the role of a relay centre receiving information from multiple sensory and motor signals. As the anterior dorsal thalamic nucleus (ADN) is a part of the head direction (HD) cell pathways, it contributes to the sense of heading direction important for navigation (Taube, 2007) and spatial cognition (Hitier et al., 2014). Then, ADN projects further to the entorhinal cortex and the presubiculum. The posterior thalamocortical pathway transports vestibular information from deep cerebellar and vestibular nuclei via the ventral posterior lateral nucleus of the thalamus (VPL) to multiple cerebral regions (e.g. parieto-insular vestibular cortex (PIVC) and ventral intraparietal area (VIP)). This way, the posterior thalamocortical pathway plays a key role in the generation of precise coordination of vestibular self-motion perception and motor activity (Clark & Harvey, 2016), (K. E. Cullen, 2019). In their publication, Clark and Harvey discuss (Clark & Harvey, 2016) the function of the thalamic nuclei and report their supposed role in spatial orientation. They suggest that the anterior thalamic nuclei uses path integration mechanisms and allocentric landmarks that are distant, whereas the lateral/posterior thalamic nuclei – relies on proximal landmarks while using visual and somatosensory stimuli.

3.1.4. Cerebral cortical regions implicated in vestibular processing

Having left the thalamus, some of the vestibular projections head towards the cerebral cortex. Neuroimaging studies during caloric and galvanic vestibular stimulation (GVS) suggested a series of brain areas receiving the vestibular signal – (1) anterior and posterior parietal cortex, (2) areas around the temporoparietal junction (TPJ) and the anterior and posterior insula, (3) the somatosensory cortex, (4) anterior and posterior cingulate cortex, (5) striate and extrastriate visual cortex, (6) frontal cortex and (7) the hippocampus and parahippocampus (Lopez & Blanke, 2011).

Some more specific and better-known/confirmed regions implicated with the vestibular system in non-human primates include (a) the parieto-insular vestibular cortex (PIVC), (b) the ventral intraparietal area (VIP), (c) the medial superior temporal area (MST) and (d) area 2v and area 3av from the somatosensory cortex (Lopez & Blanke, 2011).

(a) PIVC

The parieto-insular vestibular cortex (PIVC) plays a core role in the vestibular cortical network and has

been implicated as the main region of the putative vestibular cortex not only in primates (Grüsser et al., 1990) but also in humans (Brandt & Dietrich, 1999). In humans, however, the PIVC is possibly homologous to the human posterior insula and temporoparietal junction (Brandt & Dietrich, 1999). PIVC neurons respond to external visual activity, and research evidence suggests that this area monitors the head and body motion relative to external environments during the process of self-motion (K. E. Cullen, 2019). It was even suggested that PIVC “seems to be a nexus for spatial orientation” because of the projections it receives (Leigh & Zee, 2015).

Researchers have been looking for the putative vestibular cortex since early 1930s, as reviewed in (Guldin & Grüsser, 1998). Once PIVC was established in non-human primates, the search for the human analogue became even more important (Brandt et al., 1994). In more recent years, the area of the Sylvian fissure between the temporal and parietal lobe has attracted much of our attention. It was suggested that the non-human PIVC might be similar to a human area termed the temporo-peri-Sylvian vestibular cortex, which includes the parietal operculum (OP2) (Kahane et al., 2003), (Eickhoff et al., 2006) and the middle and posterior sections of the first and second temporal gyri (Kahane et al., 2003). Later, another prominent study suggested that only the parietal operculum area (OP2) might be the real core of the ‘vestibular cortex’ as it may be exclusively processing vestibular and no other multisensory information (Zu Eulenburg et al., 2012). In addition, all regions showing activity to vestibular stimulations were linked to the OP2 area, and interestingly a right hemispheric dominance was suggested (Zu Eulenburg et al., 2012). Finally, more recent studies show that the “human vestibular cortex” might be indeed more than a single region (Frank & Greenlee, 2018), as initially proposed, and possibly a group of two areas. These two areas comprise (1) a vestibular region located in the parietal operculum (OP2) next to the posterior insula and corresponding to the non-human PIVC, and (2) a visual-vestibular area, located in the retro-insular cortex. The visual-vestibular area is called a posterior insular cortex (PIC) (Frank & Greenlee, 2018) and was shown to be distinct from PIVC (Frank et al., 2016).

(b) VIP

The second area I review is the ventral intraparietal area (VIP). Its neurons are not exclusively vestibular and show activity towards visual, proprioceptive and general somatosensory signals, although their responses to optic flow are weaker than to vestibular signals (Avillac et al., 2005), (A. Chen et al., 2011), (K. E. Cullen, 2019). Interestingly, in non-human primates, the VIP neurons also respond to passive whole-body linear vestibular, visual and bimodal (i.e. vestibular and visual) stimulations (i.e. translations), especially in the dark (Schlack et al., 2002). The differences in response after a unimodal and bimodal stimulation, contributed to the understanding of the mechanisms needed to discriminate self-motion from other objects’ motion and prevent a misinterpretation that could happen if only relying on one sensory system alone (Schlack et al., 2002).

(c) MST

Another critical area for the study of visual-vestibular interaction (Britten, 2008), (Ventre-Dominey, 2014) is the MST - a medial superior temporal area that is shown to be sensitive to vestibular input in the dark (Goldberg et al., 2012), (K. E. Cullen, 2019). Importantly, in the dark, the rhesus monkeys' MST neurons combine visual and vestibular signals to increase self-motion detection and improve the discrimination of optic flow arising from the self-movement or the movement of some big objects nearby (Duffy, 1998). Later, it was shown that in rhesus monkeys, it is the dorsal MST neurons that are sensitive to vestibular and optic flow stimuli (Takahashi et al., 2007). In humans, Brodmann area 37 of the middle temporal gyrus might be the equivalent to the MST, as discussed in (Hitier et al., 2014). In addition, the human MST area is essential for “vestibular perception and especially motion sensitivity and direction of heading” (Leigh & Zee, 2015). Importantly, VIP and PIVC also have their role in “vestibular heading, each with its pattern of head, body or eye-centred reference frame” (Leigh & Zee, 2015).

3.2. Special aspects of vestibular processing with regard to spatial orientation and postural control

3.2.1. Acceleration – Velocity – Position

The vestibular system helps us with the sense of self-motion by answering questions such as “am I moving at all?” or “how much have I moved?” (i.e. travelled distance) and the more complicated question for spatial orientation - “where exactly am I now?” (questions adapted and modified from (Kaski et al., 2016)). Thus, the vestibular system provides signals of self-motion, crucial for gaze and postural control, and also signals for travelled distance, important for spatial navigation, especially in the dark where vision is not available and the proprioceptive system – not always reliable.

However, the peripheral vestibular organs provide inertial cues of self-motion in the form of head acceleration signal that the brain needs to convert to conscious perception of “head velocity” and further to position to maintain our sense of spatial orientation during self-motion in the dark (Kaski et al., 2016). So, the peripheral vestibular system integrates the head acceleration signal with respect to time to get the head velocity signal, which is later sent to the brain to be translated (i.e. integrated with respect to time) to head position information, i.e. location. However, the brain must accomplish a more sophisticated task than a pure mathematical equation, but at present little is known regarding how the central vestibular system fulfils this velocity-to-position transformation task.

3.2.2. Self-motion

Self-motion is a crucial part of spatial orientation. Self-motion cues are provided by multiple sensory systems, including the vestibular, visual and somatosensory systems. Thus, they all contribute to gaze, postural stability and navigation.

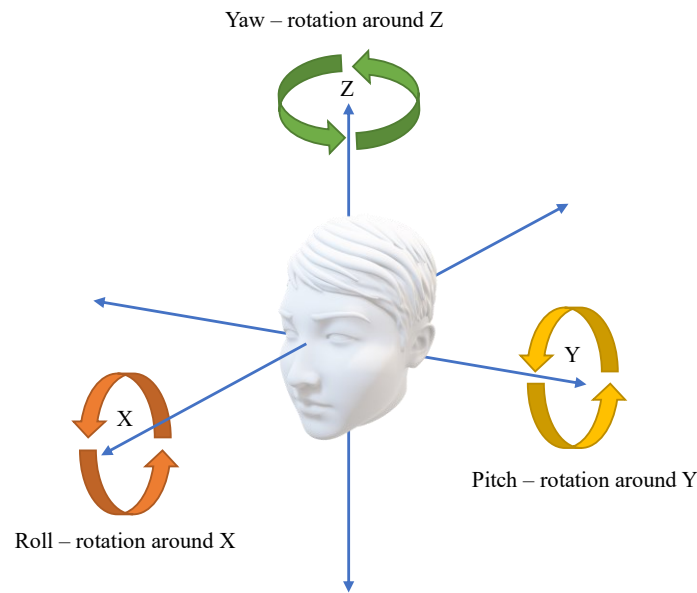


Figure. 6. Head movements in six dimensions (adapted from (Purves et al., 2017)).

The peripheral vestibular organs detect head movements in six dimensions (i.e. three axes of translation via the otoliths (forward/backwards, up/down, left/right) and three axes of rotation via the semicircular canals (yaw, pitch and roll) (Fig.6). This way they give the brain a comprehensive account of the process of self-motion (K. E. Cullen, 2011), (K. E. Cullen, 2019). As previously discussed in the section on “brainstem processing”, this simultaneous incorporation of linear and rotational movements requires “linear - nonlinear cascade models” (K. E. Cullen, 2019) to explain the full complexity of natural vestibular self-motion.

Extra-vestibular cues, i.e. visual and proprioceptive (as part of the somatosensory system) signals, are also crucial for how the brain computes its estimate of self-motion. Illusory self-motion (i.e.vection) is produced by the visual optic flow that is capable of producing a powerful sensation of motion even when we are motionless (Britten, 2008). Most often in our life, however, we are moving. Thus, we activate not only vestibular but also proprioceptive signals in the muscles/joints and other somatosensory receptors in the skin close to the moving muscles (Lackner & DiZio, 2005).

Recent findings indicate that some multisensory and motor signals are combined early in the vestibular processing, while others - later during central vestibular processing (K. E. Cullen, 2019). Thus, in the case of peripheral vestibular loss, the substitution of extra-vestibular sensory and motor information at the stage of the early vestibular pathways may help with gaze stability and balance improvement (K. E. Cullen, 2019). Interestingly, Prof. Adolfo Bronstein and colleagues (Kleinschmidt et al., 2002) observed that the flocculonodular lobe (i.e. the vestibular cerebellum) becomes active during self-motion and damage to this nodulus affects the normal perception of self-motion. Thus, it was suggested that the cerebellum is also involved in the perception of self-motion (Kleinschmidt et al., 2002) in humans and plays a crucial part in the generation of the signal. In addition, a more recent study discussed further in

the “3.2.5. Velocity storage” section suggests that in humans, there might be different vestibular mechanisms for vestibular reflex and perceptual processing within the cerebellum (Nigmatullina et al., 2015).

Still, although vestibular and extra-vestibular cues provide most of the information needed for the generation of the proper signal of self-motion, additional aspects also need to be considered.

3.2.3. Tilt – Translation ambiguity

A central function of the peripheral vestibular organs, crucial for navigation and balance, is the transduction of the head acceleration, both linear and rotational, into neural signals detected by the brain. This way, the vestibular system serves as an inertial sensor that codes the motion of the head relative to the world (Merfeld et al., 1999), (Angelaki & Cullen, 2008).

However, if looking at semicircular canals and otolith organs separately, the signal they provide is ambiguous. Two issues arise relating to “inertial motion”: (1) a “rotation issue” due to the stable fixation of the vestibular sensors to the head and the consequent inability to discriminate how the head moves relative to the world, and (2) a “linear acceleration issue” that arises as a consequence of the “rotation issue”. The linear acceleration issues develop as the otoliths (afferents) cannot differentiate between translational and gravitational components of linear acceleration (Angelaki & Cullen, 2008), which leads to them responding identically to translational motion (lateral and forward/backward) and head tilt relative to gravity (pitch and roll) (Angelaki & Yakusheva, 2009), (K. E. Cullen, 2019). As discussed in (K. E. Cullen, 2019), “Einstein’s equivalence principle posits that these inputs are physically indistinguishable from one another, meaning that the otolith afferents transmit ambiguous information to the brain”. An example from everyday life would be the feeling of a backward tilt while the airplane is accelerating and is still on the racing track before the actual “take-off”. In fact, at this point, we are still in an upright position.

However, the brain, converging the signals coming from both peripheral organs together, seems able to overcome these issues and deliver an accurate interpretation. An earlier idea of how this happened was suggested by Merfeld and colleagues (Merfeld et al., 1993) and developed further by Angelaki and colleagues (Yakusheva et al., 2007), as described in (Angelaki & Cullen, 2008): in brief, by using the rotational signals from the semicircular canals, the brain calculates an estimate of the linear acceleration for the head during tilt. This estimate is subtracted from the otolith's net linear acceleration, and the result is the actual translational acceleration (Yakusheva et al., 2007), (Angelaki & Cullen, 2008).

Later, in the central part of the vestibular processing, central neurons show some preference to encode translational or both ‘translation and net gravito-inertial’ acceleration for frequencies $> 1\text{ Hz}$ (Yakusheva et al., 2007), (Angelaki & Cullen, 2008), (Angelaki & Yakusheva, 2009). Importantly, it becomes clear that both the otoliths (Green & Angelaki, 2003) and the semicircular canals (Merfeld et al., 1999) are crucial for the correct interpretation of the general vestibular signal and our position in space, relative

to gravity at all stages of the vestibular processing as inactivation of any of the peripheral vestibular organs leads to limitation of this result.

However, vestibular receptors for postural control and spatial orientation do not rely solely on inertial motion but are activated by both “self-generated and externally applied head movements” (K. E. Cullen, 2019).

3.2.4. Passive vs active motion

Discrimination between passive (externally applied) and active (self-generated) movements is essential for postural and perceptual stability during spatial navigation (K. E. Cullen et al., 2011), (Angelaki & Cullen, 2008), (K. E. Cullen, 2019). Research has shown that the vestibular cerebellum, “a region likely to be involved in generating an internal model of self-motion” (K. E. Cullen et al., 2011), is implicated in the multimodal integration of proprioceptive and vestibular information. This multimodal integration is essential for the elimination/cancellation of self-generated, i.e. active vestibular signals (happening in the vestibular nuclei) from any subsequent implementation in the process of orientation and postural control (K. E. Cullen et al., 2011).

However, regardless of whether passive or active movements, the vestibular system appears to similarly process information at the early stages of vestibular processing, i.e. at the level of the vestibular afferents (K. E. Cullen & Roy, 2004). Nevertheless, later, at the first-level of central vestibular processing, i.e. at the level of the vestibular nuclei, this is no longer true (K. E. Cullen & Roy, 2004), and a special class of neurons contributing to our posture and spatial orientation called vestibular only (VO) neurons, show less response towards active movements (K. E. Cullen & Roy, 2004), (K. E. Cullen et al., 2011).

As previously mentioned, the vestibular nuclei complex receives inputs not only from the vestibular afferents via the vestibulocochlear nerve (CN VIII) but also from multiple cortical, cerebellar and brainstem regions, thus being supplied with numerous extra-vestibular cues that can guide the discrimination between passive and active head movements (K. E. Cullen & Roy, 2004). As the individual afferents and vestibular nuclei show very low sensitivity to whole-body motion (Sadeghi et al., 2007), ascending vestibular pathways need information from a significant number of vestibular nuclei neurons to ensure that this signal would be detected at a perceptual level (K. E. Cullen, 2019).

The primary discrimination of active versus passive moves is conveyed by the VO neurons - the neurons that contribute to posture and spatial orientation. This discrimination does not occur in the PVP or EH neurons, the latter two of which are involved in gaze control (Leigh & Zee, 2015), (K. E. Cullen, 2019). This model is consistent with von Holst and Mittelstaedt's suggestion from 1950 that the brain “compares an ‘efference copy’ of the motor command generated during voluntary movements with an incoming sensory input to distinguish between exafference and reafference” (K. E. Cullen et al., 2011). However, the idea of the efference copy was first suggested by von Helmholtz in his “*Handbook of*

Physiological Optics” (1876) and only further developed by von Holst and Mittelstaedt, as discussed above.

3.2.5. Velocity storage

Velocity storage, a concept initially defined by (Raphan et al., 1979), is crucial for the way the brain “stores”/“memorizes” its position in space over time (P. Smith, 2019). After the start of an angular movement, i.e. a rotation, the cupula of the semicircular canals is said to usually deflect for 4-7s, whereas the rotational nystagmus via the VOR prolongs this time up to 15-20s as a consequence of a central process occurring in the brainstem, i.e. the velocity storage (Seemungal et al., 2007), (Bronstein et al., 2008). Velocity storage is compared to “as if vestibulo-ocular velocity signals were ‘stored’ and then released long after the rotation has ended” (Bronstein et al., 2008). This mechanism uses semicircular canal, saccule, utricle and optokinetic information to “align the axis of eye velocity towards the spatial vertical when head orientation is off-vertical axis” (Yakushin et al., 2017). In addition, VO neurons play the central role in the coding mechanism of velocity storage, and the PVP neurons serve as a link between the vestibular and oculomotor systems to support the VO neurons (Yakushin et al., 2017). Moreover, Right- and Left-sided rotational signals of velocity storage are coded by neurons located on both sides of the vestibular nuclei and the brainstem. Their interaction, however, is crucial as a potential lesion of the interconnections reduces/abolishes the velocity storage function (Katz et al., 1991).

Research evidence suggested that as the cerebellum is involved in the perception of self-motion (Kleinschmidt et al., 2002), cerebellar networks contributing to velocity storage project not only to VOR pathways but possibly also to vestibulo-cortical regions (Bronstein et al., 2008). Usually, “perceptual responses are tightly coupled with low-order reflex responses allowing a prediction of one from the other” (Nigmatullina et al., 2015). Consequently, it was assumed that there is a link between vestibular-ocular (i.e. VOR as a low-order reflex) and perceptual time constants (Okada et al., 1999), (Bronstein et al., 2008), (Bertolini et al., 2012) pointing to a single mechanism for both these processings located in the cerebellum. Whereas this remains true for healthy controls (Okada et al., 1999) and cerebellar patients (Bronstein et al., 2008), (Bertolini et al., 2012), it might be different for professional ballet dancers who have experienced long-term vestibular training. A study reported that when ballet dancers participated in a spatial task with a rotational chair moving in the yaw plane, while in the dark, there was no link between dancers’ vestibular perceptual function (i.e. measured via the rotation of a tachometer wheel meant to mirror the velocity rotation of the chair they perceive) and their oculo-motor reflex (i.e. VOR measured via electro-oculography) (Nigmatullina et al., 2015). In addition, scientists noticed a reduced GM density and less developed WM network in the vestibular cerebellum for the dancers (Nigmatullina et al., 2015), in contrast to healthy controls. Thus, authors suggested a possible cerebellar gating of the vestibular signals of self-motion perception trying to reach the cerebral cortex

and become conscious, thus possibly allowing for the “dancers to perform pirouettes at ease with little dizziness” (Nigmatullina et al., 2015).

3.2.6. Cognitive function

The vestibular system is involved in mediating a number of ecologically relevant cognitive functions, including self-motion perception, spatial orientation and balance (Camicioli et al., 1997), (P. Smith, 1997), (Brandt et al., 2005), (P. Smith et al., 2010), (P. Smith & Zheng, 2013), (Previc, 2013), (Hitier et al., 2014), (Yoder & Taube, 2014), (Seemungal, 2014), (Mast et al., 2014), (Bigelow & Agrawal, 2015). Scientists discuss four or probably five possible pathways sending vestibular information to the “vestibular cortex”. These I present in Fig. 7. (Hitier et al., 2014). The widespread area these pathways cover is another example of the multimodal nature of the vestibular connections throughout the brain and “the absolute necessity for the brain to know exactly where the body is and where it is going to be in the next fraction of a second as it plans the next movement of the eyes, arms or legs in the fight for survival” (Leigh & Zee, 2015).

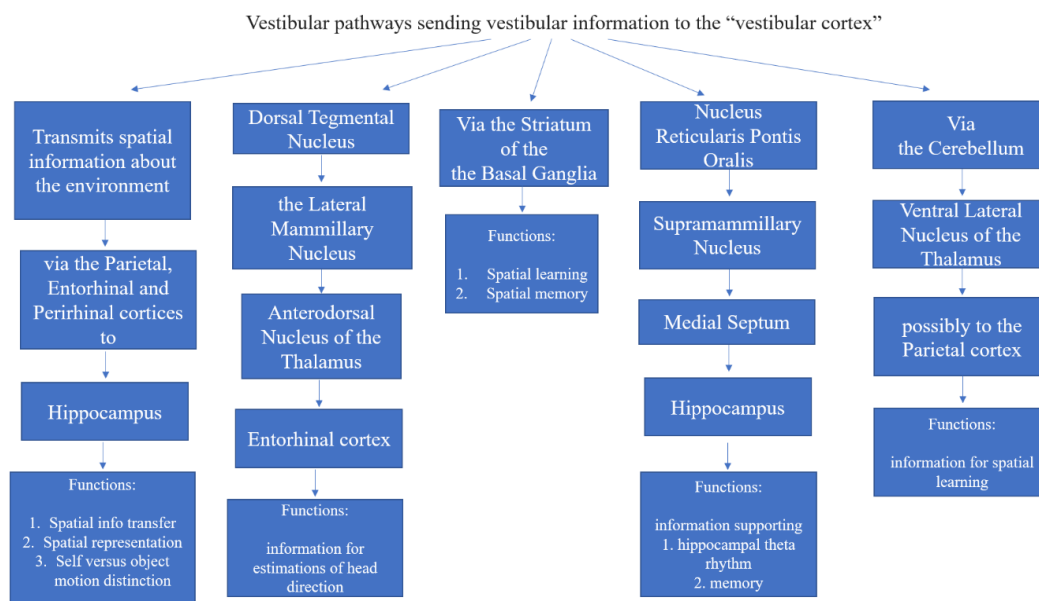


Figure. 7. Vestibular pathways sending vestibular information to the “vestibular cortex”, adapted from (Hitier et al., 2014).

Hitier and colleagues (Hitier et al., 2014) noted that as per non-human and human-based research, there are several main vestibular areas we can distinguish from the vestibular pathways contributing to spatial cognition: (1) hippocampal and parahippocampal cortices, (2) PPC, medial superior temporal area and ventral intraparietal area, (3) parietal anterior cortex, (4) PIVC and TPJ, (5) cingulate gyrus and retrosplenial cortex and (6) Brodmann areas 7a, 39, 40.

The formation of a “spatial cognitive map” relies on the contribution of multiple spatial cells. Importantly, the lack of vestibular input to place cells and HD cells has been shown to result in abnormal location (Stackman et al., 2002) and direction-specific firing (Stackman & Taube, 1997), respectively.

Lastly, cognitive decline and vestibular dysfunction have shown their effects on spatial navigation in spatial cognitive disorders (K. E. Cullen, 2019) that may, for instance, arise after a diffuse axonal lesion as a short- or long-term consequence of a traumatic brain injury (TBI) event or a neurodegenerative disease such as Alzheimer's disease (AD). However, the exact way in which cognitive and vestibular impairment link to the spatial and also postural modalities in these two patients' populations is unclear, and further research is needed to unveil the neural mechanisms of vestibular-guided spatial and postural central processing.

4. Introduction of the study populations for this thesis

My literature review provides multiple examples of how the vestibular system takes part in a complex network of connections throughout the brain. However, scientific evidence about the neural mechanisms of two crucial vestibular-dependent modalities, such as spatial navigation and postural control, is sparse, especially in patients with brain disease. Two groups of neurological patients that are prominent with their spatial and postural dysfunction and where vestibular research is lacking are traumatic brain injury (TBI) patients and also patients with memory impairments, such as those with Alzheimer's disease (AD).

Non-vestibular research evidence (i.e. evidence based on research that does not mention the “vestibular system” as a contributor or investigates the “vestibular” effects) indicates that acute TBI patients exhibit a decreased cognitive ability to learn their orientation during active locomotion (McFarlane et al., 2020). In addition, they experience increased body sway (i.e. imbalance) and are thus more prone to falls up to six months into their chronic state (Akin & Murnane, 2011).

Similarly, early in the disease, a third of AD patients complain of getting lost during visually-guided orientation in their local environment (Henderson et al., 1989). Importantly, even if the imbalance is a well-described impairment during the later stages of AD, it is a less recognised feature of the early stage of the disease. Still, AD patients might experience postural impairment also at the beginning of the AD pathology (Agrawal et al., 2019).

4.1. Traumatic brain injury (TBI) patients – non-vestibular research evidence

Traumatic brain injury is dynamic brain damage that does not obligatorily terminate at the point of the initial brain insult but can manifest with many secondary processes and complications (Werner & Engelhard, 2007), (Jolly, 2020). The most frequent causes for injury are road traffic accidents, falls, events linked to military service or general violence (Jolly, 2020). Injuries can vary substantially among TBI patients and depend on the force exerted during the TBI and the brain location where they were applied (Jolly, 2020). Depending on the aetiology of the brain insult, it can have various and profound consequences on different brain modalities, some of which affecting not only functional but also cognitive performance, e.g. among others – postural and spatial processing.

Animal studies have contributed significantly to our better understanding of TBI in humans. Still, such models are difficult to develop due to the various aetiology of TBI and the unpredictable cascade of events following the initial injury. A Morris Water Maze (MWM) study in rats with bilateral perforant path transections interrupting cortico-hippocampal connections to the whole or just the dorsal hippocampus showed a significant impairment in spatial recall and spatial learning (Skelton, 1998). Even if time and training contributed to improvement (i.e. recall improved after two weeks and learning – in four-five weeks), the recovery was considered incomplete as every movement of the platform caused the rats' performance to deteriorate again (Skelton, 1998). The latter issue makes an important point about distinguishing between “recovery of function” and “behavioural compensation”(Skelton, 1998), which is essential for a return to “normal daily life” after a TBI.

A long-lasting cognitive decline was also reported in a study where children aged 6-12yrs who survived severe trauma displayed restored spatial learning only four years post-trauma, despite persisting cognitive mapping skills deficit (Lehnung et al., 2003). Again, this indicated the far-reaching consequences that the injury might have not only during the acute phase but also later in life.

Further, adolescent hockey players with a history of brain injury showed decreased accuracy in a spatial navigation task compared to their fellows without concussion (McFarlane et al., 2020). Being unable to spatially orientate in a task that is less complex than the hockey game itself puts concussed athletes in a disadvantaged position of being injured again (McFarlane et al., 2020). In another study, clinically asymptomatic concussed individuals were able to pass the balance and spatial clinical tests, but EEG baseline measures managed to show the masked damage by revealing reduced whole brain beta and frontal theta power bands during all postural task conditions (Teel et al., 2014). Scientists argue that this might be due to “functional resolution happening faster than physiological” recovery or clinical tools that are not sensitive enough to uncover subtle deficits (Teel et al., 2014). Consequently, these studies are another example that an early return to “play or normal daily life” can inevitably lead to an increased risk of injury and recurrent traumatic events (Teel et al., 2014), (McFarlane et al., 2020), (Buckley et al., 2021).

Visual impairment is yet another disability often present after TBI that can manifest as various abnormalities in visual acuity, vergence, saccadic and smooth pursuit movements, visual perception, and visuospatial functions (Armstrong, 2018). Generally, oculomotor dysfunction is present in approximately 90% of TBI cases (Alhilali et al., 2014) and thus greatly contributes to decreased spatial orientation and postural imbalance. Because of the reduced ability of concussed patients to orient their spatial attention during navigation, patients were reported to make more frequent obstacle contacts with their leading foot (Catena et al., 2009). This stresses a crucial functional link between spatial and postural impairment and the closely connected risk of new falls and/or re-injury, with every following injury contributing to permanent damage (Murray et al., 2019).

In summary, TBI patients are often left to deal with long-term disabilities (Lehnung et al., 2003), (Jolly, 2020), showing a great dependence during activities such as keeping their balance/postural control and

spatial orientation, among others, that can persist across their lifetime. Consequently, this becomes a serious concern, both for the TBI patients and their families, and for the medical service.

4.2. Patients with memory and (balance) impairment – non-vestibular research evidence

Alzheimer's disease (AD) is the most common form of dementia, with approximately 46 million people and increasing worldwide prevalence ("2020 Alzheimer's Disease Facts and Figures," 2020), (Alzheimer's & Dementia: Global Resources, 2021). The disease results in a marked decline in navigational skills that are initially prominent in unfamiliar environments and later start also occurring in familiar settings. In addition, people with AD are at a high risk of falls and are two to three times more likely to fall and get an injury as compared to healthy elderly (Cronin et al., 2017), (Agrawal et al., 2019), (Yesantharao et al., 2022). Still, their imbalance is a less recognised feature of early Alzheimer's disease (Cronin et al., 2017). This may be related to the fact that falls often come before cognitive decline and thus may remain "unnoticed". In trying to avoid the huge burden that imbalance and spatial disorientation can have on affected individuals, enormous research effort is performed to explore how the spatial and postural modalities develop during healthy and pathological ageing.

Even if the decline in episodic memory has been a gold standard in diagnosing AD (Dubois et al., 2014), (Coughlan et al., 2018) for a long time, the pronounced visuospatial disorientation suggests being a more sensitive biomarker than episodic memory (Johnson et al., 2009). This is based on the fact that brain regions affected early in the disease pathology (e.g. hippocampus (Nedelska et al., 2012), (Parizkova et al., 2018) and entorhinal cortex (Killiany et al., 2000)) are "key nodes in the spatial navigation network" (Coughlan et al., 2018).

With a considerable variety of studies reporting a severe spatial navigational decline in Alzheimer's disease, it has remained ambiguous for a long time whether egocentric or allocentric navigational strategies are the first to deteriorate during Alzheimer's disease. Early research in AD compared a real-world hidden goal task and a computer version of the same task to establish similar results between methodologies and significant allocentric impairment in the AD group when compared to controls (Kalová et al., 2005). Further, research in amnesic MCI (aMCI) and AD patients showed that during a virtual Y-maze task for assessing strategy of navigation, patients expressed a higher preference for egocentric skills over allocentric corresponding to the severity of their condition: aMCI showed 67% vs 33%, AD showed 94% vs 6%, while age- and education-level matched controls - 39% vs 61% (Parizkova et al., 2018). Moreover, both real-world MWM and computer-based MWM spatial impairment in aMCI, mild and moderate AD was proportional to right hippocampus (Nedelska et al., 2012), (Parizkova et al., 2018) and basal forebrain volume loss (Parizkova et al., 2018). Another principal study supporting the idea of "allocentric first" decline is the PREVENT Dementia Program (Ritchie et al., 2018). It suggests that when examining the allocentric (with the Four Mountain task

(Chan et al., 2016),(Wood et al., 2016)) and egocentric (with the Supermarket trolley task (Tu et al., 2015)) strategies in APOE $\epsilon 4$ carriers, allocentric deficit served as a better predictor of risk in the allele carriers than egocentric navigation or episodic memory performance. Thus, the earliest cognitive changes might be partially steered by tau-related pathology in the medial temporal lobe and not exclusively by amyloid depositions in the medial parietal lobe (Ritchie et al., 2018).

Further, postural control research evidence in Alzheimer's disease revealed that the most common reason for falling in AD was stumbling, with those with lower MMSE scores experiencing more falls (Perttola et al., 2017). One of the first studies to establish a link between mental load and abnormalities during locomotion (i.e. via a dual-task design) reported that "talking while walking" leads to a significant decline of speed in Alzheimer's patients performing a verbal fluency task (i.e. reciting names) while walking (Camicioli et al., 1997). Using cognitive resources to compensate for postural control inevitably leads to a lack of ability to address the "anticipating" postural changes during walking, which are a form of a cognitive modality. Thus, at first glance, pure postural preference might be enough to ensure stable posture for AD patients, but further consideration reveals that such a strategy is not rigid in the long-term postural safety of the individual, as "adaptation"/"anticipation" is a crucial part of balance. The reason lies in the fact, that posture is not a purely mechanistic task (Manckoundia et al., 2006), but a complex, cognitively involved process.

All this spatial/postural impairment has serious consequences for the patients and their families, not only from a physical and psychological point of view but also from a financial perspective. However, the understanding of the brain mechanisms underlying this decline is still limited (Pai & Jacobs, 2004), (Stangl et al., 2018).

5. Current limitations

While extensive non-vestibular research is advancing our understanding of the spatial and postural decline in TBI and in patients with memory impairment (e.g. Alzheimer's disease), it also indicates the current gaps in the management of these patients and the lack of knowledge about the neural mechanisms behind this decline. However, to better understand the aetiology of these impairments, one needs a more comprehensive perspective approach. One system that gets often underestimated in its importance in the way to solving these issues is the vestibular system. Consequently, much less is known about how the vestibular system contributes to the spatial and postural processing in these two neurological populations.

6. Aim/Hypotheses/Objectives

My aim for this thesis was to investigate the contribution of the vestibular signal in the spatial orientation and postural control of patients with acute traumatic brain injury or patients with memory and (balance) impairment. Consequently, I hoped to improve our understanding about how the

vestibular-guided mechanisms of spatial navigation and postural control were affected in these two patient groups and increase awareness about the importance of the vestibular-based diagnosis that could lead to the improvement of the subsequent prognostication and outcome for the patients. Clinical and non-clinical research-based behavioural testing was the basis of my research, along with brain imaging analysis (DTI and VBM) for the acute TBI cohort.

I. HYPOTHESIS

Central nervous system dysfunction due to TBI or memory impairment affecting the processing of vestibular signals will manifest with spatial disorientation and postural imbalance.

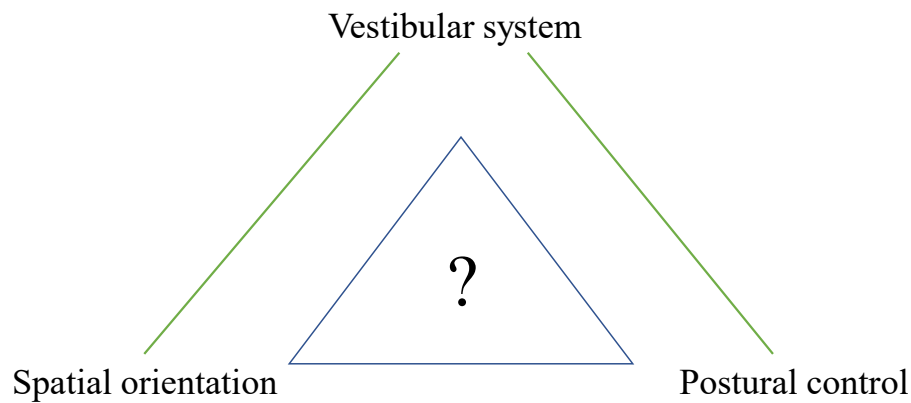


Figure. 8. Schematic presentation of Hypothesis I.

As seen throughout my literature review, research has established a link between the vestibular system and spatial orientation performance (P. Smith, 1997), (Stackman et al., 2002), (Brandt et al., 2005), (K. E. Cullen, 2019). In addition, the vestibular system has been inextricably linked to balance/postural control (Fig. 8). Still, there is a lack of understanding on how the vestibular system affects the spatial and postural modalities, especially during a central nervous system dysfunction due to an acute TBI or memory impairment. In addition, it is unclear if there are specific brain regions involved in these neural mechanisms and where these are located.

When looking at all three modalities, i.e. the vestibular system, the spatial navigation and postural control, it is similarly ambiguous if they share a link and if so, whether the '*spatial – postural*' link could be via the vestibular system. Brain research has not yet reported a link that mechanistically connects spatial orientation and postural control processing. Still, (1) the brain processing of the vestibular signals of self-motion is used for guiding both spatial orientation and postural control, (2) postural control is a crucial part of spatial navigation, and (3) spatial orientation and postural control

are two modalities that mutually impact our quality of life as two faculties concurrently engaged in a crucial ecological behaviour such as foraging. Therefore, a logical question arises on whether they could be connected.

Considering proprioception, vision and the vestibular system are all crucial components of balance, all three of them could potentially establish this '*spatial-postural*' link. If we look at vision, then it becomes clear that when they eyes are closed, vision can no longer work as a link between the postural control and spatial orientation. The same holds true for proprioception, when we are standing on unstable surface, i.e. when the proprioceptive signal is unreliable. Thus, the vestibular system seems like a possible candidate mediating this link.

Clinical and non-clinical behavioural testing was used to address this hypothesis, alongside whole-brain DTI and VBM analyses for the acute TBI patients. To further investigate the *vestibular – spatial – postural* relationship, I considered looking at the general cortical/subcortical morphology. The whole-brain imaging analyses also confirmed that it was meaningful to further look at ROI imaging analysis and consequently, a set of specific vestibular-involved cortical/subcortical regions, alongside the biggest commissural WM tract in the brain – the CC, were investigated.

OBJECTIVES:

1. To investigate how the brain mechanisms of vestibular spatial orientation or vestibular balance are affected during acute TBI and what WM/GM regions are implicated based on DTI and VBM analyses? Alternatively, how such mechanisms are affected in patients with acute TBI or patients with memory and (balance) complaints based on behavioural testing alone?
2. To investigate if vestibular-guided spatial and postural modalities share a common neuronal network and where these network regions are located?
3. To investigate whether the cortical/subcortical morphology (i.e. volume, thickness, local gyrification index) links to vestibular spatial and vestibular postural impairment in acute TBI using VBM analysis?
4. To investigate if the integrity of the Corpus Callosum is linked to loss of vestibular motion perception or vestibular imbalance during acute TBI using DTI and VBM analyses?
5. To investigate if the integrity of cortical and subcortical regions known to receive vestibular input, is linked to loss of vestibular motion perception/vestibular imbalance during acute TBI using DTI and VBM analyses?

II. HYPOTHESIS

Vestibular-guided spatial orientation can be viewed as a continuous and hierarchically organised three-step process (vestibular self-motion, egocentric and allocentric level), where each step is incorporated in the subsequent one.

I hypothesise that vestibular-guided spatial navigation can be viewed as a continuous and hierarchically organised three-step model (Fig. 9) that consists of (1) vestibular self-motion perception, (2) vestibular egocentric and (3) vestibular allocentric navigation, all of which crucial for our proper spatial orientation. Once the spatial information from the environment has entered the vestibular system, the first level of the model is the vestibular motion perception test. It assesses the perception of self-motion and helps answer the question “Am I moving at all?” (question adapted and modified from (Kaski et al., 2016)) or an even more complicated question such as “Am I moving to the Right or to the Left?”. Considering my research concentrates on the investigation of the vestibular system during passive angular movements/chair rotations, I consider right/left rather than forward/backward movements.

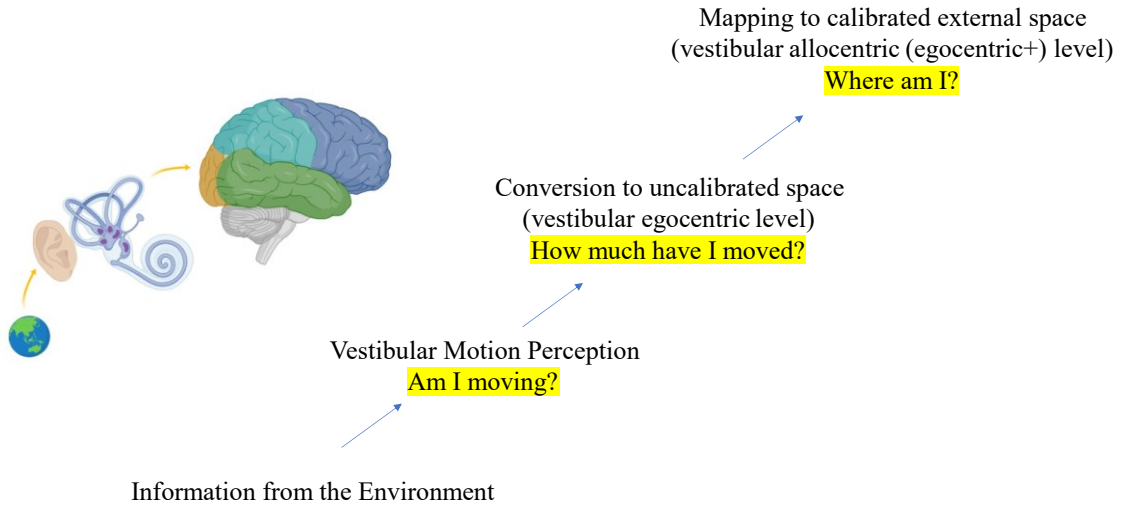


Figure. 9. Schematic presentation of Hypothesis II.

The subsequent level of complexity is the egocentric level (i.e. JOYSTICK task), which in itself incorporates the vestibular self-motion perception level. It assesses the perception of uncalibrated travelled distance and answers the question “How much have I moved?” (question adapted and modified from (Kaski et al., 2016)) or “How much of a distance have I travelled/covered?” (Fig.9).

Lastly, the allocentric component of the three-step model is the MOUNTAIN task. It links the travelled distance to a remembered visual map, answering the question “where am I exactly?” (question adapted and modified from (Kaski et al., 2016)) (Fig. 9). Further, it presents an example of a strategy where we

need to calibrate our perception of travelled distance to external visual landmarks. It incorporates in itself the vestibular motion perception and the egocentric level skills. All these components are linked together, but “how exactly” is a question that remains open. Little is known about the actual mechanism of switching between these steps and how they all work together/affect each other under vestibular guidance.

To address these questions, I first investigated the feasibility of such a hypothetical three-step model by testing healthy controls, before inviting patients with memory impairment to take part in my study.

OBJECTIVES:

1. To investigate if it is feasible to look at the vestibular-guided spatial navigation as a three-step process testing healthy controls from three age groups?
2. To investigate how vestibular spatial navigation (i.e. the three-step model) is affected during passive navigation in patients with memory impairment?

III. HYPOTHESIS

Patients experiencing greater cognitive load will not find the information from the vestibular cues helpful but rather burdensome during spatial navigation or balance.

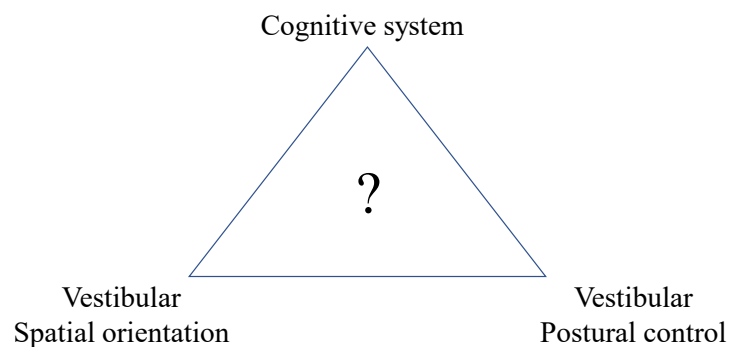


Figure. 10. Schematic presentation of Hypothesis III.

I hypothesise that, the additional information coming from the vestibular cues will not be helpful but rather burdensome to the already heavily loaded pathological brain of an individual with a central dysfunction of the nervous system due to acute TBI or memory impairment. Whereas the healthy brain is able to operate multiple sensory systems and draw some benefit from receiving multiple types of cues

to execute high order functions such as maintaining balance and proper spatial navigation with precision and accuracy, the situation for the pathological brain is different.

Although additional information can in many cases work as a compensatory mechanism when other systems are rendered dysfunctional, there is no single working formula for the pathological brain, which is constantly changing and adapting to its progressively decreasing resources. Thus, the information coming from the vestibular system is no longer optimal at a certain stage of the disease. It will force the brain into additional, heavy computational calculations while the brain is already under “pressure” due to lack of resources and the inability to coordinate those that are left in the correct way.

Research has shown that vestibular dysfunction is associated with hippocampal damage (P. Smith, 1997), (Brandt et al., 2005). However, no causal link between vestibular loss and cognitive decline has been established (Harun et al., 2016), even if vestibular impairment is suggested to affect certain domains of cognitive control. Importantly, postural control and spatial orientation are two highly cognitively involved processes that might be affected. While research gives examples about the link between ‘*cognition and (vestibular) spatial navigation*’, the association between ‘*cognition and (vestibular) balance*’ is less clear.

The latter is especially true, when we consider the “posture first” principle that has been seen in healthy elderly and also in patients with memory impairment. Using cognitive resources to compensate for postural instability leads inevitably to inability to address the “anticipating” postural changes during walking or standing. These “anticipating” changes are a form of a cognitive modality. Thus, even if at first glance, pure postural preference (i.e. the “posture first” principle) might be enough to ensure stable posture, a further consideration reveals that such a strategy is not rigid in the long-term, as “adaptation”/“anticipation” is a crucial part of balance. The reason lies in the fact, that posture is not a purely mechanistic task, but a complex, cognitively involved process (Manckoundia et al., 2006).

Thus, currently, it is unclear how vestibular spatial orientation, vestibular postural control and cognition link and how this system works altogether (Fig. 10).

To address this lack of understanding, I decided to look at the vestibular spatial and vestibular postural performance of patients with acute TBI or patients with memory complaints and try to link this performance to their cognitive level based on a set of cognitive tests.

OBJECTIVES:

1. To investigate how the computational burden in the brain of acute TBI patients or patients with memory and (balance) impairment links to/affects their spatial orientation and postural control under vestibular guidance while using a set of cognitive tests that patients performed?
2. To investigate the link between cognitive dysfunction (using the MMSE/ACE III-R tests) and vestibular-mediated spatial navigation via the three-step spatial model in patients with memory impairment?

Chapter II

Materials and Methods

1. Summary of methods

Tests for the Acute TBI study

- 1) Video Head Impulse Test (vHiT).
- 2) Vemps (cVemps and oVemps).
- 3) Questionnaires – Addenbrooke's cognitive examination III- R (ACE III-R), ABC, Trail making (A, B), DIH, GAD-7, PHQ-9
- 4) Visual Reaction Times test.
- 5) Vestibular motion perception in the horizontal (i.e. yaw) plane with EOG measurement.
- 6) Posturography.
- 7) Imaging – VBM, DTI.
- 8) Neurological examination (for patients).

Tests for the Memory patients' study

- 1) Video Head Impulse Test (vHiT).
- 2) Questionnaires – Mini-Mental State Exam (MMSE), Addenbrooke's cognitive examination III- R (ACE III-R).
- 3) Posturography.
- 4) Vestibular motion perception in the horizontal (i.e. yaw) plane with EOG measurement.
- 5) Visual Reaction Times test.
- 6) Egocentric task (i.e. Joystick task).
- 7) Allocentric (egocentric+) task (i.e. Mountain task).
- 9) Neurological examination (for patients).

2. Recruitment of participants

This doctoral study and its sub-studies was conducted following the principles of the Declaration of Helsinki and was approved by the local Research Ethics Committee, with REC reference number 17/LO/0434. All participants mentioned in this thesis, i.e. healthy controls and patients, signed an informed written consent form for voluntary participation.

2.1. Acute Traumatic Brain Injury study

Participants were recruited mainly from the Major Trauma Ward of St. Mary's Hospital, London, UK, and during the last six months of the study, also from King's College Hospital, London, UK. A team of MRC-funded researchers that included me, two neurologists (Dr Heiko Rust and Dr Barry Seemungal) and two other researchers (Dr Elena Calzolari and Ms Rebecca Smith), prospectively screened 918 acute admissions, assessed 146 and was able to recruit 37 acute TBI patients (mean age = 42.35yrs $\pm$ 12.98, 11F) and 37 healthy age-matched controls (mean age = 40.78yrs $\pm$ 14.75, 21F). However, as in this study, I mainly concentrate on the patients' results from DTI and VBM acute imaging analysis and their link to behavioural spatial and postural testing under vestibular guidance, it is essential to note that only 30 acute TBI patients and 36 healthy controls completed the imaging part of the study with the same protocol/scanning machine. MRI radiological reports were examined by an expert radiologist Dr Maneesh Patel.

The inclusion/exclusion criteria for the acute TBI patients were as follows (cited literally from (Calzolari and Chepishcheva *et al.*, 2021)):

The inclusion criteria for acute TBI patients were:

1. blunt head injury resulting in admission to the major trauma ward,
2. age 18–65yrs,
3. preserved peripheral vestibular function.

The exclusion criteria for acute TBI patients were:

1. additional active pre-morbid medical, neurological or psychiatric condition (unless inactive or controlled),
2. musculoskeletal condition impairing the ability to balance,
3. substance abuse history,
4. pregnancy,
5. inability to obtain consent or assent.

The inclusion criteria for the healthy participants were:

1. No history of substance abuse or neurological disorder(s),
2. An intact peripheral vestibular system,
3. Age > 18yrs (best age match for the recruited TBI patients).

Notably, the 37 age-matched controls' performance helped establish what is a “*normal performance*” and “*abnormal performance*” for the behavioural tasks, with patients performing above “**controls' mean + 3SD**” being considered “*abnormally performing/abnormal performance/abnormal*” (Calzolari and Chepishcheva et al., 2021).

In this thesis, I used the Mayo classification system for TBI, and its criteria are outlined below (Table.1):

Moderate-severe (definite)	One or more of the following criteria Presentation: § Death due to TBI § Loss of consciousness > 30 minutes § Post-traumatic anterograde amnesia >24h § Glasgow coma score <13 in the initial 24h § Intracerebral/Subdural/Epidural hematoma § Cerebral/Hemorrhagic contusion § Penetrating TBI (dura penetrated) § Subarachnoid hemorrhage § Brainstem injury
Mild (probable)	One or more of the following criteria Presentation: § Loss of consciousness momentarily to < 30 minutes § Post-traumatic anterograde amnesia momentarily to < 24h § Depressed basilar or linear skull fracture (dura intact)
Symptomatic (possible)	One or more of the following criteria Presentation: § None of the moderate-severe or mild criteria § One or more of the following are present: blurred vision, confusion (mental status changes), dizziness, dazed, focal neurologic symptoms, headache, nausea.

Table. 1. Mayo classification system for TBI as per (Malec et al., 2007).

For participants' convenience, there were: (1) refreshments and snacks during the breaks between tasks, (2) secure transportation from and back home and (3) monetary compensation.

2.2. Memory and (balance) patients - a pilot study

This was a pilot study. Participants were recruited from several locations in London, United Kingdom:

1) Memory Clinic as part of Imperial Healthcare Trust at Hammersmith Hospital, London, UK (Dr Paul Edison), 2) General Neurology Clinic as part of Imperial Healthcare Trust at Charing Cross Hospital, London, UK (Dr Heiko Rust and Dr Barry Seemungal) and 3) Alzheimer's Society, Hammersmith and Fulham Branch, London, UK. I screened or talked to 94 possible participants during Memory Clinics, General Neurology Clinics or Memory Cafes at the Alzheimer's Society and selected to invite 24 based on the following criteria:

1. Recent memory (and balance) complaints; people with memory complaints throughout their life were not appropriate,
2. No history of substance abuse,
3. Only participants with MMSE ≥ 20 (i.e. to be able to deal with the research equipment),
4. An intact peripheral vestibular system,
5. Age – up to 95yrs,
6. People with a diagnosis of probable Alzheimer's disease or suggestion of Mild Cognitive Impairment (MCI) were appropriate.

Some participants decided not to take part in the study for reasons connected to their health (4 participants), English language difficulty (3 participants) or uncertainty about whether they will be able to cope with the equipment needed for the study (2 participants). Therefore, after a careful discussion with the other participants, I was able to recruit 15 people (8F) with a mean age of 75.6yrs ± 10.34 and an age range of 50 – 93yrs.

For participants' convenience, I provided: (1) refreshments and snacks during the breaks between tasks, (2) adjusted the time of testing to their preferred hours of the day, (3) provided secure transportation from and back home and (4) provided monetary compensation.

I was able to recruit 16 healthy adult controls (10F) with a mean age of 69.63yrs ± 8.83 (age range 61-88yrs) through an advertisement on the hospital board (Charing Cross Hospital, London, UK) and several visits to the local Age UK Hammersmith and Fulham Club, based on the following criteria:

1. No history of substance abuse or neurological disorder(s),
2. No memory or balance complaints,
3. An intact peripheral vestibular system,
4. Age – up to 95yrs.

The testing battery of the “memory and (balance) patients” pilot study was based on the hypothesis that spatial navigation can be viewed as a three-step model (*hypothesis II*). The feasibility of the three-step model was tested with the help of 60 healthy controls, which I separated into three groups based on age:

(<40yrs, age range 18-39yrs, n = 30), (between <(40 – 60)>yrs, n = 14) and (> 60yrs, age range 61-88yrs, n = 16). They were recruited via an advertisement on the hospital board (Charing Cross Hospital, London, UK) based on the following criteria:

1. No history of substance abuse or neurological disorder(s),
2. No memory or balance complaints,
3. An intact peripheral vestibular system,
4. Age 18 – 95yrs.

The group of 16 healthy older adults that were an age-matched control group for the patients with memory and (balance) control complaints are the same people who also belong to this group of 60 healthy volunteers helping to test the feasibility of the three-step model before any patient testing was performed.

All participants, patients and healthy controls for all studies mentioned, signed an informed consent form stating that they are volunteers and willing to participate in the study without any obligation to remain if they think they want to leave. All participants received monetary compensation for their participation after the completion of the required testing battery.

3. Laboratory Testing

3.1. Vestibular system testing – neurophysiology

3.1.1. Video Head Impulse Test (vHiT)

The video Head Impulse test (vHiT) was used to assess the horizontal vestibular-ocular reflex (VOR) and establish an intact peripheral vestibular system. I used EyeSeeCam Software of Interacoustics A/S to measure the right and left horizontal semicircular canals (SCCs) and determine the VOR gain. Participants were asked to remain still while seated and to concentrate on an indicated visual target to successfully complete the test. They underwent a short introductory phase during which they were made aware of the type of quick movements they had to expect during the real testing. Importantly, the order of the rotations (i.e. to the right or the left) was randomised as to avoid prediction by the participants. Calibration was always performed before testing. During the testing, a minimum of 20 turns to the left and 20 – to the right were executed to measure the VOR gain. In my study, a sub-cohort of healthy controls and a sub-cohort of memory and (balance) patients were tested with vHiT (i.e. not all memory and (balance) patients were tested with vHiT because of technical limitations or health-related issues of the patients, e.g. pain in the neck).

In addition, VOR was also recorded via electrooculograms (EOG), discussed further during the vestibular self-motion perception (VMP) testing/procedure.

3.1.2. Vemps (cVemps and oVemps)

Vestibular-evoked myogenic potentials (Vemps) are used to examine for an intact otolith function. The cervical Vemps (cVemps) tests the ipsilateral saccular function and the inferior vestibular nerve, whereas ocular Vemps (oVemps) tests for contralateral utricular function via the inferior oblique muscle. In this study, I used Eclipse Software by Interacoustics A/S. The preparation of the patient for testing was critical, as the locations where the electrodes were put must be well cleaned to decrease skin impedance. For cVemps, a patient turned their head to the side, e.g. 90° to the left, so that the sternocleidomastoid (SCM) muscle on the right side of the neck became well visible. An electrode was placed on the belly of the muscle, after which the same procedure was performed for the left SCM muscle. Lastly, two more electrodes – (1) on the ground of the forehead and (2) on the clavicular joint and an earplug in each ear finished the patient's preparation for testing. After the impedance was checked and the needed technical adjustments in Eclipse Software were performed, the patient was asked to remain still with their head turned to one side. The testing itself began with a sequence of short repetitive auditory stimuli (in this case -100dB).

The preparation for oVemps was similar, but with different locations of the electrodes – (1) one underneath the right and (2) one underneath the left eye, (3) one on the chin, and (4) one remained as before – on the ground of the forehead. In the case of oVemps, the participant was asked to direct their gaze at a point located well above them so as to strain the ocular muscles on which the electrodes were placed. This way, they brought the belly of the inferior oblique muscle closer to the position of the electrodes and eased the detection of the signal. Participants were asked to remain in this position until told to relax.

3.2. Vestibular system and Cognition alongside Dizziness/Anxiety/Depression questionnaires

3.2.1. MMSE and ACE III -R

I used two standardised clinical tests for cognitive assessment. First, the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) is a short test consisting of questions regarding (1) Orientation, (2) Registration of new information, (3) Attention, (4) Calculation, (5) Recall, (6) Language and (7) Copying of a figure with a maximum score being 30 points. Based on Molloy's 1997 and 1999 guidelines (Molloy & Standish, 1997), (Molloy & Clamette, 1999), people with 30-25 points are considered "normal", further, those with 24-21 points are viewed as "early-mild" cognitive impairment, with 21-10 points are "moderate" and with 9-0 points are "severe".

The second cognitive test I used is the ACE III- R (Addenbrooke's cognitive examination, revised) (Mioshi et al., 2006). It is a more detailed cognitive examination testing five domains: (1) Attention (max score 18), (2) Memory (max score 26), (3) Fluency (max score 14), (4) Language (max score 26), (5) Visuospatial skills (max score 16) with a total maximum score being 100 points.

3.2.2. Trail Making (A, B)

The Trail Making test ((Partington & Leiter., 1949) citation not available) is a standard clinical test assessing for information processing speed (format A) and executive functioning (format B). The test in this study was performed in the ‘paper and pencil’ format.

During this test (format A of the test), participants needed to manually draw a line between numbers in ascending numerical order, i.e. 1 -> 2 -> 3 and so forth until the last number. Format B is more complex than format A as it incorporates numbers and letters. Participants were instructed to draw a line in ascending numerical and alphabetical order starting with a number and its corresponding letter and so on, i.e. 1 -> A -> 2 -> B -> 3 -> C, etc. For this test, it is essential that the participant does it as quickly as possible but also correctly at the same time. If a mistake is made, then the participant is shown the place with the error, and the participant needs to correct themselves as soon as possible and continue to complete the task. The test is timed, and the faster it is completed, the better the information processing and/or executive functioning is.

3.2.3. Dizziness Handicap Inventory (DIH)

The dizziness handicap inventory (Jacobson & Newman, 1990) is a self-administered questionnaire of 25 questions that assesses the quality of life after a vestibular disorder. It comprises three categories concentrating on physical (max score 28), emotional (max score 36) and functional (max score 36) self-perceived handicap on life because of dizziness. Possible answers are yes/no/sometimes and the final total result ranges from 0 to 100 points. The higher the result, the higher the level of self-perceived handicap because of dizziness.

3.2.4. Generalized Anxiety Disorder 7-item (GAD-7)

The GAD-7 is another self-administered questionnaire considered a “valid and efficient tool for screening for GAD and assessing its severity in clinical practice and research” (Spitzer et al., 2006). It consists of seven questions assessing the effect of anxiety on life. Possible answers are that one feels a certain way “several days”/”more than half of the days”/”nearly every day” or “not at all”. The maximum score is 21 points, with scores ranging from mild, moderate to severe anxiety.

3.2.5. The Patient Health Questionnaire (PHQ-9)

The patient health questionnaire (Kroenke et al., 2001) is also a self-administered test, comprising of 9 questions that assess the general state of depression. Possible answers are that one feels a certain way “several days”/”more than half of the days”/”nearly every day” or “not at all”. The maximum score is 27 points, with scores ranging from mild, moderate to severe depression.

3.3. Vestibular system and Postural control testing

3.3.1. Posturography test

This task assesses the balance and sway (natural rhythmical movements of the living body) in medio-

lateral/lateral (ML/L) and antero-posterior (AP) direction while participants stand either on a static hard surface, i.e. a force platform or on a static soft surface (in this case a foam (50 × 41 × 6 cm, Airex®) put on top of a force platform). In my study, the force platform (51.5 × 51.5 × 18 cm) contained four force sensors in a rectangular configuration to give a combined centre of pressure (CoP) output. Calibration was obtained using a 1.44 kg weight on four locations while also considering participants' weight that was recorded. During the task, participants were asked to stand in a relaxed manner with their arms hanging loosely by their sides, with their head up and gaze looking straight ahead while trying to keep their balance as best as they could. In addition, they were secured from falls by wearing a harness attached to the ceiling.

Generally, the task requires the use of the (1) visual, (2) proprioceptive and (3) vestibular systems in the different aspects of the test. It includes four conditions for 60s each, as indicated in Fig.9. and assumes that the different conditions give information about the working of these three sensory systems implicated in balance/ postural control.

The balance task was analysed in a Software called ANALYSIS (Inhouse Software, property of Imperial College London, Neuro-Otology Unit, developed by Mr David Buckwell). This way, I was able to record antero-posterior (AP) = “channel 0” and lateral (L) = “channel 1” Sway performance of my participants (as indicated in Fig. 11). For each channel, I calculated **(a)** the path, **(b)** the RMS (the rambling aspect/trajectory of the stabilogram) and **(c)** the mean. In addition, taking both channels together, I calculated – **(a)** the path, **(b)** the RMS and **(c)** the 95% confidence ellipse (expected to enclose approximately 95% of the points on the centre of pressure path along the anteroposterior and (medio)lateral planes combined).

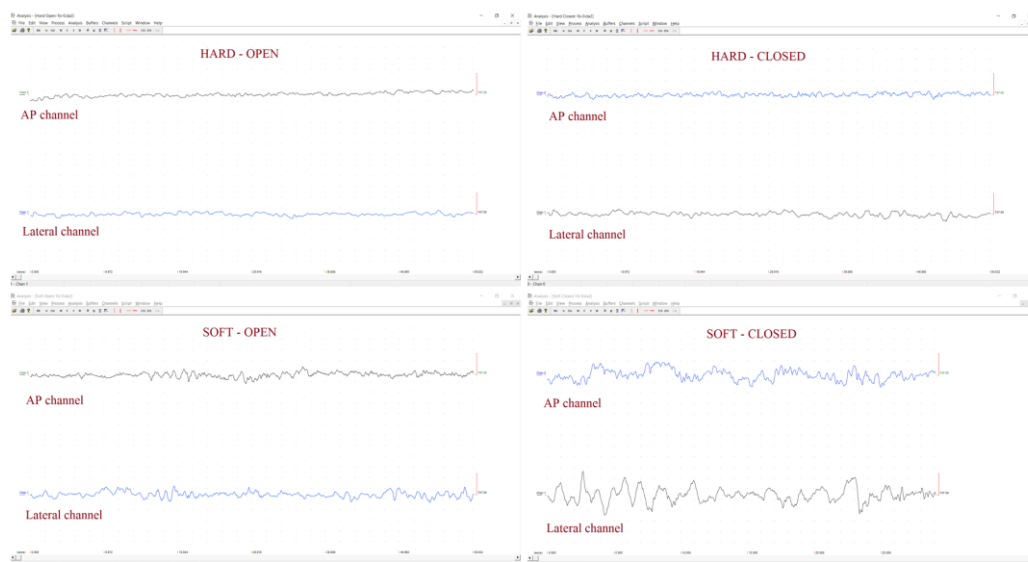


Figure. 11. Program ANALYSIS (Inhouse Software) used to calculate the stabilogram/posturography test. The test includes four conditions: **(a)** with eyes-open on a hard surface (HO) (all three systems provide a reliable signal); **(b)** with eyes-closed on a hard surface (HC) (the proprioceptive and the vestibular system provide a reliable signal); **(c)** with eyes-open on a foam (SO) (the visual and the vestibular systems provide reliable signal) and **(d)** with eyes-closed on a foam (SC) (only the vestibular system provides a reliable signal).

3.3.2. Activities-specific Balance Confidence (ABC) questionnaire

The ABC balance test (Powell & Myers, 1995) is a short questionnaire aiming to assess perceived postural stability in different situations (e.g. walking on an icy surface or strolling around one's house while in the dark) based on self-reported, i.e. subjective, balance performance. In this study, participants had to indicate how safe they felt in different situations, using a scale from 0 -100%, with 0 indicating a lack of any feeling of safety/a feeling that they would fall, while 100% showed that they felt entirely safe and in control of the situation. The ABC balance test was performed in a 'paper and pencil' format while participants were safely seated.

3.4. Vestibular system and Spatial Orientation testing

3.4.1. Vestibular motion perception (VMP) task

The VMP task was performed on a computer-controlled, motorised rotating chair in complete darkness and audio-controlled conditions (white noise) to assess the minimum angular acceleration threshold that was perceived by a participant. The chair rotated only in the horizontal, i.e. the yaw plane. This task requires an intact peripheral vestibular system and the cognitive ability to perceive the vestibular-mediated signal of self-motion (Seemungal et al., 2004), (Calzolari and Chepishcheva *et al.*, 2021). It was initially developed based on the Modified Binary Search (MOBS) (Tyrrell & Owens, 1988) staircase procedure by (Seemungal et al., 2004).

During the task, the participants experienced angular rotations (lasting max 5s) at a specific constant angular acceleration determined by the MOBS algorithm (Tyrrell & Owens, 1988) in the horizontal, i.e. the yaw plane in a randomised fashion either to the right or to the left. Participants were instructed to press a right or a left button, respectively, depending on the direction of the rotation as soon as they "detected or thought they had detected" that the chair was in movement while remaining in the dark (Fig. 12 (a)). If, after 5s, they had not indicated the correct side of movement or they had not pressed any button because they did not perceive the rotation, the chair started to decelerate for a max of 5s over a triangular velocity profile ((Fig. 12 (b)). After the chair stopped moving, the lights were switched on to hinder further perception of self-motion and/or any remaining nystagmus (i.e. involuntary, rapid eye movement). After 20-30s, the lights were switched off again, and the experiment continued in the same way. A more detailed explanation of the setup is available in Calzolari and Chepishcheva *et al.* (Calzolari and Chepishcheva *et al.*, 2021).

Lastly, **electrooculograms (EOG)** of the right and left eye were recorded as an additional measurement for the performance of the peripheral vestibular system (Fig. 12 (b)). In preparation for the testing, electrodes were placed on the right and left temporal bones and on the forehead, as a baseline. Calibration involving looking to the right or left was always performed before testing could commence. However, as patients with elevated vestibular motion threshold (i.e. decreased perception of self-motion) had perceptual thresholds that were many times higher than their vestibular ocular reflex (VOR)

(Calzolari and Chepicheva *et al.*, 2021), the MOBS algorithm that increased its magnitude if the participant gave incorrect or no response, was not a proper way to detect the minimum vestibular-ocular threshold. Thus, a stepwise algorithm with an increasing acceleration ($0.3^\circ/\text{s}^2$ every 3s) was implemented for a total of six rotations, three to each direction (i.e. right or left) and in a randomised order while using a DC-coupled horizontal electrooculography with a sampling rate of 250 Hz to record the eye movements (Calzolari and Chepicheva *et al.*, 2021).

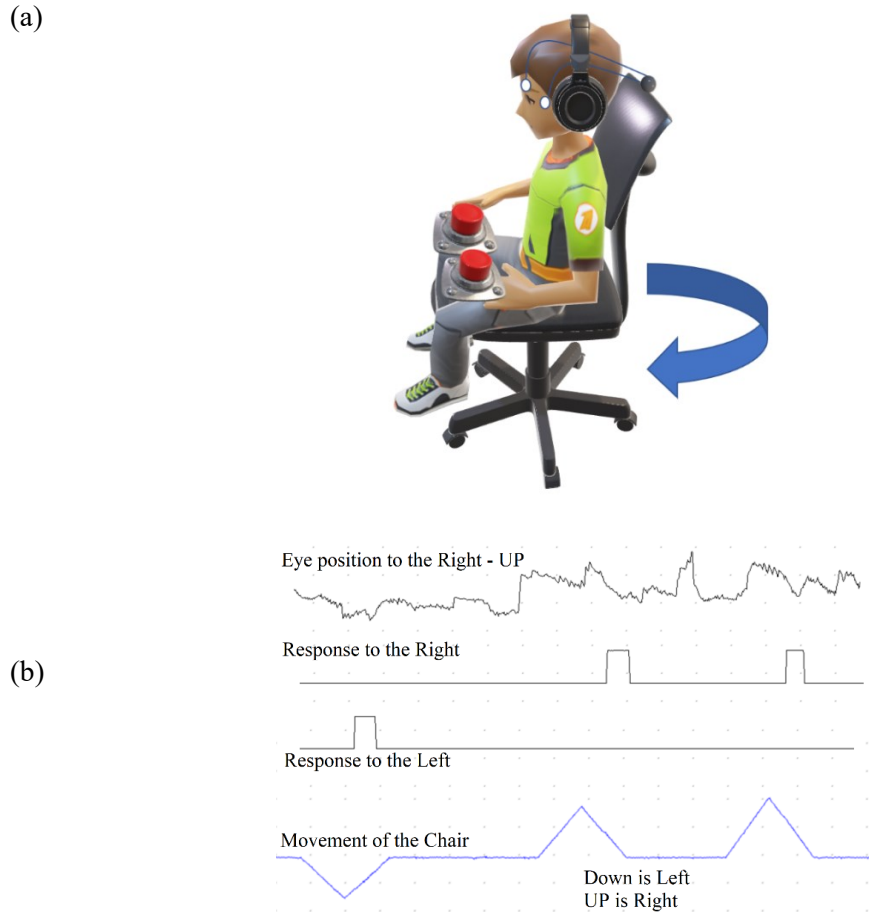


Figure. 12. Vestibular motion perception task (a) setup of the task - participants sat on a computer-controlled rotating chair having to indicate their perceived direction of motion by pressing a button (in this case – rightward rotation). (b) Electrooculograms (EOG) were recorded via electro-nystagmograph. In this case, rotation at constant acceleration was first to the Left and then - two times to the Right. The graph indicates that the participant indicated all three chair rotations correctly.

3.4.2. Visual Reaction Time test

The visual reaction time (RT) test was a complimentary task to the vestibular motion perception task to control for the delay in the response latency, which could erroneously lead to an elevated vestibular perceptual threshold. The task was done in MATLAB with the help of the PsychToolbox. The goal was to test whether the reactions of the participants with abnormal VMP ($> 2.02^\circ/\text{s}^2$) were delayed in general or they were indeed not able to detect the angular movement of the chair. The task showed a centrally located horizontal line with an arrow pointing either to the right or left on a computer screen

($d_{\text{screen}} = 40 \text{ cm}$, resolution 1,200 x 750). Seated 40 cm away, the participants had to press a right or left button on a button press to indicate the direction of the arrow they just saw. As the performance was timed, participants were instructed to act “as soon as possible”. The next stimulus appeared randomly in 2,000-3,000ms for a total of 22 trials, irrespective of whether the participant had already answered, i.e. if they were late with one answer, the program did not wait but gave the “next challenge”.

In addition to this task, there was a second, simpler variant of the test, where only an “X” appeared in the centre of the screen, and the participant needed to press a button “as soon as they saw the “X” appearing on the screen”.

3.4.3. Egocentric task – JOYSTICK task

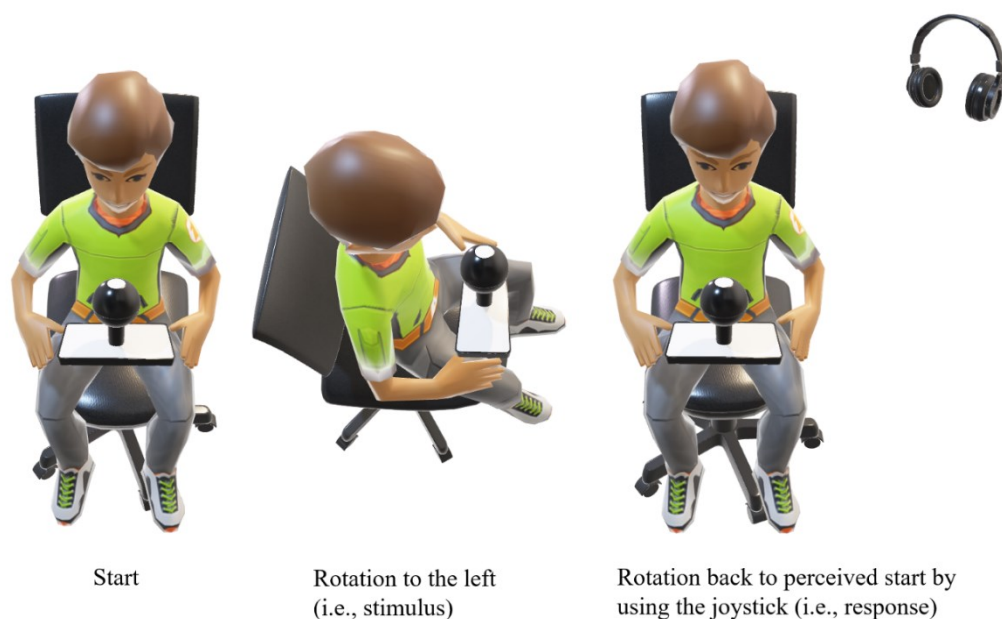


Figure. 13. JOYSTICK task (i.e. egocentric task) – procedure of the task - [top view] – from left to right, respectively – (1) starting position, (2) rotation to the left, (3) back to starting position.

The egocentric (i.e. uncalibrated) task is a spatial orientation task performed with respect to the self, i.e. body-centred. The task used in my study was initially developed by Prof. Michael Gresty (Brevern et al., 1997) and modified through two developmental phases for the current study. The task lasted between 25 – 30min and consisted of four blocks, each with 12 rotations, i.e. 48 in total. No breaks or “lights on” were allowed as a potential break and “lights on” would disrupt the experiment indicating where the participant was and lead to “re-calibration” of the vestibular signal. None of the participants felt dizzy or tired for the duration of the testing.

Participants underwent a training phase during which they learned to control the chair by using a joystick. Therefore, from now on, I will call this task a JOYSTICK task. During the training phase, participants got used to controlling the chair with the help of the joystick, and thus no previous experience was needed to perform the task. Importantly, this was also the time when I checked for any

motor disability of the patients (i.e. trembling, letting the joystick go because they could not control it, feeling uncomfortable, etc.) and observed their independent performance while operating the joystick. No motor abnormalities were detected in any of the participants during the task, irrespective of whether these were controls or patients.

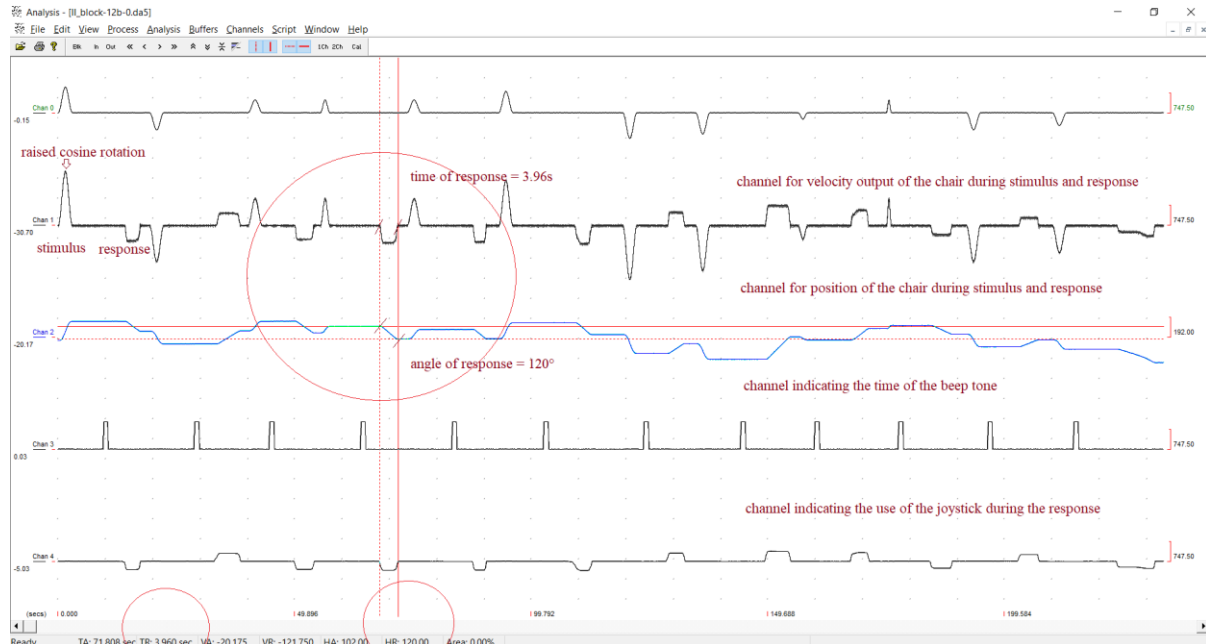


Figure. 14. Analysis of JOYSTICK data - (1) the information each channel encodes, (2) how to measure an angle response and (3) how to measure the time for a response.

The joystick velocity was intentionally reduced to prevent participants from mimicking the stimulus movement (i.e. the angular chair movement) or its velocity by simply replicating the rotations they had just experienced. Following the formula $angle = (velocity * time) / 2$, I prepared raised cosine chair rotations for the angular movements of the chair in a Software called ARBWAVE. Then, I used these raised cosine rotations during the testing in a program called ACQUIRE and analysed all results in a third Software package called ANALYSIS (the three programs are Inhouse Software, a property of Imperial College London, Neuro-Otology Unit, developed by Mr David Buckwell). Whereas the peak velocity of the stimulus for the different raised cosine rotations was 30, 45, 60, 80, 100 and 120°/s, the velocity of the joystick, with which the response was performed, was between 44-60°/s. This allowed for a variety of rotational stimuli with multiple angles, peak velocities and timings (1s, 2s, 3s or 4s) to avoid prediction.

After the training phase, the participants were ready for the real test. They experienced discrete passive rotations to the right or to the left to one of six different angles (range 30-180°, in steps of 30°). While doing so, they were seated in the already known computer-controlled rotating chair, remaining in the dark and in an audio-controlled condition (white noise) for the duration of the whole task. After the end of each rotation, the chair stopped, and participants waited for an interval of either 1.5s or 6.5s before

hearing a beep tone. This was a signal for them that they were allowed to “answer” by moving the chair back to their perceived start with the help of the joystick (See Fig. 13).

The difference between the actual and the self-generated rotation was calculated. Any rotations that were performed in contrast to the instructions given, i.e. wrong direction of movement during the response or any response rotations lasting over 7s with continuous speed, were excluded from the analysis. To analyse the rotations, I manually measured the movements of the chair in ANALYSIS (i.e. 48 rotations per participant) as shown in Fig.14. Lastly, I calculated the time between the onset of the beep tone and the start of the movement of the joystick by the participant as to control for the arousal of the participants and their speed of response after the beep tone.

3.4.4. Allocentric (egocentric⁺) task – MOUNTAIN task

This is a spatial orientation task I designed for my doctoral study/research, inspired by the “Curtain task” used in (Seemungal, 2006). This task has been through five phases of development/improvement (Please check Appendix). This allocentric task builds upon the egocentric type of navigation and adds the usage of a reference to stable environmental landmarks, in this case – mountains. Therefore, from now on, I will call this task a MOUNTAIN task.

The test lasted around 40min and consisted of 48 outbound and 48 inbound rotations for healthy controls (four blocks in total) and of 24 outbound and 24 inbound rotations (two blocks in total) for patients to avoid exhaustion. Breaks for fresh air were suggested to the participants after each block (i.e. approximately every 10-15 min). In fact, participants took a maximum of one break, i.e. no one needed more breaks. For the task setup, I used the already known motorised, rotating chair as the physical stimulus of rotational movement, creating raised cosine chair rotations, similar to what I described in the JOYSTICK task. For the preparation of the visual stimulus, i.e. the natural scene, I used Unity 2018.3.6f1 and developed an automated code in C# to analyse the data by calculating the Euler angle in the horizontal, i.e. yaw plane. During the spatial testing itself, I used an Alienware Aurora R8 personal computer with Intel Core i7-9700 (running at 3GHz), NVIDIA GeForce RTX 2070 GPU and 16GB RAM. Complimentary to the computer, I used an HTC Vive Pro headset with a Dual AMOLED 3.5" diagonal screen, resolution of 1440 x 1600 pixels per eye (2880 x 1600 pixels combined), a refresh rate of 90Hz and a field of view of 110°. The headset contains multiple sensors: SteamVR Tracking, G-sensor, gyroscope, proximity and Eye Comfort Setting (IPD) and is equipped with lens distance adjustment to make observation comfortable. In addition, there are two base stations to check for the position of the headset.

All participants underwent an introductory phase during which they had time to get used to the Virtual Reality (VR). Therefore, no previous experience of working with VR was needed, as the training phase provided enough time to get used. They learned a simple continuous natural scene consisting of four mountains, while seated in the computer-controlled rotating chair (see Fig. 15). Importantly, this was

the time when I checked for participants' visual acuity, i.e. whether they could see the screen clearly with/without glasses (the use of glasses was possible with this VR HTC Vive Pro headset) and based on their instructions, I adjusted the headset display. All participants assured me that the screen was clear at the start of the testing, and they could see the mountains.

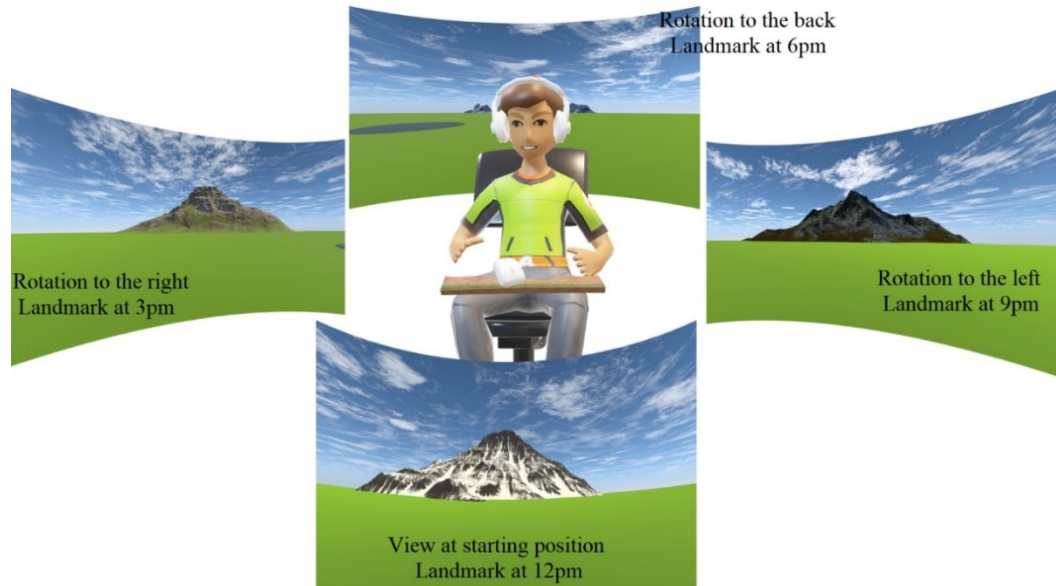


Figure. 15. Allocentric (egocentric+) task, i.e. the MOUNTAIN task – presenting a participant surrounded by a 360 degrees continuous natural scene, that is displayed on a VR headset, while wearing headphones and operating a computer mouse.

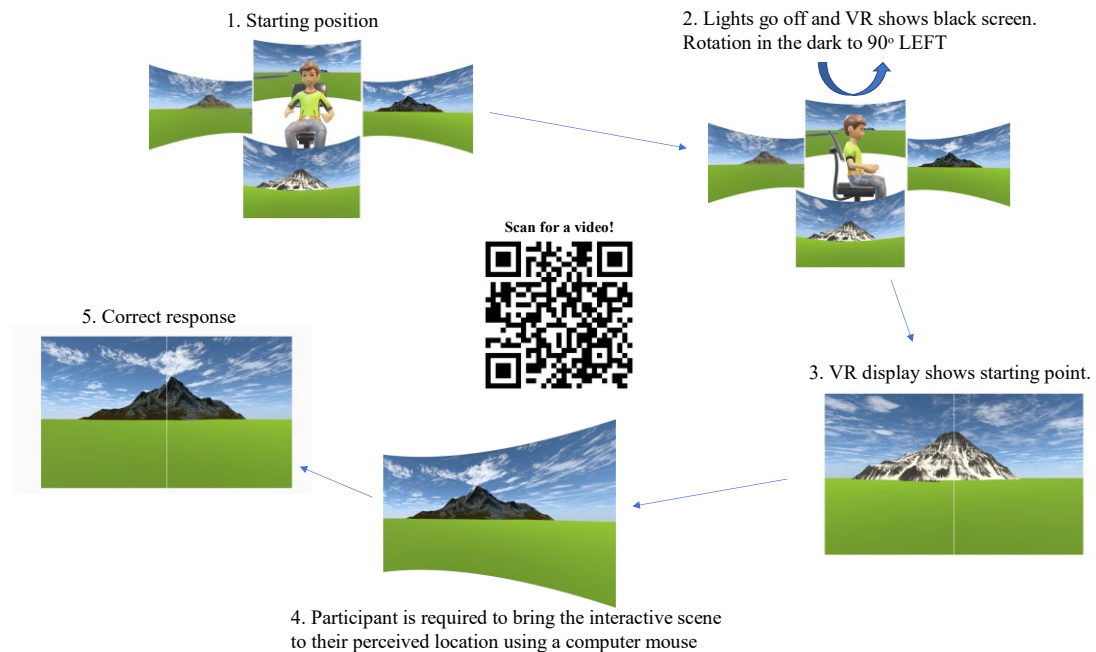


Figure. 16. MOUNTAIN task (i.e. allocentric (egocentric+) task) – procedure (example with a rotation 90° to the Left). Arrows indicate the direction of steps: (1) starting position; (2) Lights go off, and VR shows a black screen. Rotation in the dark to 90° LEFT; (3) VR display shows the starting point; (4) After hearing a beep tone, the participant is required to bring the interactive scene to their perceived location using a computer mouse; (5) Correct response.

Once the participants were ready to start and in an audio-controlled state (white noise) that masks any audio stimuli, then the VR display turned black, and a raised cosine rotation in the dark moved the chair from its starting point, i.e. from the landmark at 12 o'clock as indicated in Fig. 15 and Fig. 16 (please

scan the QR code in Fig. 16 for a video of the MOUNTAIN task). When the chair stopped, the VR scene displaying the starting position became visible again immediately after the stop of the chair in order to prevent any post-rotational sensation (i.e. nystagmus). Importantly, I imposed delays in responding (by a ‘beep’ tone) of 1.5s or 6.5s. Thus, only after the “beep” was audible the participants were allowed to indicate which landmark they “believed they were facing” after the rotation by using the computer mouse provided.

Participants experienced only discrete passive rotations to the right or to the left to one of six different angles (range 30-180°, in steps of 30°), whose sequence was randomised among all participants to avoid bias or prediction. The difference between the actual and the self-generated rotation was calculated. Any rotations that were performed in contrast to the instructions given, i.e. wrong direction of movement (e.g. right instead of left) during the response, were excluded from the analysis.

3.5. Vestibular system and Imaging

Neuroimaging data were acquired for the acute TBI study at two locations in London, UK: (1) Charing Cross Hospital, Imaging Facility, where the first six acute TBI patients were scanned (1.5T Siemens scanner) and (2) Hammersmith Hospital, Biological Imaging Centre (3T Siemens scanner), where we scanned all other TBI patients and all of the healthy controls.

I present Voxel-based morphometry (VBM) and Diffusion Tensor Imaging (DTI) analyses based only on the scans acquired at Hammersmith Hospital, where the scanner is a 3T Siemens Magnetom Verio Syngo with a 32-channel head coil. Thirty ($n = 30$) acute TBI patients and 36 controls were scanned using the same MRI machine and acquisition protocol (MRI protocol available to examiners upon request).

3.5.1. Voxel-based morphometry (VBM)

Brain magnetic resonance imaging (MRI) is a non-invasive medical technique that utilises magnetic fields and radio waves to produce detailed, three-dimensional anatomical images of the brain. The basic idea behind MRI is linked to the movement of the hydrogen atoms, which are naturally abundant in the human body, especially in water and fat. This PhD study was a multi-imaging effort comprising whole-brain and ROI VBM and DTI analyses. VBM whole-brain and VBM ROI analyses are available in Appendix.

Voxel-based morphometry is one of several neuroimaging/MRI techniques. It presents as an automated computational approach in neuroscience that measures local concentrations of brain tissue and compares such concentrations between regions via a voxelwise comparison of multiple brain images (Ashburner & Friston, 2000). Since its introduction (Wright et al., 1995), (Ashburner & Friston, 2000), VBM has become largely used because it is relatively simple to implement and provides valid results (Whitwell, 2009). In this study, I have used high-resolution T1-weighted images (voxel dimension 1mm^3) to acquire grey matter (GM), white matter (MW) and cerebrospinal fluid (CSF) volumes in acute

TBI patients and healthy age-matched controls, relying on the pipeline displayed on Fig.2.7 (please check Appendix).

In short, the VBM pipeline involved the preparation of the raw images by converting them to nifty format and subsequent segmentation into GM, WM and CSF. Then, a study-specific template was created based on the TBI patients and controls in my study, using SPM DARTEL registration for non-linear spatial normalisation. The study-specific template was then registered to standard space, and the images were normalised and smoothed by an 8mm Gaussian kernel (Cole et al., 2018). At this point, I was ready for statistical analysis, which took one of the two pathways: (1) general volumetric exploration of the GM, WM and CSF and (2) voxelwise statistical analysis via FSL GLM, either whole-brain or ROI.

I used FSL GLM via contrast and design matrices to examine my measures of interest, i.e. parameters linked to spatial orientation and postural control under vestibular guidance from the behavioural/laboratory tests presented in 2.3. Laboratory Testing. For analysis of the whole-brain GLM results, I used two FSL incorporated atlases: (1) Harvard-Oxford cortical structural atlas (Desikan et al., 2006) and (2) Harvard-Oxford subcortical structural atlas (Desikan et al., 2006). In addition, for the preparation of ROI VBM masks, I used (1) JHU ICBM-DTI-81 white-matter labels atlas (Mori et al., 2008), (2) Harvard-Oxford cortical structural atlas (Desikan et al., 2006), (3) Harvard-Oxford subcortical structural atlas (Desikan et al., 2006), (4) Mars TPJ connectivity-based parcellation atlas (Mars et al., 2012) and (5) Juelich Histological Atlas (Eickhoff et al., 2005). All imaging analysis was conducted on Ubuntu Debian and Jupyter.

Calculation of Local gyrification index (LGI) using Freesurfer

Voxel-based morphometry (VBM) was also conducted with Freesurfer as part of the process of calculation of the Local Gyrification Index (LGI) (Schaer et al., 2012). The Freesurfer VBM pipeline consists of 31 steps, described in (Fischl et al., 1999a), (Fischl et al., 1999b), (Fischl et al., 2002), (Fischl et al., 2004).

After completing these steps, a procedure developed by Prof. M. Schaer for the calculation of the LGI was applied (Schaer et al., 2012) (i.e. by using the *recon-all* command and the needed specifications), and a statistical analysis was performed based on the derived results.

Lastly, a separate statistical investigation (outside of the LGI) of the volume of individual ROIs and thickness was performed as an addition to the general VBM analysis based on the already processed structural images in Freesurfer. The Freesurfer software uses two main atlases - the Destrieux atlas (Destrieux et al., 2010) and the Desikan-Killiany atlas (Desikan et al., 2006), with the main difference between these two well-validated atlases for automated parcellation being the number of parcellations performed - the Destrieux atlas parcellates each hemisphere in 74 ROI, where the Desikan-Killiany in 34 ROI. The analyses discussed in this section are available in Appendix.

3.5.2. Diffusion Tensor Imaging (DTI)

Diffusion tensor imaging (DTI) is another example of a promising neuroimaging method. It is a novel and advanced MRI technique for “characterizing microstructural changes or differences with neuropathology” (Alexander et al., 2007) in white matter *in vivo* (Basser, P. J. et al., 1994). It has gained popularity within TBI research due to its high sensitivity and precision in detecting white matter damage (Rutgers et al., 2008), (Soares et al., 2013), (Jolly, 2020) especially subtle or microscopic lesions after TBI/concussion, which are often undetectable by the traditionally used computed tomography (CT) in the clinic or the emergency room (Jolly, 2020).

DTI is achieved through diffusion-weighted imaging (DWI), and in this study, diffusion-weighted volumes were acquired using a 64-direction protocol (32-channel head coil): 64 slices, in-plane resolution = 2 x 2 mm, slice thickness = 2 mm, a field of view = 256 x 256 mm, matrix size = 128 x 128 (voxel size = 2 x 2 x 2 mm³), repetition time = 9500 ms, echo time = 103 ms, b-max value = 1000 s/mm² (Calzolari and Chepicheva *et al.*, 2021).

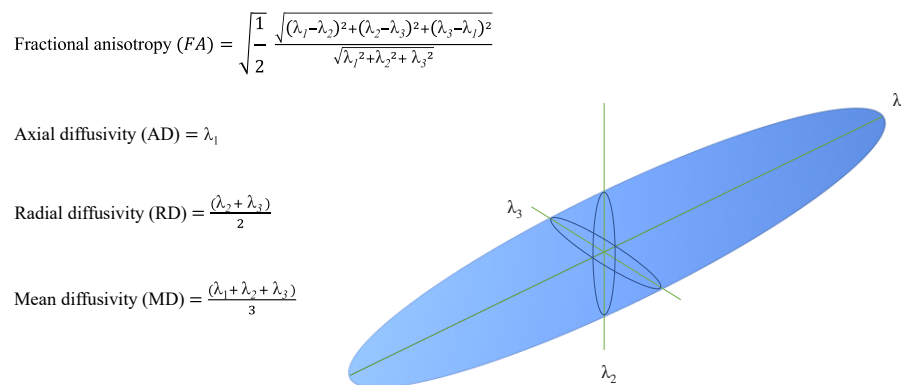


Figure. 17. DTI tensor and calculation of FA, MD, AD and RD – image adapted from (Feldman et al., 2010), (Alexander et al., 2011).

Diffusion tensor imaging (DTI) is based on the water diffusion rate in the tissue (Soares et al., 2013). The main idea behind DTI is that the water molecules in the brain diffuse differently in the different brain environments (i.e. GM, WM, CSF) (Mori & Zhang, 2006), (Soares et al., 2013). This diffusion depends on the integrity, the architecture of the tissue and the presence of obstacles in it, providing information about the tissue’s orientation and quantitative anisotropy (Soares et al., 2013). Via DTI, we measure not only the amount but also the direction of water diffusion by using a “tensor”, which is an ellipsoid with a specific direction (Fig. 17). The tensor “summarises diffusion-weighted imaging data collected in multiple directions” (Feldman et al., 2010). It can be calculated by using three orthogonal eigenvectors (which are the axes of the tensor) with corresponding eigenvalues (eigenvalue is the length of the axes (= amount of diffusion) of the tensor for each of these vectors) (Jolly, 2020). The whole brain can be presented as a collection of tensors whose specific values are calculated using different methods with the help of the eigenvalues.

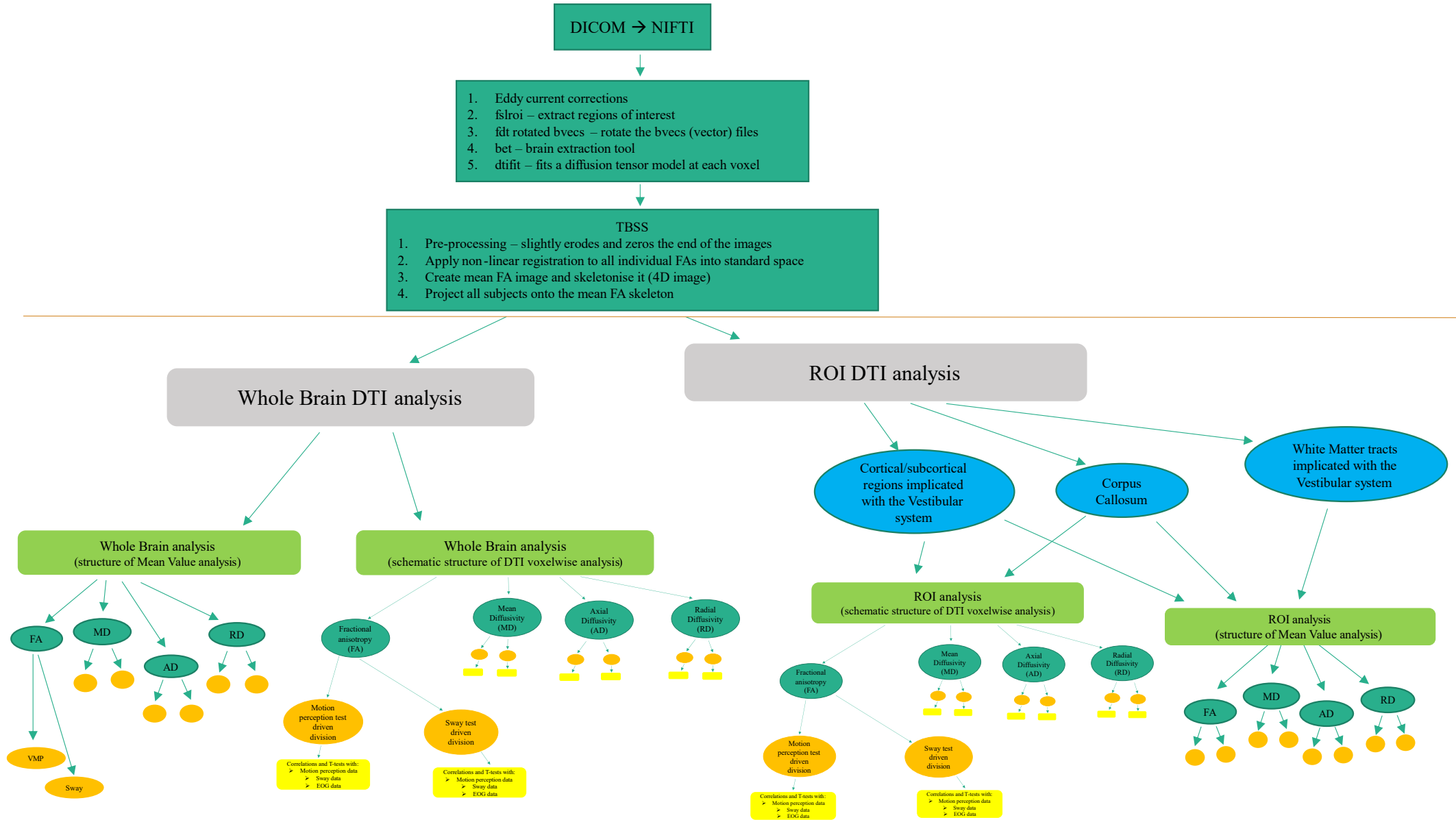


Figure. 18. DTI pipeline (above the orange line) and statistical analysis (below the orange line) (mean value and voxelwise analysis).

In this study, I used DTI to analyse white matter microstructure in acute TBI patients by calculating four DTI-derived parameters - fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). Whereas fractional anisotropy is a ratio measure of the length to width of the tensor, the axial diffusivity calculates the diffusion rate parallel to the white matter tract, the radial diffusivity – the rate of diffusion perpendicular to the white matter tract and the mean diffusivity is an average measure of the other diffusion values (Feldman et al., 2010), (Alexander et al., 2011). To calculate these measures, we can directly relate to the eigenvalues of the tensor, which are called λ_1 , λ_2 , λ_3 , as presented in Fig 17. (Alexander et al., 2011).

Image processing and analysis in this study were performed using a variety of packages. Figure 18. displays the standard DTI pipeline (S. M. Smith, 2002), (Behrens et al., 2003), (S. M. Smith et al., 2004), (S. M. Smith et al., 2006), (S. M. Smith & Nichols, 2009), (Woolrich et al., 2009), alongside a schematic overview of the statistical analysis performed after the tract-based spatial statistics (TBSS) (Fig. 18). All imaging analysis was conducted on Ubuntu Debian and Jupyter.

Based on Fig. 18., after tract-based spatial statistics (TBSS) was accomplished, I was able to perform two types of statistical analysis. In particular, I completed (1) whole-brain statistical analysis based on mean value DTI parameters' measures derived from TBSS (Behrens et al., 2003), (2) whole-brain voxelwise statistical calculation via FSL GLM, (3) ROI statistical analysis based on mean value DTI parameters' measures (i.e. for white matter tracts, cortical and subcortical regions) and (4) ROI voxelwise analysis via FSL GLM (i.e. for the Corpus Callosum, cortical and subcortical regions).

I used FSL GLM to set contrast and design matrices with the parameters of interest, i.e. the values that participants achieved for the spatial orientation and postural control tests under vestibular guidance, which were presented in 2.3. Laboratory testing. For analysis of the whole-brain GLM results, I used two FSL incorporated atlases: (1) JHU ICBM-DTI-81 white-matter labels atlas (Mori et al., 2008) and (2) JHU white matter tractography atlas (Hua et al., 2008).

Further, to prepare masks for the ROI DTI analysis (both mean value and voxelwise), I used (1) JHU ICBM-DTI-81 white-matter labels atlas (Mori et al., 2008), (2) JHU white matter tractography atlas (Hua et al., 2008), (3) Harvard-Oxford cortical structural atlas (Desikan et al., 2006), (4) Harvard-Oxford subcortical structural atlas (Desikan et al., 2006), (5) Mars TPJ connectivity-based parcellation atlas (Mars et al., 2012) and (6) Juelich Histological Atlas (Eickhoff et al., 2005). These masks were applied to the FA/MD/AD/RD images to extract the corresponding DTI metrics for the regions of interest (ROI) as per (Jolly et al., 2021). Notably, white matter tract data from Chapter VI were used for mean value statistical analysis only. On the other hand, specifically for the CC and a set of cortical and subcortical structures, I performed both mean value statistical and further voxelwise statistical DTI analyses.

Chapter III

Psychophysics, behaviour,
neuropsychology and
neurophysiology - TBI study

1. Introduction

Depending on the aetiology of the brain insult, TBI can have various and profound consequences on different brain modalities, some of which affecting functional performance, cognitive performance or both, functional and cognitive as in e.g. postural and spatial processing.

While the literature highlights the current gaps in our understanding of spatial and postural disability mechanisms after TBI, it also draws our attention to an often underestimated but crucial aspect of spatial and postural processing – the vestibular system. Thus, not surprisingly, “defining the spectrum of vestibular diagnoses in acute TBI should clarify vestibular diagnoses in chronic TBI. There are, however, no relevant acute TBI data” (Marcus et al., 2019). The latter also applies if we consider the spatial and postural processing under central vestibular guidance during acute TBI.

Whereas vestibular studies discussing acute traumatic brain injury patients from a spatial orientation point are practically lacking, there are some examples of vestibular postural studies. One such study concluded that brain injuries often result in vestibular dysfunction with an incidence of dizziness and imbalance ranging from 24% to 83% after mild TBI (Akin & Murnane, 2011). Whether the postural disturbance is with a peripheral (Davies & Luxon, 1995), central (Franke et al., 2012), (Alhilali et al., 2014) or combined vestibular (Arshad et al., 2017), (Marcus et al., 2019) aetiology, however, depends on the type of the brain insult. Often, especially in the acute TBI state, patients can end up underreporting symptoms, possibly because of TBI affecting perceptual mechanisms, and thus vestibular dysfunction can be masked (Marcus et al., 2019). It is assumed that an isolated peripheral vestibular lesion rather than a central vestibular lesion results in a better outcome for a TBI patient, while a combination of peripheral and central vestibular damage would have the poorest prognosis (Peterson, 2010). Scientists have reported that in cases of a peripheral vestibular lesion after TBI, otolith damage rather than semicircular canal damage was more often the reason for abnormal balance (Basta et al., 2005), (Akin & Murnane, 2011). A study also reported a more pronounced sway for athletes with acute mild TBI, not only when on a soft surface or a moving platform, but also in a vision-deprived condition (i.e. eye-closed or covering the head of the participant to produce a vestibular-visual conflict situation) (Guskiewicz et al., 1996). The latter study indicated the possibility of some vestibular impairment, which however remained unclarified by the authors.

Thus, even if the vestibular system is a crucial component of the spatial and postural modalities, vestibular-based postural and spatial research in acute TBI is highly lacking. Consequently, the role of the vestibular system is poorly understood. Therefore, it is not known if the vestibular system can serve as a possible contributor or a burden to the spatial navigation and maintenance of postural control during the acute state of TBI and how the brain manages the cognitive load during injury from a vestibular system point of view. This makes the need for a better understanding of how to support patients in the acute setting of traumatic brain insult even more pronounced. In this Chapter, I investigated the effect of acute TBI on the spatial and postural performance under vestibular guidance, while also looking for a possible link between “spatial – postural” modalities under vestibular guidance (i.e. Hypothesis I). I

also observed the impact of cognitive performance on these two vestibular modalities (i.e. Hypothesis III). My objectives for this Chapter were:

1. To investigate how the brain mechanisms of vestibular spatial orientation or vestibular balance were affected in acute TBI based on behavioural testing alone?
2. To investigate if vestibular-guided spatial and postural modalities shared a common neuronal network in acute TBI based on the relationship between the vestibular spatial and vestibular postural tests?
3. To investigate how the computational burden during acute TBI linked to/affected the vestibular spatial orientation and vestibular postural control using a set of cognitive tests?

2. Materials and Methods

2.1. Recruitment of Acute Traumatic Brain Injury patients

Nr	Gender	Age	CT brain lesions	Mayo criteria	DAI on scan	MOI	PTA Duration (days)	GCS at scene	GCS in A&E	Lowest GCS
1	M	65	R, L SDH, SAH	Moderate-severe	no	Vehicle accident	9	14	12	5
2	M	22	R, L SDH	Moderate-severe	no	Vehicle accident	7	14	14	14
3	M	49	R, L SDH, SAH	Moderate-severe	yes	Fall	6	9	14	9
4	F	48	L SAH	Moderate-severe	no	Vehicle accident	0	15	15	15
5	F	41	None	Mild/probable	no	Vehicle accident	0	14	14	14
6	M	40	R, L SDH, SAH	Moderate-severe	no	Fall	20	13	13	6
7	F	43	None	Mild/probable	no	Vehicle accident	0	15	15	15
8	M	23	R, L SDH, SAH	Moderate-severe	yes	Assault	0	13	13	13
9	F	54	R SDH	Moderate-severe	no	Other	0	15	15	15
10	F	59	R, L SDH	Moderate-severe	yes	Fall	0	14	14	14
11	M	65	R SDH, L SAH	Moderate-severe	no	Fall	13	15	14	12
12	M	37	None	Moderate-severe	yes	Vehicle accident	20	3	14	3
13	F	62	None	Mild/probable	no	Fall	0	14	15	14
14	M	40	R SAH	Moderate-severe	yes	Fall	0	8	15	8
15	M	35	R, L SAH	Moderate-severe	no	Vehicle accident	0	15	15	15
16	M	26	None	Moderate-severe	no	Fall	0	15	15	15
17	M	58	L SAH	Moderate-severe	yes	Fall	0	13	15	13
18	M	42	R, L SDH, SAH	Moderate-severe	yes	Vehicle accident	0	15	15	15
19	M	30	None	Moderate-severe	no	Fall	0	15	15	15
20	M	43	R, L SAH	Moderate-severe	no	Fall	0	12	14	12
21	F	60	R, L SDH, SAH	Moderate-severe	no	Fall	0	walked to A&E	15	15
22	M	47	L SDH, SAH	Moderate-severe	no	Fall	0	13	15	13
23	M	49	R, L SDH, SAH	Moderate-severe	no	Fall	10	13	14	13
24	M	41	R, L SDH, SAH	Moderate-severe	yes	Vehicle accident	20	11	13	11
25	M	47	R, L SDH	Moderate-severe	no	Fall	12	14	15	13
26	F	34	R, L SDH, SAH	Moderate-severe	no	Fall	31	4	14	4
27	M	24	R, L SDH, SAH	Moderate-severe	yes	Assault	9	8	8	8
28	F	33	R SDH, SAH	Moderate-severe	no	Vehicle accident	12	14	14	14
29	F	40	L SDH, SAH	Moderate-severe	yes	Fall	0	13	13	13
30	M	56	R, L SDH	Moderate-severe	no	Fall	0	14	14	14
31	M	39	R, L SDH, SAH	Moderate-severe	no	Fall	0	15	15	15
32	M	18	None	Moderate-severe	yes	Vehicle accident	9	15	15	12
33	M	34	R, L SDH	Moderate-severe	no	Assault	24	n/a	n/a	3
34	M	48	R, L SDH, SAH	Moderate-severe	no	Fall	14	14	14	13
35	M	59	None	Mild/probable	yes	Fall	0	15	15	15
36	M	36	L SDH, SAH	Moderate-severe	yes	Vehicle accident	61	3	12	3
37	F	20	R, L SDH, SAH	Moderate-severe	yes	Vehicle accident	12	3	15	3

Table. 2. Acute TBI patients – demographics. Abbreviation: GCS = Glasgow Coma Scale; L/R = left/right; PTA = post-traumatic amnesia; SAH = subarachnoid haemorrhage; SDH = subdural haemorrhage; DAI – diffuse axonal injury, MOI – mechanism of injury.

The study cohort consisted of 37 acute TBI patients (mean age = 42.35yrs $\pm$ 12.98, 11F) and 37 healthy age-matched controls (mean age = 40.78yrs $\pm$ 14.75, 21F). Please refer to Chapter II for the inclusion/exclusion criteria of this study.

Table. 2 presents the demographics of the acute TBI patients. According to the Mayo TBI severity classification (Malec et al., 2007), there are patients classified as ‘mild-probable’ = n(4) and ‘moderate-severe’ = n(33), with patients being mostly “moderate”.

2.2. Methodology

As previously stated, the acute TBI study was part of a wider research initiative. To specifically address my hypotheses and their objectives, I selected several of the clinical and non-clinical tests.

Standardised neurophysiological examination (i.e. vHiT and cVemps/oVemps, alongside EOG as part of the spatial VMP testing) was applied to test for an intact peripheral vestibular system (i.e. an obligatory inclusion criteria for this study). In addition, a neurological examination by an expert vestibular neurologist was performed to confirm these results.

I assessed the cognitive state during acute TBI with the help of the well-validated ACE III-R test (Mioshi et al., 2006) that comprises five categories, i.e. attention, memory, fluency, language and visuospatial skills. In addition, I tested processing speed (Trail making part A) (Partington & Leiter., 1949) and executive functioning (Trail making part B) (Partington & Leiter., 1949). Considering vestibular patients are reported to experience general decrease in quality of life which might affect cognitive performance (e.g. decreased self-esteem, increased anxiety, decreased quality of sleep) (Smith et al., 2019), I also briefly report the results of the DIH (Jacobson & Newman, 1990), GAD-7 (Spitzer et al., 2006) and PHQ-9 (Kroenke et al., 2001) assessing the impact of dizziness on life, anxiety and depression level, respectively.

Further, postural performance was tested with a four-condition behavioural task assessing posturography (i.e. eyes open/closed on a hard/soft surface), followed by the self-assessment ABC questionnaire (Powell & Myers, 1995) as an additional posturography measure. Lastly, spatial orientation was tested with the help of the vestibular self-motion perception (VMP) task (Seemungal et al., 2004), which is a form of a basic spatial orientation. To complement the VMP task, a visual reaction time (RT) test was separately applied to control for the delay in the response latency, which could erroneously lead to an elevated VMP.

Please refer to Chapter II. for a detailed explanation of the tasks used in this Chapter.

2.3. Statistical analysis

For the acute TBI cohort analysis, I use three types of division: (1) patient/control, (2) based on their vestibular motion perception performance (VMP) (i.e. into normal/abnormal performance), and (3) based on their Sway/posturography performance in the eyes-closed condition on a foamy surface, i.e. vestibular-driven posturography condition (similarly, into normal/abnormal performance).

Notably, in this Chapter III and further in Chapters VI and VII, patients' performance is referred to as "abnormal (elevated)"/"normal", e.g. "abnormally performing patients for the VMP/ Sway task" (i.e. with elevated = worse (in the case of VMP and Sway tasks) values of their performance) or "normally performing patients for the vestibular motion perception/Sway task". Thus, to keep it short, on plots and in the text, I often use "abnormal/normal Sway patients" or "abnormal/normal VMP patients".

The Shapiro-Wilk test informed the use of parametric statistics for this cohort of acute TBI patients. For all analyses, the alpha-level was set at 0.05. Results are reported as mean $\pm$ SD.

Vestibular neurophysiology:

A group-level comparison between acute TBI patients and controls was applied using the independent sample t-test for the vHiT, cVemps, oVemps and EOG tests to confirm an intact peripheral vestibular system. To quantify the effects reported, t-statistics data were included.

Cognitive tests and Dizziness/Anxiety/Depression - questionnaires:

For ACE III-R, Trail making part A/B, DHI, PHQ-9 and GAD-7, I investigated the difference between abnormal/normal VMP and separately abnormal/normal Sway-performing patients using the independent sample t-test. To quantify the effects reported, t-statistics data were included. In addition, correlation analysis using the Pearson's test was performed between all cognitive tests/questionnaires and the VMP/ vestibular Sway test to look for a possible relationship to spatial and postural performance under vestibular guidance.

Posturography and ABC questionnaire:

Repeated measures ANOVA was applied to investigate the difference between controls, abnormal VMP and normal VMP patients for the four posturography conditions, aiming to stress the greater effect of imbalance during the vestibular-based condition compared to the other posturography conditions. To quantify the effects reported, partial eta squared values for F-tests were included. All results were corrected for multiple hypothesis testing via Bonferroni corrections. Lastly, one-way ANOVA was performed for all four posturography conditions (i.e. outside of the repeated measures ANOVA) to look for the difference between abnormal/normal VMP patients.

Based on the vestibular Sway posturography condition (i.e. eyes closed on a soft surface), patients were classified as having "abnormal balance" if their performance was higher than 'mean + 3SD' of controls performance.

Further, the ABC questionnaire was administered to assess the difference in the self-perceived imbalance of patients with abnormal/normal VMP or abnormal/normal Sway groups using the independent sample t-test. To quantify the effects reported, t-statistics data were included. In addition, correlation analysis to VMP and the vestibular Sway measures was performed using the Pearson's test.

Vestibular motion perception and visual RT test:

A group-level comparison between acute TBI patients and controls was performed for mean value, Left-sided and Right-sided VMP threshold using the independent sample t-test. Then, a paired sample t-test was applied to check for differences between Right/Left-sided thresholds, alongside a possible correlation between them via the Pearson's test. Further, TBI patients' mean values of VMP and EOG

were compared to assess the vestibular perceptual/vestibular reflex difference using the independent sample t-test. Same analysis was performed for controls.

Based on the vestibular motion perception performance, patients were classified as having “abnormal VMP” if their performance was higher than ‘mean + 3SD’ of controls performance.

One-way ANOVA was used to assess the difference between mean VMP threshold values of controls/abnormal VMP/normal VMP participants, followed by a repeated measures ANOVA for Left- and Right-sided difference comparison among the same three groups. To quantify the effects reported, partial eta squared values for F-tests were included. All results were corrected for multiple hypothesis testing via Bonferroni corrections.

Lastly, I tested the patient/control difference in visual RT test using the independent sample t-test. I finished the analysis with a more detailed check of the difference between abnormal VMP/normal VMP performance via the independent sample t-test for patients only analysis. To quantify the effects reported, t-statistics data were included.

Vestibular motion perception/ Vestibular Sway:

I tried to correlate VMP and vestibular Sway performance using the Pearson’s test to directly look for a link between the spatial and postural modalities under vestibular guidance via the main spatial/postural tests of this behavioural analysis.

3. Psychophysics, behaviour, neuropsychology, neurophysiology - Results

3.1. The peripheral vestibular system

Test - TBI study	all patients	controls	Patient/control difference (t -test)
vHiT (% asymmetry)	4.71 ± 2.47	3.85 ± 2.96	(t(70) = -1.34, p = 0.18)
Left Gain vHiT	1.04 ± 0.14	1.01 ± 0.09	(t(70) = -1.24, p = 0.21)
Right Gain vHiT	1.04 ± 0.12	1.00 ± 0.09	(t(70) = -1.41, p = 0.16)
N1-P1 Amplitude to the Right (cVemps)	0.77µV ± 0.39	0.95µV ± 0.46	(t(70) = 1.76, p = 0.08)
N1-P1 Amplitude to the Left (cVemps)	0.78µV ± 0.32	1.01µV ± 0.53	(t(70) = 2.28, p = 0.02*)
N1-P1 Amplitude to the Right (oVemps)	0.31µV ± 0.37	0.33µV ± 0.41	(t(70) = 0.22, p = 0.82)
N1-P1 Amplitude to the Left (oVemps)	0.35µV ± 0.38	0.30µV ± 0.25	(t(70) = -0.62, p = 0.53)
EOG	0.62°/sec ² ± 0.21	0.53°/sec ² ± 0.20	(t(70) = -1.65, p = 0.10)

Table. 3. TBI - Vestibular Neurophysiology – descriptive statistics (mean + SD).

3.1.1. Video Head Impulse Test (vHiT) - (high-frequency semicircular canal testing)

Lateral (i.e. horizontal) semicircular canal function was tested with the video head impulse test (vHiT), and an intact peripheral vestibular function was established for both patients and controls (Table.3). Patients group % asymmetry, left GAIN and right GAIN were not different from controls: $p = 0.18$, $p = 0.21$ and $p = 0.16$, respectively.

3.1.2. Vestibular-evoked myogenic potentials (cervical/ocular) – otolith testing

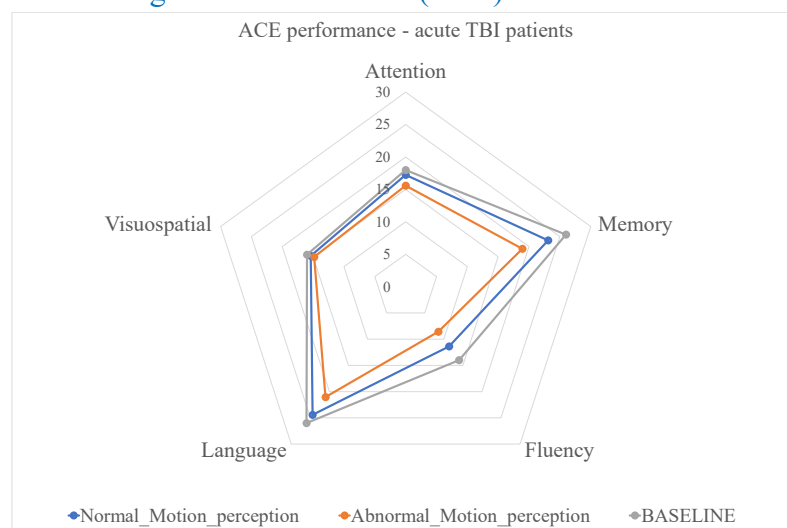
The saccular and utricular function were tested with the cervical vestibular myogenic potentials, i.e. cVemps and ocular vestibular myogenic potentials, i.e. oVemps, respectively. Patients showed within normal range results for both tests compared to their age-matched controls (Table.3).

3.1.3. Electrooculography (EOG) – (low-frequency semicircular canal testing)

During the vestibular motion perception task, a vestibular ocular reflex (VOR) was recorded with the help of electrooculography (EOG) for both eyes. Acute TBI patients and controls displayed close and not significantly different values ($p = 0.102$), with group acceleration thresholds being $\alpha = 0.62^\circ/\text{sec}^2 \pm 0.21$ for TBI patients and $\alpha = 0.53^\circ/\text{sec}^2 \pm 0.20$ for controls (Table.3). Plots based on division for vestibular motion perception (VMP) are available in Appendix.

3.2. Cognitive skills and Dizziness/Anxiety/Depression - questionnaires

3.2.1. Addenbrooke's Cognitive Examination (ACE)



Test - TBI study	abnormal VMP	normal VMP	abnormal VMP/normal VMP difference (t-test)
ACE Total/100 points	78.93 points $\pm$ 11.01	91.52 points $\pm$ 8.78	(t(34) = -3.81, $p < 0.001$ ***)
ACE Attention/18 points	15.58 points $\pm$ 2.34	17.23 points $\pm$ 1.33	(t(34) = -2.68, $p = 0.011$ *)
ACE Memory/26 points	18.92 points $\pm$ 4.29	23.09 points $\pm$ 3.88	(t(34) = -3.04, $p = 0.004$ **)
ACE Fluency/14 points	8.57 points $\pm$ 3.52	11.38 points $\pm$ 2.17	(t(34) = -2.95, $p = 0.006$ **)
ACE Language/26 points	21.03 points $\pm$ 3.07	24.42 points $\pm$ 1.91	(t(34) = -4.08, $p < 0.001$ ***)
ACE Visuospatial/16 points	14.82 points $\pm$ 1.15	15.38 points $\pm$ 1.20	(t(34) = -1.38, $p = 0.17$)

Figure. 19. ACE performance in acute TBI patients based on Vestibular Motion Perception (patients only). *legend- BASELINE means maximum score for each component. Statistical information is organised in the table attached below (mean + SD).

Patients only, without healthy controls, performed the Addenbrooke's cognitive examination III- R (ACE III-R) and achieved 86.27 points $\pm$ 11.49 (i.e. average mean $\pm$ SD) from 100 points being the maximum for this test.

In Fig.19., I display the cognitive performance of patients divided based on their VMP score and the accompanying statistical information. When comparing the performance of abnormal VMP and normal

VMP patients, they showed notable difference for the Total score ($p < 0.001^{***}$) and all subcomponents, except visuospatial skills (Attention $p = 0.011^*$, Memory $p = 0.004^{**}$, Fluency $p = 0.006^{**}$ and Language $p < 0.001^{***}$). In contrast, when divided based on vestibular Sway performance, abnormal/normal Sway patients showed no difference for ACE and its subcomponents.

Lastly, I correlated the two behavioural tests that are central to this vestibular study, i.e. the VMP test and the vestibular Sway, with ACE TOTAL and its sub-components (Fig. 20). While VMP correlated significantly with ACE TOTAL and all of its subcomponents (with exception to ACE visuospatial), there was no significant correlation between ACE TOTAL (and its sub-components) and either of the posturography measures for vestibular Sway (i.e. Sway 95% confidence ellipse SC, RMS SC and GAIN SC/SO).

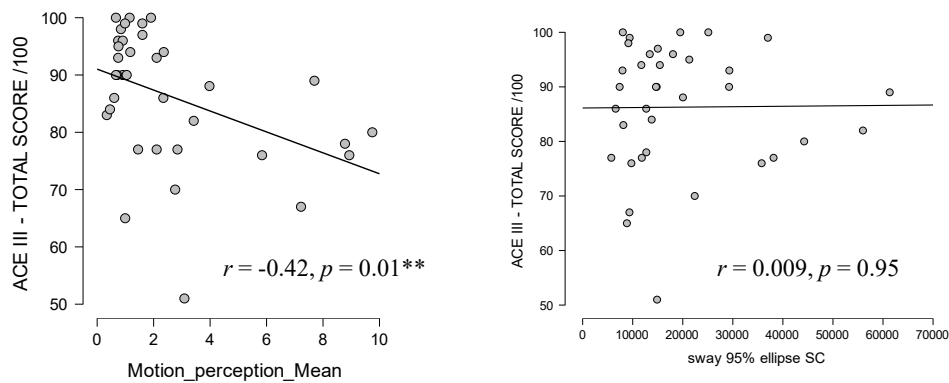


Figure. 20. Correlation between ACE TOTAL and VMP (left) and Sway 95% confidence ellipse SC (right).

3.2.2. Trail-making test - A and B

The Trail making test was completed by the acute TBI participants with an average time in seconds for Trail making part A: $39.26s \pm 19.86$ and for Trail making test part B: $101.65s \pm 75.60$. Normative data as per (Tombaugh, 2004) for the age group with range 35-44yrs ($n = 39$) showed that Trail-making test A took approximately 30s, whereas Trail-making test B - 60s.

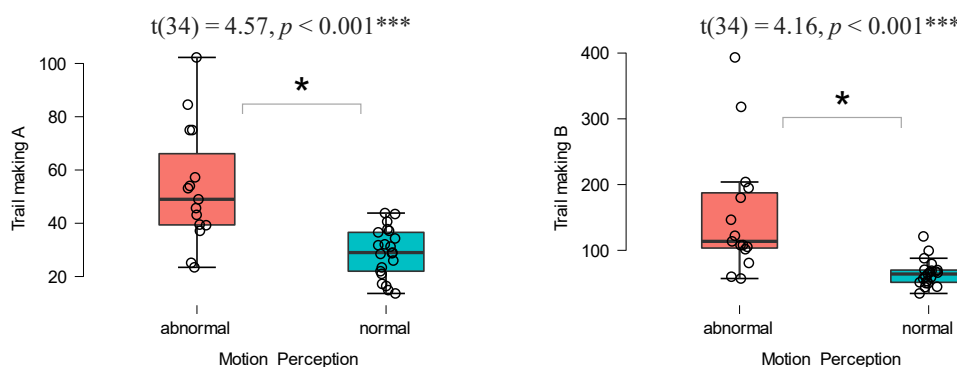


Figure. 21. Trail-making test [sec] performance in acute TBI (patients only) based on VMP division (median + IQR).

If divided by their VMP performance (Fig. 21), the patients with abnormal motion perception showed an increased time needed to complete both parts of the test when compared to the patients with normal

VMP (i.e. for part A, $p < 0.001^{***}$ and for part B, $p < 0.001^{***}$). No difference between abnormal/normal Sway patients was noted.

Lastly, similarly to the ACE test, there was no correlation between the vestibular Sway measures (i.e. 95% confidence ellipse SC, RMS SC and GAIN SC/SO) and the Trail making tests A or B. However, the VMP showed a significant result with both - the Trail A test ($r = -0.64$, $p < 0.001^{***}$) and the Trail B test ($r = 0.49$, $p = 0.002^{**}$).

3.2.3. DHI, PHQ-9 and GAD-7

Test - TBI study	all patients	abnormal VMP	normal VMP	abnormal Sway	normal Sway
DHI-Physical/24 points	7.44 ± 5.84	6.26 ± 5.33	8.28 ± 6.17	6.00 ± 4.89	8.36 ± 6.31
DHI-Emotional/36 points	6.11 ± 5.19	5.6 ± 4.29	6.47 ± 5.82	5.85 ± 4.47	6.27 ± 5.7
DHI-Functional/40 points	12.83 ± 11.16	10.66 ± 9.52	14.38 ± 12.19	11.71 ± 12.09	13.54 ± 10.76
DHI-Total/100 points	26.38 ± 20.64	22.53 ± 17.04	29.14 ± 22.87	23.57 ± 20.33	28.18 ± 21.1
PHQ-9/27 points	9.17 ± 5.65	9.07 ± 4.53	9.23 ± 6.4	10.38 ± 5.39	8.45 ± 5.81
GAD-7/21 points	7.22 ± 4.98	8.28 ± 5.16	6.52 ± 4.86	7.00 ± 4.95	7.36 ± 5.12
ABC/100 points	73.51 ± 20.92	68.65 ± 20.11	76.99 ± 21.27	73.49 ± 22.63	73.53 ± 20.31

Table. 4. TBI questionnaires (mean + SD).

Patients only, without controls, performed the DHI, PHQ-9 and GAD-7 questionnaires. Their performance was significantly decreased as compared to the baseline/max score (Table.4). T-test between abnormal/normal VMP and abnormal/normal Sway division was not statistically significant for any of these questionnaires.

Abnormal VMP patients showed a notable correlation between VMP - GAD-7 ($p = 0.006^{**}$), but this one was not present for the normally performing VMP patients. Similarly, abnormally performing Sway patients showed a significant correlation between VMP - GAD-7 ($p = 0.027^{*}$), but it was again not present for the normally performing Sway patients. In addition, for abnormal Sway patients, there was also a notable correlation between total DHI – ABC ($p = 0.005^{**}$).

3.3. Postural control

3.3.1. SWAY test/ Posturography

Before considering a vestibular-only condition for posturography performance (i.e. soft surface and eyes-closed), I present data of the 95% confidence ellipse for all four Sway conditions tested (Fig. 22). Figure 22. displays the difference in performance based on the VMP division. It shows that patients with abnormal VMP were more unstable in all four conditions, whereas the patients with normal VMP performed similarly to age-matched controls for all conditions, except the vestibular-driven (i.e. SC) condition (Calzolari and Chepishcheva et al., 2021). A repeated measures ANOVA showed a notable main effect of (1) Sway condition ($F[3,213] = 13.43$, $p < 0.001^{***}$; $\eta_p^2 = 0.66$), (2) Group division ($F[2,71]$

= 15.94, $p < 0.001^{***}$; $\eta_p^2 = 0.31$), and (3) the interaction between ‘Sway condition and Group division’, ($F[6,213] = 16.04$, $p < 0.001^{***}$; $\eta_p^2 = 0.31$) (Calzolari and Chepishcheva et al., 2021).

Further, a Post Hoc analysis confirmed that the main effect of the Sway condition was driven by the difference of all other conditions HO, HC and SO with the vestibular SC condition (i.e. Soft surface, eyes-Closed), all three with $p_{(bonf)} < 0.001^{***}$. Second, when looking at ‘Group division’, the main drivers of the notable result were the differences between (1) ‘control – abnormal VMP patients’, $p_{(bonf)} < 0.001^{***}$, and (2) ‘normal VMP patients – abnormal VMP patients’, $p_{(bonf)} < 0.001^{***}$ and (3) ‘control – normal VMP patients’, $p_{(bonf)} = 0.002^{**}$. Lastly, for the interaction between ‘Sway condition and Group division’, the main effect was driven by the difference with the vestibular SC condition (e.g. abnormal VMP patients' SO performance significantly differed from abnormal VMP patients' SC).

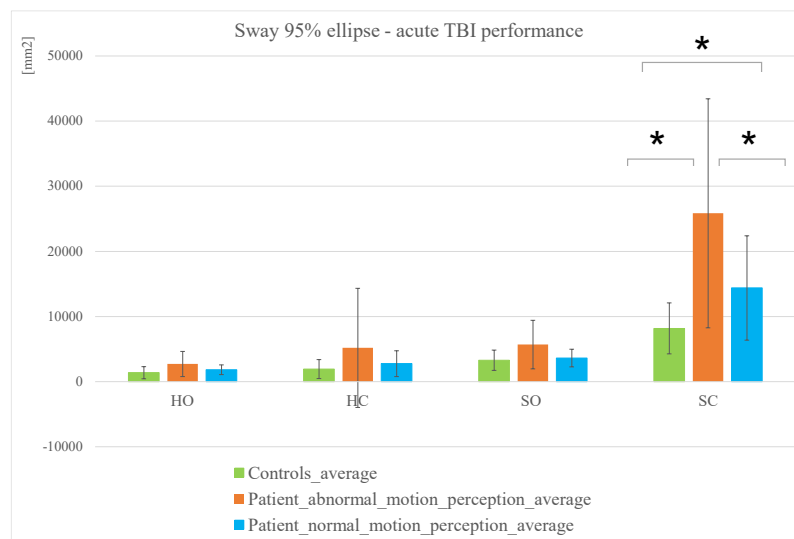


Figure. 22. Sway area 95% confidence ellipse [mm²] – acute TBI and healthy controls performance (mean + SD). The plot displays four posturography conditions: HO (hard surface, open eyes), HC (hard surface, closed eyes), SO (soft surface, open eyes) and SC (soft surface, closed eyes, i.e. vestibular-driven condition).

If looking at posturography performance separately for all four conditions, then individual ANOVAs pointed to some additional statistically significant results other than the SC condition - for HO condition (‘abnormal VMP patients – controls’) and for SO condition (‘abnormal VMP patients – controls’ and ‘abnormal VMP patients – normal VMP patients’). Still, the SC condition showed the most notable within group differences. These results are available in Appendix, alongside vestibular driven analysis for RMS (SC) and the Sway 95% ellipse GAIN SC/SO .

3.3.2. ABC balance questionnaire

The ABC questionnaire (performed only by patients) showed an average group estimate $\pm$ SD of 73.51 points $\pm$ 20.92 (a maximum of 100 points), with patients with abnormal VMP showing a decreased level of their self-reported confidence about their balance when compared to their counterparts with normal VMP (Table.4). The independent sample t-test showed no statistical difference between the two sub-

groups ($t(34) = -1.18, p = 0.24$), followed by no difference between abnormal/normal Sway patients ($t(34) = -0.006, p = 0.99$).

ABC performance did not show any statistically significant correlations to mean VMP, Left/Right-sided VMP, Sway 95% confidence ellipse, RMS (SC) or GAIN (SC/SO). The latter holds true when patients were taken as one group or divided based on VMP/Sway performance. These results alongside performance plots based on VMP/ vestibular Sway are attached in Appendix.

3.4. Spatial navigation

3.4.1. Vestibular motion perception test

The VMP task displayed a clear difference between the acute TBI patients and healthy controls (Fig. 23), with a lower acceleration value of the threshold (presented here in $^{\circ}/\text{sec}^2$) indicating better performance. There was a notable patient/control difference for the Mean VMP threshold ($t(71) = -4.01, p < 0.001^{***}$), Left VMP threshold ($t(71) = -3.9, p < 0.001^{***}$) and Right VMP threshold ($t(71) = -3.80, p < 0.001^{***}$).

When looking only at patients' Left and Right VMP thresholds, there was a significant Pearson's correlation $r = 0.88, p < 0.001^{***}$ between them and no statistical difference, $t(35) = -0.12, p = 0.89$.

Notably, the average TBI patients' VMP threshold of $\alpha = 2.56^{\circ}/\text{sec}^2 \pm 2.64$ was higher than their average vestibular-ocular (VOR) threshold measured via the EOG - $\alpha = 0.62^{\circ}/\text{sec}^2 \pm 0.21, p < 0.001^{***}$. In addition, for controls, no notable difference between their average vestibular self-motion threshold (α

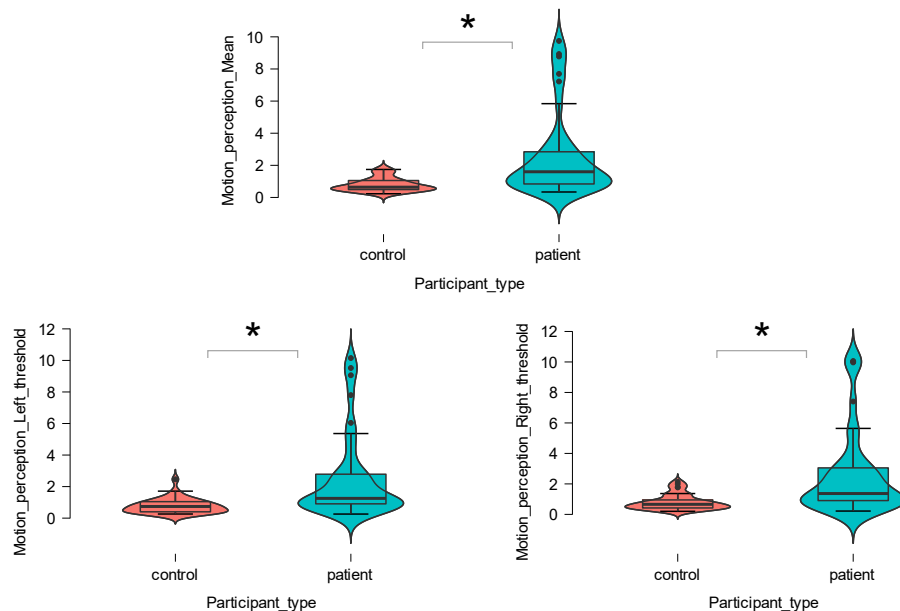
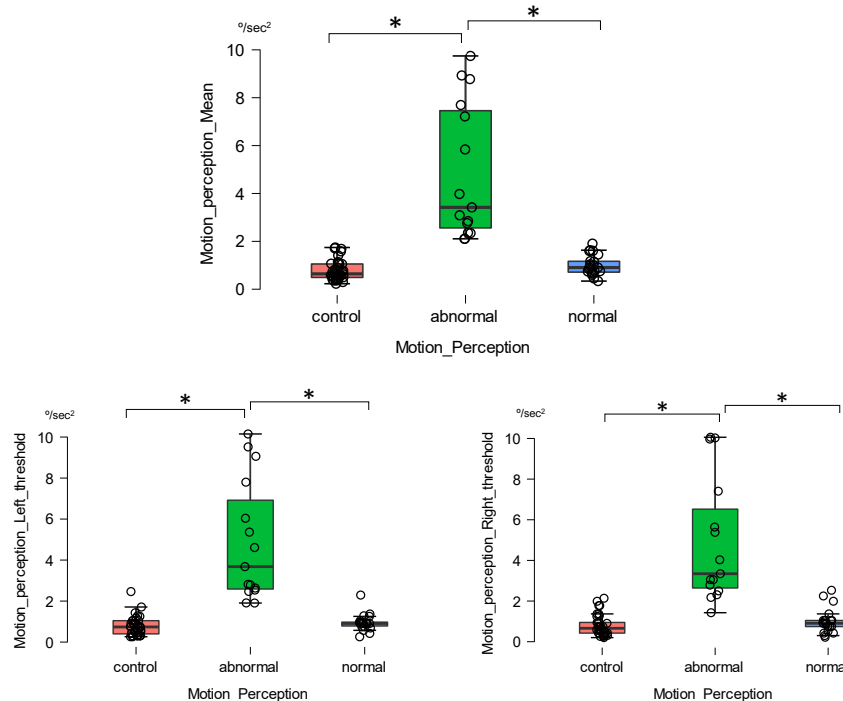


Figure. 23. Vestibular Motion Perception performance [$^{\circ}/\text{sec}^2$] – patient/control division (median + IQR) – Mean VMP threshold, Left VMP threshold and Right VMP threshold.
 $= 0.77^{\circ}/\text{sec}^2 \pm 0.41$) and their vestibular-ocular threshold (VOR) via the EOG ($\alpha = 0.53^{\circ}/\text{sec}^2 \pm 0.20$), $p = 0.19$ was established (Calzolari and Chepishcheva et al., 2021).

A threshold of $2.02^{\circ}/\text{sec}^2$ (Calzolari and Chepisheva et al., 2021) of the healthy controls $\text{mean} + 3SD$ ($0.77^{\circ}/\text{sec}^2 \pm 0.41$) established that any value above this threshold indicates “abnormal VMP performance” and all values below it – “normal VMP performance”. Consequently, when dividing patients based on their VMP performance into normally/abnormally performing, the difference between sub-groups became even more apparent (Fig. 24). Abnormally performing patients showed a Mean VMP threshold that was 4.9times higher than the mean threshold of normally performing VMP patients (Left threshold – 5.2 times higher and Right threshold – 4.9 times higher) (Fig. 24).

An ANOVA showed that there was a significant main effect of sub-group for Mean VMP threshold ($F[2,70] = 55.30, p < 0.001^{***}; \eta_p^2 = 0.61$) and a Post Hoc informed that it was the difference between (1) ‘abnormal VMP patients – controls’ ($p_{(bonf)} < 0.001^{***}$) and (2) ‘normal VMP patients – abnormal VMP patients’ ($p_{(bonf)} < 0.001^{***}$) that caused this significance (Fig. 24).



Test - TBI study	all patients (average + SD)	abnormal VMP (average + SD)	normal VMP (average + SD)
Vestibular motion perception test - Mean	$2.56^{\circ}/\text{sec}^2 \pm 2.64$	$4.88^{\circ}/\text{sec}^2 \pm 2.83$	$0.99^{\circ}/\text{sec}^2 \pm 0.41$
Vestibular motion perception test - Right sided	$2.57^{\circ}/\text{sec}^2 \pm 2.75$	$4.87^{\circ}/\text{sec}^2 \pm 3.07$	$1.00^{\circ}/\text{sec}^2 \pm 0.58$
Vestibular motion perception test - Left sided	$2.54^{\circ}/\text{sec}^2 \pm 2.70$	$4.88^{\circ}/\text{sec}^2 \pm 2.94$	$0.94^{\circ}/\text{sec}^2 \pm 0.39$

Figure. 24. Vestibular Motion Perception performance [$^{\circ}/\text{sec}^2$] – acute TBI and controls (median + IQR). Mean, Right and Left-sided thresholds as based on what is considered normal/abnormal VMP performance. Statistical information is organised in the table attached below (average + SD).

Lastly, a repeated measure ANOVA for the Left and Right VMP threshold confirmed the results for the Mean VMP threshold. In particular, there was a main effect of Group within each Right or Left threshold for the repeated measure ANOVA - $F[2,70] = 55.65, p < 0.001^{***}; \eta_p^2 = 0.61$. Similarly, a Post Hoc showed that it was the difference with the abnormal VMP group ($p_{(bonf)} < 0.001^{***}$) that drove this difference (Fig. 24).

3.4.3. Visual Reaction time test

Lastly, there was also a visual reaction time test of two variations. In general, patients showed a slight delay compared to controls, i.e. for the simple Reaction time test (i.e. indicating if an object was present on the screen as soon as they see it), $p = 0.02^*$; and also for the task where they needed to indicate a Right or Left direction, Total RT, $p = 0.0007^{***}$, Left-sided threshold RT, $p = 0.001^{**}$ and Right-sided threshold RT, $p = 0.0009^{***}$. In addition, there was a significant correlation between Right and Left sided RT results for patients with Pearson's $r = 0.77$, $p < 0.001^{***}$ and a no notable difference, $t = 1.89$, $p = 0.067$.

All plots, along with division based on VMP and vestibular Sway, are attached in Appendix. Importantly, Total RT (i.e. the test distinguishing between Right/Left direction) for the abnormal motion perception group was $0.44s \pm 0.09$, whereas for the normal motion perception group, it was $0.40s \pm 0.07$ with no statistical difference between them, $p = 0.26$ (Calzolari and Chepishcheva et al., 2021).

3.5. Vestibular mediated balance and Vestibular Motion Perception

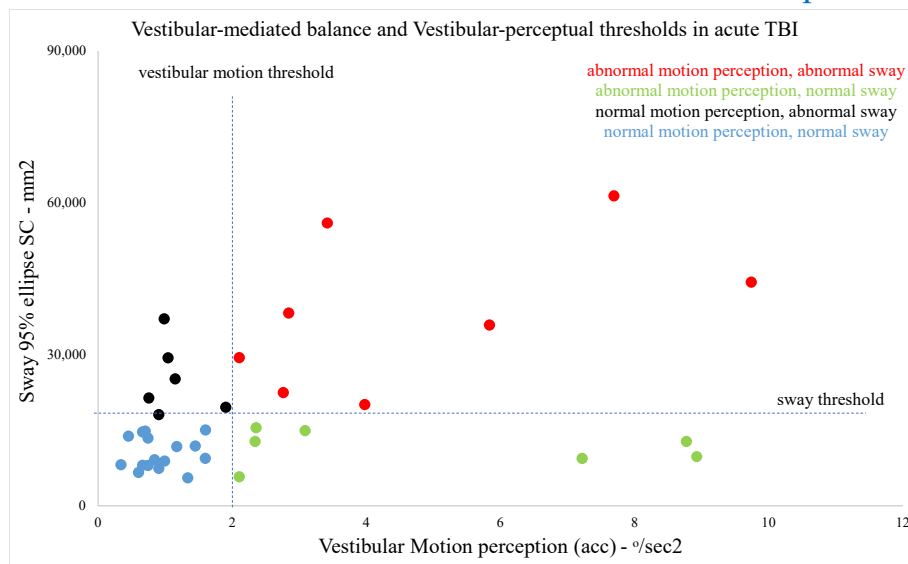


Figure. 25. Vestibular-mediated balance (Sway area 95% confidence ellipse, SC condition) and Vestibular-perceptual thresholds in acute TBI. The scatter plot displays the performance of acute TBI based on their overlapping vestibular motion and vestibular-driven Sway performance. The dashed lines present the thresholds for each of the tasks, dividing the patients into normal/abnormal performance.

Vestibular motion perception and Vestibular mediated balance showed a significant correlation ($r = 0.39$, $p = 0.018^*$). Figure 25. displays a summary of this correlation via the performance of patients for the vestibular self-motion perception task and the posturography 95% confidence ellipse SC condition. I note that the two groups of vestibular impairment overlap, with 8 out of 37 participants exhibiting both decreased VMP and decreased posturography for SC condition.

Notably, there were 15 out of 37 patients who had VMP impairment, and 14 out of 37 who had impaired vestibular balance. Further, as previously noted during the Sway analysis, acute TBI patients with an

attenuated perception of VMP showed a clear tendency towards a higher postural instability in comparison to patients without this attenuation of VMP. This difference was most evident when looking at the Soft surface, eyes-Closed, i.e. vestibular condition, where the magnitude of Sway was highly increased compared to the other three Sway conditions.

4. Summary/Conclusion

In this first sub-section of the acute TBI study, which also continues with detailed imaging analyses in Chapters VI and VII, I investigated the psychophysics, behavioural, neuropsychology and neurophysiology aspects of acute TBI. Specifically, I concentrated on the changes of vestibular spatial and vestibular postural processing during acute TBI and a potential link between these two modalities. In addition, I assessed how the cognitive state in the acute setting of TBI affected this spatial and postural performance under vestibular guidance.

My main findings were that (1) vestibular spatial and vestibular postural processing were decreased during acute TBI, (2) spatial and postural modalities showed a link through mechanisms of central vestibular processing confirmed via a significant positive correlation (Fig. 25), (3) vestibular motion perception as a basic vestibular spatial navigation process showed a link to cognition. No such links were established between vestibular derived posturography measures and cognitive tests.

An intact peripheral vestibular system was an obligatory inclusion criterion for the acute TBI patients. They showed close to and/or within normal range performance for the horizontal video head impulse test and vestibular evoked myogenic potentials (cervical/ocular), alongside a normal clinical examination by an experienced vestibular neurologist.

VMP – EOG – RT

When performing the vestibular self-motion test, some of the acute TBI patients showed a decreased perception of self-motion, which the vestibular neurologists termed “vestibular agnosia”, i.e. “the attenuation of vestibular sensation of self-motion, despite intact peripheral and reflex vestibular function” (Calzolari and Chepishcheva et al., 2021). Indeed, as 15 out of 37 acute TBI patients (or 10 out of 30 if I consider only the participants who took part in the imaging analysis) displayed abnormal VMP threshold, it seems that this condition is not rare among acute TBI (Calzolari and Chepishcheva et al., 2021).

In addition, irrespective of whether patients’ vestibular self-motion perception was decreased or not, they presented with a preserved vestibular-ocular reflex (VOR) (measured via the EOG). Importantly, the vestibular self-motion perception threshold was significantly higher for patients compared to EOG thresholds.

Lastly, there were differences for the visual reaction time tests between acute TBI patients and controls. When dividing based on VMP performance, the visual test did not manage to discriminate between normal/abnormal VMP patients. Thus, these results were insufficient to explain the elevated VMP threshold in abnormally performing patients (Calzolari and Chepishcheva et al., 2021), where multiple contributors might be present.

Cognition – VMP – vestibular Sway

The VMP impairment might have affected cognitive performance resulting in decreased ACE memory, ACE fluency and ACE attention scores, Trail making A and B test scores, along with a decreased self-reported balance confidence via the ABC balance test. Consequently, the VMP test showed a statistically notable correlation to ACE total and most of its subcomponents and the Trail making test A and B.

Importantly, there was no correlation between any of the vestibular Sway measures (i.e. the 95% confidence ellipse SC, RMS SC or GAIN SC/SO) and the cognitive tests – ACE total and its sub-components or the Trail making A and B tests.

Patients performed the DHI, PHQ-9 and GAD-7 questionnaires and showed that their results were notably lower compared to baseline.

Vestibular Sway

Another interesting finding is that the postural impairment in acute TBI was mainly and most significantly of a vestibular nature (Calzolari and Chepishcheva et al., 2021). Still, it was present *by observation* in all four posturography conditions (i.e. HO, HC, SO and SC) and statistically – in HO, SO and SC. There were 14 out of 37 acute TBI patients presenting with impaired vestibular-driven Sway performance and 11 out of 30 patients, if I consider only the participants who took part in the imaging analysis (Chapters VI and VII). These findings underline the importance of vestibular-mediated balance impairment in the acute state of TBI. Indeed, research shows that imbalance post-TBI, especially with vestibular features such as dizziness (Chamelian & Feinstein, 2004), is a key “predictor of failure to return to work” (Chamelian & Feinstein, 2004), (Calzolari and Chepishcheva et al., 2021), even after six months post-injury.

Vestibular Sway – VMP

Spatial and postural modalities showed a link through mechanisms of central vestibular processing confirmed via a significant positive correlation between them (Fig.25). In addition, compared to patients without attenuated perception of self-motion, those with the condition were more unbalanced (Calzolari and Chepishcheva et al., 2021).

Chapter IV

Psychophysics, behaviour,
neuropsychology and
neurophysiology - Memory and
(balance) patients - a pilot study

1. Introduction

Vestibular impairment is suggested to affect many domains of cognitive control, among which are spatial navigation, gait and locomotion (Brandt et al., 2005), (P. Smith et al., 2010), (P. Smith & Zheng, 2013), (Previc, 2013), (Hitier et al., 2014), (Yoder & Taube, 2014), (Seemungal, 2014), (Bigelow & Agrawal, 2015), (P. Smith, 2022). The vestibular system becomes especially relevant during turning movements in the dark, such as when walking in our garden or at home at night, where the vestibular signal is crucial (Kaski et al., 2016). Still, a detailed overview of the literature reveals that while non-vestibular spatial and postural research is abundant, peripheral vestibular spatial/postural testing in patients with memory impairment is rare. What is even more concerning is that spatial/postural testing looking for central vestibular aetiology in those patients is hardly attempted at all.

Spatial orientation

A peripheral vestibular study reported a significant link between bilateral saccular dysfunction and self-reported driving difficulties in a visuospatial questionnaire in MCI and AD patients (Wei et al., 2017). Although the connection was mediated by the spatial performance on the Money Road Map test, further data are needed for a causal link to be implied. Importantly, even if saccular impairment can positively be one of the multiple contributors to spatial navigation decline in AD, the assessment of the saccular function (via the cVemps) is an indirect measure of otolith integrity (Ji & Zhai, 2018) and should be interpreted with caution (Chepishcheva, 2022).

In a vestibular-based spatial task (i.e. path integration) on a rotatory chair, “at genetic risk” AD participants ($\epsilon 3\epsilon 4$ carriers) and $\epsilon 3\epsilon 3$ carrier controls were tested while in complete darkness (Coughlan et al., 2022). The discrepancies in the participants’ vestibular-derived performance made authors hopeful that the early identification of vestibular dysfunction might give better chances for “at genetic risk” individuals to receive targeted treatment (Coughlan et al., 2022). This and the few other available vestibular spatial studies in AD are further discussed in Chapter V (sub-section about patients with memory and (balance) complaints), which concentrates specifically on vestibular spatial navigation.

Postural control

Strong evidence exists that static and dynamic postural stability is impaired in Alzheimer’s disease as compared to healthy elderly (Mesbah et al., 2016) and peripheral vestibular loss might contribute to this decline (Biju et al., 2022). Attentional demand in AD during dual-task activity and loss of visual input were shown to be critical factors affecting balance in Alzheimer’s patients (Mesbah et al., 2016). Still, controversy exists on whether increased antero-posterior (AP) or (medio)lateral (ML/L) sway is more challenging for AD patients. Leandri et al. reports increased antero-posterior (AP) sway in aMCI and AD patients during an eyes-closed posturography condition, thus implying a possible vestibular and/or somatosensory impairment (Leandri et al., 2009). Moreover, the AP sway showed that balance is an issue not only for AD but also for aMCI (Leandri et al., 2009). Notably, the patients in this study were

screened for extrapyramidal signs and had no history of “recorded falls, or relevant cardiovascular, metabolic, rheumatologic, orthopaedic or other neurological conditions.” (Leandri et al., 2009). On the other hand, a recent study (Biju et al., 2022) reported that the more preserved the semicircular canal and otolith function were for AD patients, the less ML and AP sway they experienced in the eyes-closed conditions. However, if AD patients’ peripheral vestibular function was impaired (i.e. in this case horizontal SCCs and otoliths), they swayed more in the ML direction, both with eyes-open and eyes-closed. The authors explain their results by mentioning that ML sway is more biomechanically challenging than AP sway and should be expected to degrade quicker (Biju et al., 2022).

A further study discusses that AD patients with normal peripheral and central vestibular processing were unable to retain proper postural control under ‘vestibular system demanding’ conditions while suppressing incongruent visual and somatosensory information, which sometimes led to falls (Chong et al., 1999). Interestingly, AD patients showed a relatively small sway on the eyes-closed condition compared to eyes-open, thus clearly indicating they are not as dependent on vision as the healthy controls (Chong et al., 1999). This way, the authors suggested that suppression of the visual input might have possibly decreased the sensory demand on the Alzheimer’s brain (Chong et al., 1999).

Lastly, researchers observed that during caloric vestibular stimulation, the visual suppression rate of AD patients prone to falls was lower than in those who were not as imbalanced (Nakamagoe et al., 2015). Thus, since peripheral vestibular system function was found to be preserved, researchers assumed a possible central vestibular system abnormality, making it one of the very few examples in the literature where the central vestibular system in AD patients is discussed based on experimental postural control data. Interestingly, the AD faller group single photon emission computed tomography (SPECT) images revealed a decreased blood flow in the inferior parietal lobule (IPL), i.e. an essential part of the putative “vestibular cortex”, thus leading to a suggested association among visual suppression, vestibular imbalance and damage in the IPL (Nakamagoe et al., 2015).

In summary, spatial and postural deficits are a huge burden felt not only on a physical but also on a psychological level by cognitively impaired patients with vestibular disabilities. Still, there is a lack of understanding about the role of the vestibular system in this population. Therefore, it is not known if the vestibular system is contributing to or rather hampering the spatial navigation and maintenance of postural control in patients with memory impairment and how their brain manages the cognitive load from a vestibular system point of view. All this lack of understanding can change if the medical service tries to better accommodate “the vestibular system” in its practice and so improves the current state of knowledge about the spatial and postural processing under vestibular guidance in this population. However, for such a change to happen, more vestibular-based data are needed. In this Chapter, I investigated the effect of memory impairment on the spatial and postural performance under vestibular guidance, while also looking for a possible spatial/postural link under vestibular guidance (i.e.

Hypothesis I). I also observed the impact of cognitive performance on these two vestibular-guided modalities (i.e. Hypothesis III). My objectives for this Chapter were:

1. To investigate how the brain mechanisms of vestibular spatial orientation or vestibular balance were affected in memory and (balance) patients based on behavioural testing alone?
2. To investigate if vestibular-guided spatial and postural modalities shared a common neuronal network in memory and (balance) patients based on the relationship between the vestibular spatial and vestibular postural tests?
3. To investigate how the computational burden in memory and (balance) patients linked to/affected the vestibular spatial orientation and vestibular postural control using two well-validated cognitive tests (i.e. MMSE and ACE III-R)?

2. Materials and Methods

2.1. Recruitment of Memory and (balance) patients

Participant #	Recruitment/Main reason to take part in the study	AGE	GENDER
subject_1	AD - Memory Clinic/memory	79	M
subject_2	MCI - Memory Clinic/memory and balance	88	F
subject_3	no formal diagnosis - General Neurology Clinic/memory and balance	62	F
subject_4	no formal diagnosis - General Neurology Clinic/memory	84	F
subject_5	AD - Memory Clinic/memory	77	F
subject_6	no formal diagnosis - General Neurology Clinic/memory and balance	93	M
subject_7	no formal diagnosis - Memory Clinic/memory issues in the recent past	50	F
subject_8	AD - Memory Clinic/memory	73	M
subject_9	AD - Memory Clinic/memory	76	M
subject_10	MCI - Memory Clinic/memory	72	M
subject_11	no formal diagnosis - General Neurology Clinic/memory and balance	78	F
subject_12	AD - Memory Clinic/memory	76	M
subject_13	AD - Memory Clinic/memory	68	F
subject_14	no formal diagnosis - General Neurology Clinic/memory and balance	77	F
subject_15	AD - Alzheimer's Society/memory	81	M

Table. 5. Demographics and clinical condition of the patients recruited.

After a careful discussion with potential participants, I was able to recruit 15 patients (8F) with a mean age of 75.6yrs (± 10.34) and with an age range of 50 – 93yrs (Table.5). Detailed information about the clinical condition of the memory and (balance) patients/medical examination/medications was removed but is available upon reasonable request. In addition, I recruited 16 healthy adult controls (10F) with a mean age of 69.63yrs (± 8.83) (age range 61-88yrs). Please refer to Chapter II for the inclusion/exclusion criteria of this study.

As previously discussed in Chapter I, some of the patients have a probable Alzheimer's disease diagnosis (recruited from a Memory Clinic, Hammersmith Hospital, London, UK), and the rest of the patients visited a General Neurology Clinic at Charing Cross Hospital, London, UK as a consequence of their memory and (balance) complaints. As all these individuals (i.e. those with complaints and mild

AD) represent a natural continuum from possible prodromal to possible early AD. I tested them as a single group and separated them based on their cognitive performance (using MMSE test) and not based on an existing or lacking diagnosis. I refer to these patients as “Memory and (balance) patients”.

2.2. Methodology

To specifically address my hypotheses and their objectives, I selected the following clinical and non-clinical tests.

All memory and (balance) patients were tested for an intact peripheral vestibular system in accordance with the inclusion criteria for this pilot study. Intact peripheries were established with one or more of the following methods: (1) with a clinical Head impulse Test (HiT) performed by an expert vestibular neurologist, (2) the automated horizontal video HiT (vHiT) or (3) based on their recorded electrooculograms (EOG) during the vestibular motion perception (VMP) test.

I assessed the cognitive state of my memory and (balance) patients with the help of two well-validated questionnaires that are used for patients with memory impairment. First, the MMSE (Folstein et al., 1975) consists of short questions about orientation, registration of new information, attention, calculation, recall, language and copying of a figure. Second, the ACE III-R test (Mioshi et al., 2006) which comprises five categories (i.e. attention, memory, fluency, language and visuospatial skills).

Postural performance was assessed with a four-condition posturography test (i.e. eyes open/closed on a hard/soft surface). Further, spatial orientation was tested with the help of the vestibular self-motion perception (VMP) task (Seemungal et al., 2004), which is a form of a basic spatial orientation. This test was performed with the help of passive chair rotations in the dark. To complement the VMP task, a visual reaction time (RT) test was separately applied to control for delay in the response latency, which could erroneously lead to an elevated VMP threshold.

Please refer to Chapter II. for a detailed explanation of the tasks used in this Chapter.

2.3. Statistical analysis

For the memory and (balance) patients’ analysis, I use three types of division: (1) patient/control, (2) based on their vestibular motion perception performance (VMP) (i.e. into normal/abnormal performance) as per a previously established acceleration threshold of $\alpha = 2.02 \text{ }^\circ/\text{s}^2$ (Calzolari and Chepishcheva et al., 2021), and (3) based on their MMSE cognitive performance. Based on Molloy’s MMSE criteria (Molloy & Standish, 1997), (Molloy & Clamette, 1999) for the developed MMSE test (Folstein et al., 1975), patients with $\text{MMSE} \leq 24$ (if not going under 20 points) are those considered with early/mild cognitive impairment (Table.6). On the other hand, patients with $\text{MMSE} > 24$, are “maybe normal” with respect to their cognitive performance. Therefore, in this study, I use the MMSE criteria to divide the memory and (balance) cohort into two groups: those with $\text{MMSE} > 24$ and those with $\text{MMSE} \leq 24$. Importantly, I use this differentiation throughout the thesis to compare performance

between patients' groups. Lastly, vestibular-driven posturography/Sway division was not reported in this memory and (balance) patients' analysis.

Area of functional impairment				
MMSE Scores	30-25	24-21	21 - 10	9 - 0
Stage	maybe normal	mild/early	moderate	severe

Table. 6. MMSE criteria based on (Molloy & Standish, 1997), (Molloy & Clamette, 1999).

The small sample size of the cohort and the Shapiro-Wilk test informed the use of non-parametric statistics. For all analyses, the alpha-level was set at 0.05. Results are reported as median + IQR.

Vestibular neurophysiology:

A group-level comparison between memory patients and controls was applied using the Wilcoxon rank-sum test for the vHiT and EOG tests to confirm an intact peripheral vestibular system. In addition, EOG results based on VMP/MMSE division were reported to allow better understanding of the vestibular-ocular reflex in this specific population.

Cognitive tests:

For MMSE/ACE III-R, I report the results for patients only (no controls performed the tests), and then for $MMSE \leq 24$ and $MMSE > 24$. For ACE III-R test, the Mann-Whitney U test was performed to look for a difference based on the MMSE division. In addition, for ACE III-R there was also a VMP division based analysis, which is not discussed as the results were similar to the MMSE-based analysis.

A correlation analysis using the Spearman's test was performed between the MMSE/ACE III-R tests and the VMP/Sway 95% SC/RMS AP SC/RMS L SC to look for a possible relationship between cognition and spatial/postural performance under vestibular guidance.

Posturography:

Considering that Alzheimer's disease-based literature makes a difference between antero-posterior (i.e. sagittal plane) and lateral/medio-lateral (i.e. coronal plane) posturography performance, here I not only looked at a standard posturography measurement such as the Sway area 95% confidence ellipse for a combined sagittal and coronal planes performance but also at root mean square (RMS). Root mean square (RMS) shows the extent of postural Sway calculated as the root mean square of the Sway angle in the antero-posterior (AP) or the lateral (L) planes separately or as a combined measure of both planes. In this study, I used them separately, which allowed me to analyse antero-posterior (RMS AP) and lateral (RMS L) planes and display the difference, both between "controls and patients" and within "patients only".

Importantly, I present all four conditions of the posturography test to allow comparison between HO, HC, SO and the vestibular SC condition, with the intention to stress the increased SC condition (i.e. the vestibular condition) sway.

The Mann-Whitney U test was applied to investigate the difference between patients/controls for the Sway 95% ellipse, RMS AP and RMS L for the four posturography conditions, aiming to stress the effect of imbalance during the vestibular-based condition compared to the other conditions.

Further, RMS AP and RMS L difference for all four conditions was investigated within patients using the Wilcoxon signed-ranked test to confirm the observed increased AP sway, and especially the AP sway in the vestibular condition.

Lastly, a Kruskal-Wallis test was performed for Sway 95% confidence ellipse, RMS AP and RMS L conditions for the MMSE and VMP division. In the main text, I presented only MMSE division for Sway 95% confidence ellipse SC, RMS AP SC and RMS L SC, whereas the rest of the plots are available in Appendix. The significant effect of the Kruskal Wallis was subsequently investigated with the help of Dunn's Post Hoc test and Bonferroni corrections.

Vestibular motion perception and visual RT test:

To improve the general understanding about the performance of memory patients during the VMP task, a patients-only-comparison between Right-sided VMP and Left-sided VMP thresholds was performed using the Wilcoxon signed-rank test. Further, the Spearman's correlation test was applied. Patients' only performance was further investigated via the Mann-Whitney U test when looking at Mean value/Right/Left-sided threshold level divided based on VMP or MMSE division.

Further, a Kruskal-Wallis test was performed to look for the difference in VMP performance with controls based on the MMSE division. A subsequent significant result was investigated with the help of the Dunn's Post Hoc test. In addition, the VMP-EOG comparison on a patient only level was performed to assess the difference in vestibular perception/vestibular reflex.

Lastly, I tested the abnormal VMP/normal VMP/control difference in visual RT using Kruskal-Wallis t-test, followed by the Dunn's Post Hoc investigation of the significant result.

Vestibular motion perception/ Vestibular Sway:

I tried to correlate VMP and vestibular Sway performance using the Spearman test to directly look for a link between the spatial and postural modalities under vestibular guidance.

3. Results

3.1. The peripheral vestibular system

Test - Memory and (balance) patients	all patients	controls	Patient/control (Wilcoxon rank-sum test)
vHiT (% asymmetry)	3.00% (IQR 3.5)	2.00% (IQR 1.00)	W = 13, p = 0.78
Left Gain vHiT	0.99 (IQR 0.19)	1.02 (IQR 0.14)	W = 15, p = 1.00
Right Gain vHiT	1.01 (IQR 0.12)	0.98 (IQR 0.1)	W = 11, p = 0.53
EOG	0.60°/s ² (IQR 0.11)	0.69°/s ² (IQR 0.24)	W = 24.5, p = 0.56

Table. 7. Memory and (balance) patients - Vestibular Neurophysiology (median + IQR).

3.1.1. Video Head Impulse Test (vHiT) - (high-frequency semicircular canal testing)

For the vHiT, patients showed a median Right GAIN, Left GAIN and vHiT asymmetry that were not statistically different from controls (Table.7).

3.1.2. Electrooculography (EOG) - (low-frequency semicircular canal testing)

Electrooculograms were recorded during the vestibular motion perception test. Memory and (balance) patients showed preserved vestibular-ocular reflex with results that were similar and not different from controls, $p = 0.56$ (Table.7).

Further, I looked into EOG performance based on VMP or MMSE score division. The results were all within normal range of $0.6^\circ/\text{s}^2$, irrespective of division and the low variance did not allow for any further statistical examination.

3.2. Cognitive skills

3.2.1. MMSE

All patients together achieved a median of MMSE = 26 points (IQR 4.5) (30 points being the maximum), with 11 participants being in the MMSE > 24 group (27.5 points (IQR 2.00)) and 4 participants being in the MMSE $\leq$ 24 group (21 points (IQR 2.5)).

A correlation analysis showed that the mean threshold for the VMP task (patients only) and the MMSE score share a significant negative Spearman correlation, $\rho = -0.78$, $p = 0.002^{**}$ (Fig.26). The significance remained also when looking into the side of rotation: for Left-sided VMP threshold ($\rho = -0.84$, $p < 0.001^{***}$) and for Right-sided VMP threshold ($\rho = -0.72$, $p = 0.007^{**}$).

However, the MMSE and the Sway task derivatives (patients only) shared non-significant Spearman correlations: RMS AP SC ($\rho = -0.28$, $p = 0.37$), RMS L SC ($\rho = 0.00$, $p = 1.00$) and 95% confidence ellipse SC ($\rho = 0.01$, $p = 0.96$).

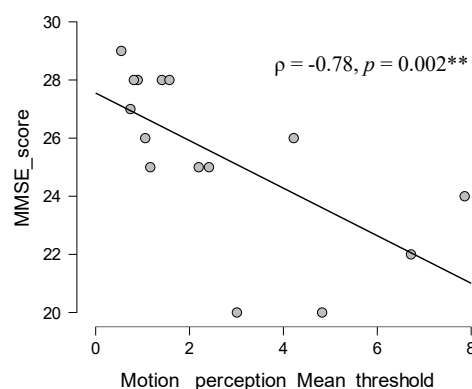


Figure. 26. Memory and (balance) patients - MMSE vs Vestibular Motion Perception (VMP) [$^\circ/\text{sec}^2$].

3.2.2. Addenbrooke's Cognitive Examination (ACE)

Patients TOTAL ACE score was 77 points (IQR 20.7) (100 points being maximum), with MMSE > 24

achieving a median ACE Total = 87.5 points (IQR 17.5), whereas MMSE ≤ 24 showed a median ACE Total = 69.7 points (IQR 12.3). The radar plot and the attached table (Fig.27) offer some detailed information of the ACE score of patients for the five ACE sub-components, with patients divided based on their MMSE score.

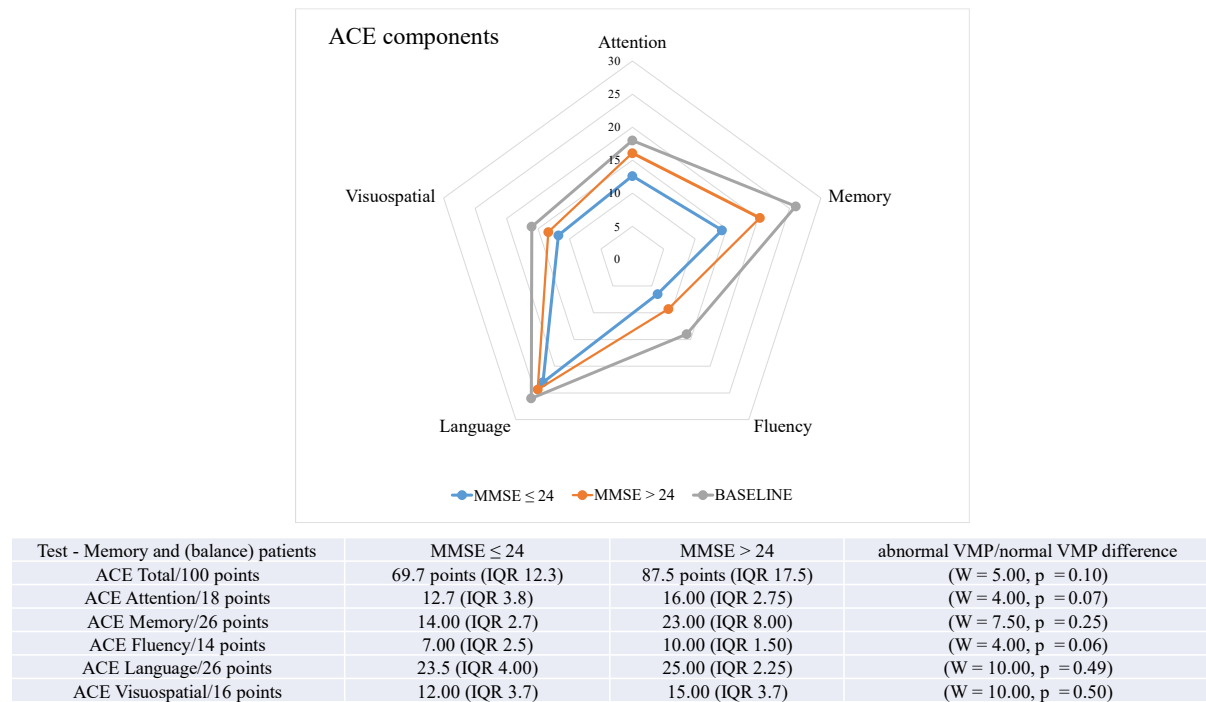


Figure. 27. Memory and (balance) patients - ACE components. The radar plot displays the differences between the performance of MMSE > 24 and MMSE ≤ 24 , comparing them with the maximum score for each ACE component (i.e. baseline). Attached is also a table presenting raw data for the MMSE division of patients for the ACE test (median + IQR) and the difference between groups (via the Wilcoxon rank-sum test).

Healthy participants for this pilot spatial study did not take part in any of the cognitive tests (i.e. MMSE or ACE). Therefore, in Fig. 27, I compared the results of the patients with the baseline/maximum performance for each of the components. *By observation*, there was a clear difference between ACE-Fluency, ACE-Memory and ACE-Attention among the patients' groups, along with a decreased ACE-Visuospatial score. At the same time, ACE-Language skills seemed to be relatively intact. Results for the VMP division were similar. For reference, normative data for the ACE-R showed that healthy controls (age = 64.4yrs $\pm$ 5.7) had an ACE TOTAL score of 93.7 points $\pm$ 4.3 (100 points being maximum) (Mioshi et al., 2006).

Further, a correlation analysis showed that the mean VMP threshold (patients only) and the ACE TOTAL score shared a non-significant negative Spearman correlation ($\rho = -0.49$, $p = 0.12$). However, there was a tendency for a significant correlation with ACE attention ($\rho = -0.59$, $p = 0.05$) and a significant result for the Left-sided VMP threshold and ACE attention ($\rho = -0.65$, $p = 0.03^*$). Lastly, when examining the Sway data (patients only) and the ACE TOTAL score, there were no statistically

notable results - $\rho = -0.47, p = 0.13$ (RMS AP SC), $\rho = -0.14, p = 0.67$ (RMS L SC) and $\rho = -0.14, p = 0.67$ (95% confidence ellipse SC).

3.3. Postural control

Memory and (balance) patients performed a four-condition posturography test: HO (Hard surface, Open eyes), HC (Hard surface, Closed eyes), SO (Soft surface, Open eyes) and SC (Soft surface, Closed eyes). Figure 28 shows the Sway performance of healthy controls >60yrs versus memory and (balance) patients, as based on the area 95% confidence ellipse and RMS in AP (sagittal) and L (coronal) planes. Notably, the performance of patients was consistently elevated for all four conditions (HO, HC, SO and SC), especially for the SC condition.

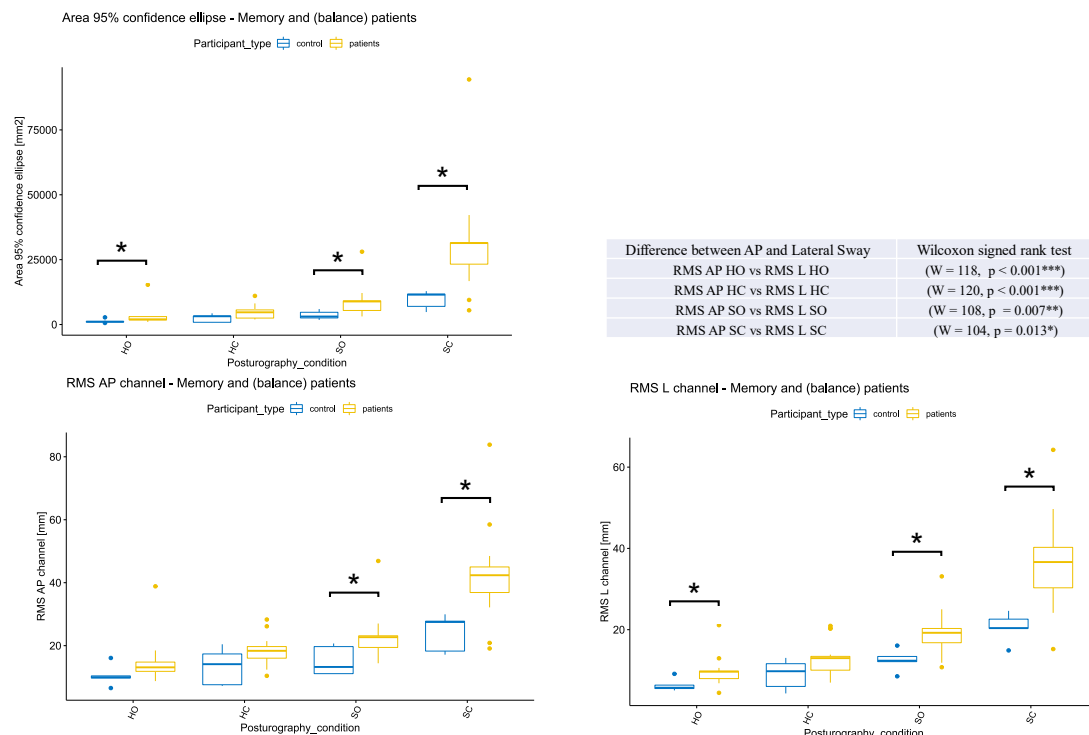


Figure.28. Sway performance of healthy controls >60yrs versus memory and (balance) patients. Panel above displays performance based on the area 95% confidence ellipse, whereas the two panels below display RMS AP (antero-posterior) (left) and RMS L (lateral) (right) performance. Significant differences in Sway condition are noted with an asterisk “*”. A table displaying the difference between AP and L Sway is attached.

The Area 95% confidence ellipse (Fig. 28., panel above) presented with three statistically notable differences between patients/controls, i.e. for HO condition ($W = 12, p = 0.028^*$), SO condition ($W = 8, p = 0.011^*$) and SC condition which is also referred as the Vestibular Sway condition ($W = 7, p = 0.009^{**}$). Further, RMS AP (Fig.28, panel below on the left) shows notable results for the SO condition ($W = 8, p = 0.011^*$) and SC condition ($W = 6, p = 0.007^{**}$). Lastly, RMS L (Fig.28, panel below on the right) shows a main effect of patient/control division for HO ($W = 11, p = 0.023^*$), SO ($W = 9, p = 0.014^*$) and SC ($W = 5, p = 0.005^{**}$) conditions.

Importantly, the RMS AP and the RMS L results showed that memory and (balance) patients swayed slightly more for the AP (antero-posterior) direction as compared to L (lateral) plane (Fig. 28, the two

panels on the lower row). The Wilcoxon signed rank test confirmed that all comparisons of the four posturography conditions within ‘patients only’ data were significantly different (Fig.28).

Next, Figure 29. displays only the vestibular-based, i.e. SC (soft surface, eyes-closed) performance for area 95% confidence ellipse, RMS AP and RMS L, where patients were divided based on their MMSE score (i.e. $MMSE \leq 24$ and $MMSE > 24$). For reference, all four posturography conditions (i.e. HO, HC, SO and SC) plots divided as per MMSE and VMP performance are available in Appendix.

A Kruskal-Wallis test for Area 95% confidence ellipse (Fig. 29, panel above) showed a main effect of sub-group ($\chi^2(2) = 7.17, p = 0.02^*$) that was driven by the difference between the controls > 60yrs and the two patients' groups.

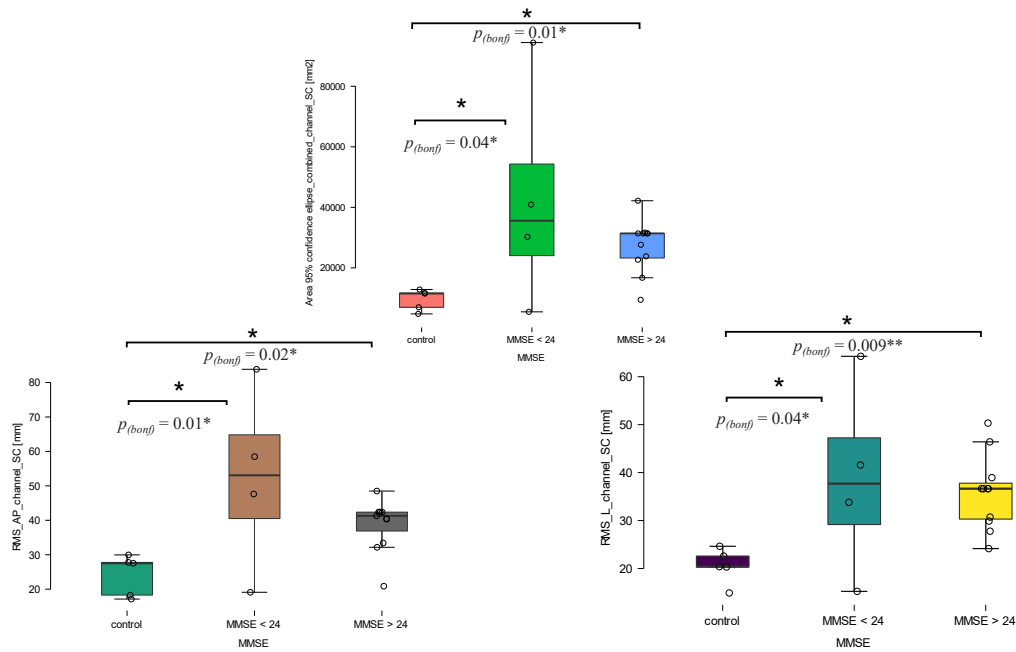


Figure.29. Sway performance (area 95% confidence ellipse, RMS AP and RMS L) of healthy controls >60yrs versus memory and (balance) patients (divided based on their MMSE scores). Multiple hypothesis testing results from the Dunn’s Post hoc test are displayed directly on the plots.

Further (Fig. 29., lower row), for RMS AP ($\chi^2(2) = 8.34, p = 0.01^*$) and RMS L ($\chi^2(2) = 8.11, p = 0.01^*$), the results were similarly statistically notable based on the Kruskal-Wallis test and there was a main effect of group. A subsequent Dunn’s Post Hoc test revealed that the difference was driven by the same sub-groups as for the area 95% confidence ellipse (Fig. 29).

3.4. Spatial navigation

3.4.1. Vestibular self-motion perception test

Vestibular self-motion perception is an example of a basic spatial orientation process, and an acceleration threshold of $\alpha = 2.02^\circ/s^2$ was established for a cohort of $n = 37$ healthy controls (Calzolari and Chepishcheva et al., 2021). In this pilot study, I use this selected threshold value and consider all values above it as “abnormal”/“abnormal performance for VMP”.

All memory and (balance) patients completed the VMP task as part of their assessment for the three-step spatial model, which I discuss in great detail in Chapter V. There, I again mention their performance for the VMP task, as it is a crucial part of the three-step testing battery.

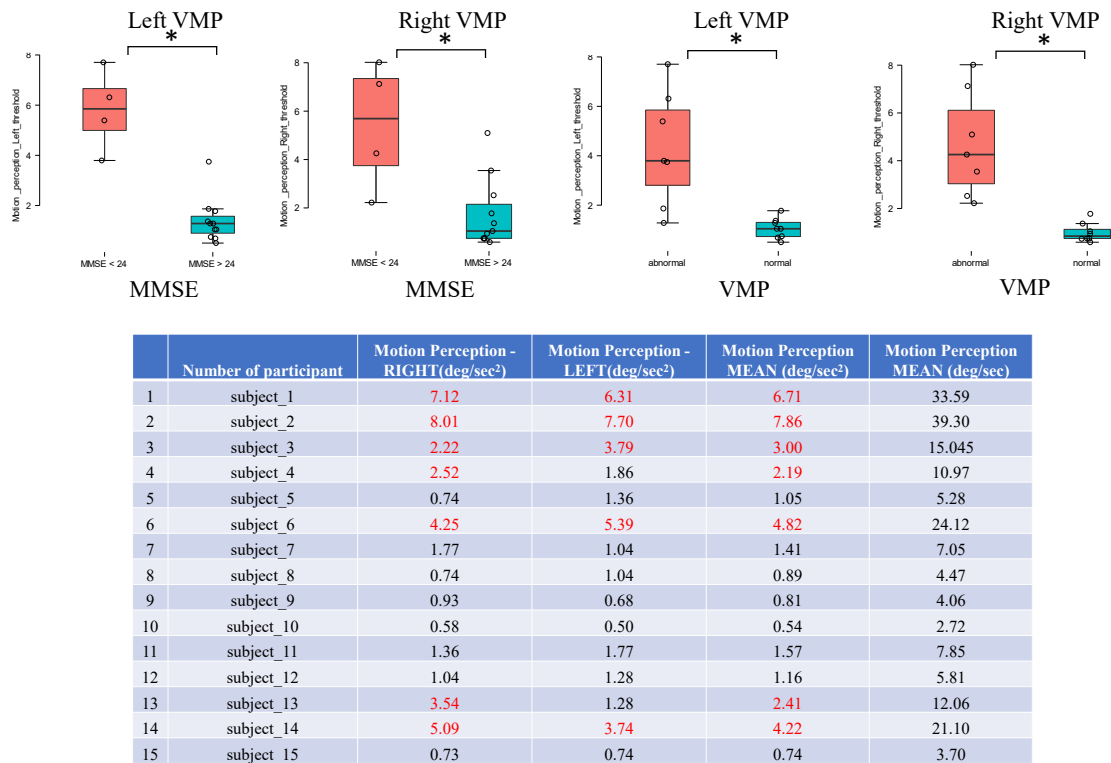


Figure.30. Memory and (balance) patients – VMP performance– Upper row (1st and 2nd plot) presents the MMSE division, whereas the 3rd and 4th plots show the VMP division itself. The table on the bottom row displays the individual performance for all patients for Right, Left, (Right + Left)/2 = Mean in acceleration/velocity (in red colour are the abnormal VMP results).

Test - Memory and (balance) patients	abnormal VMP	normal VMP	MMSE ≤ 24	MMSE > 24
Vestibular motion perception test - Mean	4.22°/s² (IQR 3.06)	0.97°/s² (IQR 0.43)	5.77°/s² (IQR 2.63)	1.16°/s² (IQR 1.03)
Vestibular motion perception test - Right sided	4.25°/s² (IQR 3.07)	0.84°/s² (IQR 0.38)	5.69°/s² (IQR 3.6)	1.04°/s² (IQR 1.40)
Vestibular motion perception test - Left sided	3.79°/s² (IQR 3.04)	1.04°/s² (IQR 0.57)	5.85°/s² (IQR 1.66)	1.28°/s² (IQR 0.67)

Table.8. Memory and (balance) patients – detailed VMP performance based on division method (median + IQR).

When looking at “*all patients*” (before dividing them into sub-groups), there was a strong significant correlation between Right- and Left-sided angular movements (Spearman $\rho = 0.86$, $p < 0.001^{***}$) and no significant difference between them ($W = 70$, $p = 0.59$). Further, Fig. 30. shows the performance of the memory and (balance) patients (i.e. ‘*only patients*’ analysis’) when Right and Left-sided rotational thresholds were divided based on the MMSE score (1st and 2nd plot) or the vestibular motion perception task itself (3rd and 4th plot). Thus, Fig. 30. gives an idea about what “abnormal and normal VMP performance” looked like for the memory and (balance) patients based on their Right-sided, Left-sided and Right + Left)/2 = Mean threshold.

I note that 7 (out of 15) memory and (balance) patients achieved an abnormal VMP, whereas the other 8 memory and (balance) patients retained within normal range VMP threshold (Fig.30). Detailed VMP information based on division is available in Table.8. In addition, there was a notable difference

between the thresholds for abnormally VMP patients versus normally VMP patients, i.e. for Mean threshold ($W = 56, p < 0.001^{***}$), for Left-sided ($W = 53.5, p = 0.004^{**}$) and Right-sided ($W = 56, p < 0.001^{***}$) thresholds.

Further, when dividing the vestibular motion perception performance based on MMSE scores, the difference between the two patients' groups seemed even more apparent (Table.8). Importantly, all patients with $MMSE \leq 24$ had abnormal vestibular motion perception, but not all patients with $MMSE > 24$ had normal vestibular motion perception, as shown in Chapter V. I note that 4 (out of 15) memory and (balance) patients had $MMSE \leq 24$, whereas 11 (out of 15) patients retained within normal cognitive range with $MMSE > 24$. Detailed VMP performance based on this division is available in Table.8. When looking at the difference between Mean, Left-sided and Right-sided thresholds within patients divided as per MMSE score, I note three statistically different results, i.e. for Mean threshold ($W = 43, p = 0.003^{**}$), for Left-sided ($W = 44, p = 0.005^{**}$) and Right-sided ($W = 40, p = 0.018^*$).

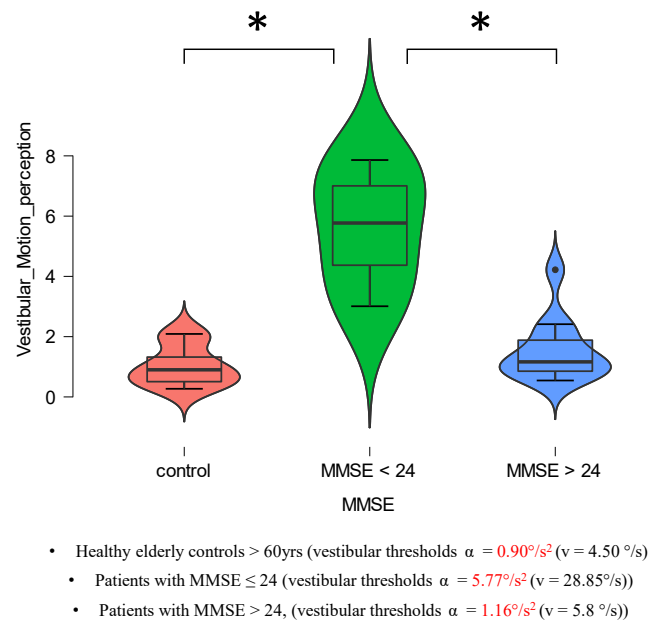


Figure.31. Memory and (balance) patients – Mean VMP test – GROUP results for memory and (balance) patients (divided based on their MMSE score performance) and healthy controls > 60yrs of age (median + IQR). In addition, results in acceleration (α) and velocity (v) for each group are presented.

Further, when comparing memory and (balance) patients' performance to controls (Fig.31), healthy controls > 60yrs achieved VMP thresholds of $\alpha = 0.9^\circ/s^2$ (IQR 0.81), as compared to $MMSE \leq 24$ ($\alpha = 5.77^\circ/s^2$) and $MMSE > 24$ ($\alpha = 1.16^\circ/s^2$). Thus, patients with $MMSE \leq 24$ performed almost 6.4 times worse than controls > 60yrs and nearly 5 times worse than patients with $MMSE > 24$.

As presented in Fig. 31., a Kruskal-Wallis test showed a significant main effect of group ($\chi^2(2) = 10.35, p = 0.006^{**}$), which was driven by the (1) controls > 60yrs - $MMSE \leq 24$ ($p_{(bonf)} = 0.002^{**}$) and (2) $MMSE > 24$ - $MMSE \leq 24$ ($p_{(bonf)} = 0.02^*$).

Notably, the EOG thresholds of memory and (balance) patients were significantly lower than their VMP thresholds ($W = 55, p = 0.002^{**}$).

3.4.2. Visual Reaction Time test

A visual reaction time task (vRT), outside of the VMP test, was performed specifically for memory and (balance) patients with abnormal VMP performance to establish whether a general decrease in their RT could not have contributed to their elevated VMP performance. I calculated the time in seconds from stimulus onset in the visual RT task to the time when the participant pressed the button (the latter indicating a “response”). Consequently, I note a slightly elevated mean RT for abnormal VMP patients at 0.78s (IQR 0.17) as compared to patients with normal VMP performance (0.43s (IQR 0.04) or healthy controls > 60yrs (0.31s (IQR 0.07)). A Kruskal – Wallis showed a main effect of sub-group ($\chi^2(2) = 6.53, p = 0.03^*$). It was driven by the ‘controls > 60yrs and abnormally performing VMP patients’ ($p_{(bonf)} = 0.02^*$), but not by the difference between the two patients’ groups (i.e. abnormally/normally performing VMP patients).

3.5. Vestibular mediated Balance and Vestibular Motion Perception

In this last section, I explored the link between the postural and spatial performance under vestibular guidance for the memory and (balance) patients. Figure 32 shows how the Area 95% confidence ellipse during the soft closed (SC) posturography condition links to the vestibular motion perception performance.

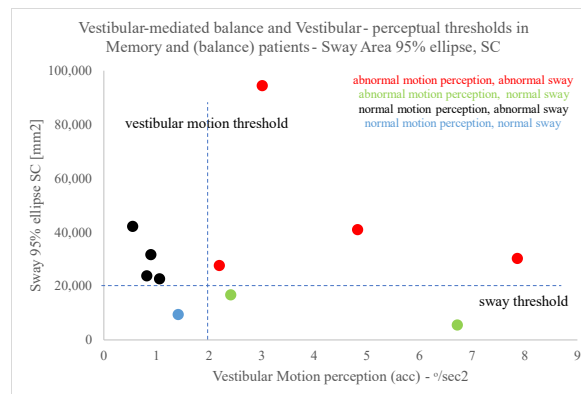


Figure. 32. Vestibular-mediated balance and Vestibular-perceptual thresholds in memory and (balance) patients. The scatter plot displays the performance of memory and (balance) patients based on their overlapping vestibular motion and vestibular-driven Sway performance. The dashed lines present the thresholds for each of the tasks (“average of controls’ performance + 3SD”), dividing the patients into normal/abnormal performance.

Based on Fig. 32, memory and (balance) patients more often showed an impaired rather than preserved balance. Still, VMP did not seem to influence this balance impairment as the number of patients with normal/abnormal VMP and poor balance was equal. Importantly, memory and (balance) patients displayed more vestibular-mediated postural impairment than vestibular self-motion perception impairment. Furthermore, patients with impaired VMP and poor balance were twice as many as those with impaired VMP alone.

For this patients’ cohort, there was no statistically notable correlation between vestibular spatial (via the 95% confidence ellipse SC) and vestibular postural processing based on behavioural testing alone (Spearman $\rho = -0.11, p = 0.73$). Considering, in this analysis, I also measured the RMS AP SC and

RMS L SC, comparison between results confirmed that the area 95% confidence ellipse SC presented as the most sensitive measure towards the vestibular mediated impairment in memory and (balance) patients among the three measurements presented in this Chapter. Still, it did not achieve a notable correlation.

4. Discussion/Conclusion

In this Chapter, I performed behavioural, psychophysics, neuropsychology and neurophysiology tests in a cohort of patients with memory and (balance) complaints. Specifically, I concentrated on the changes of vestibular spatial and vestibular postural processing and a potential link between these two modalities. In addition, I assessed how the cognitive state of these patients affected their spatial and postural performance under vestibular guidance.

My main findings were that (1) vestibular spatial and vestibular postural processing were decreased in memory and (balance) patients, (2) vestibular spatial and vestibular postural modalities did not show a link confirmed via the lack of a significant correlation, which however could be due to the small sample size, (3) vestibular motion perception as a basic vestibular spatial navigation process showed a clear link to the MMSE but not to the ACE test (only Left-sided VMP links to ACE-attention). No such links were established between vestibular derived posturography measures and the two cognitive tests.

Intact vestibular peripheries were an obligatory inclusion criterion for this pilot study. Thus, a clinical examination by a vestibular neurologist, the horizontal vHiT (high frequency horizontal semicircular canal automated testing) and/or an electrooculography (EOG) were performed for the patients.

VMP – EOG – RT

The vestibular motion perception task has never been administered in memory and (balance) patients as of now and, therefore, presents the first example allowing for a more detailed exploration of the vestibular-guided spatial navigation in these patients. It showed that patients with $MMSE \leq 24$ had a decreased VMP threshold and performed almost 6.4 times worse when compared to healthy controls > 60yrs and nearly 5 times worse when compared to patients with $MMSE > 24$. Notably, patients' VMP and EOG thresholds were significantly different, with EOG thresholds being notably lower. Thus, EOG thresholds showed a capacity to remain preserved even when VMP thresholds were not intact, i.e. this suggested some “reflex/perception uncoupling” between EOG and VMP in patients with memory and (balance) complaints (Previc, 2013), (P. Smith, 2013), (Harun et al., 2016). Such uncoupling has been noted in the vestibular literature before, but it is of different nature and will not be discussed here.

In addition, as the visual reaction time (RT) test was slightly elevated for patients, it might have contributed to their generally impaired VMP performance. Still, it is crucial to make a difference between a borderline abnormal/normal VMP threshold and a VMP which is several times higher than the borderline (i.e. the threshold), where RT could not have been the main contributor. Importantly, there was no difference between the total visual RT tests of normally and abnormally VMP patients

(and even for MMSE division), which confirmed that “slower RT were insufficient to explain the elevated vestibular motion perceptual thresholds” (Calzolari and Chepishcheva et al., 2021). In addition, in this cohort of memory and (balance) patients, we must consider the truly multimodal nature of spatial navigation, where some contribution from various sources might exist.

Cognition – VMP – vestibular Sway

The cohort of memory and (balance) patients showed that four participants achieved $MMSE \leq 24$ points and 11 participants scored higher than 24 points. For the second cognitive test, they showed a decreased performance for ACE-Fluency, ACE-Memory and ACE-Attention and less for the ACE-Visuospatial component. The lack of visuospatial impairment at this point might be seen as a positive finding, allowing patients to possibly perform better in the allocentric task of the three-step model (Chapter V). The MMSE score showed a tendency towards a strong negative correlation with the VMP test (Spearman correlation $\rho = -0.78$, $p = 0.002^{**}$). Further, only the Left-sided VMP threshold correlated notably with ACE attention, with attention being a crucial part of spatial orientation. Thus, it contributed to the idea of the Right-hemispheric spatial and vestibular dominance (Atkinson & Egeth, 1973), (Dieterich et al., 2003), but is not enough to imply it.

A study with unilateral vestibular hypofunction (UVH) patients with abnormal (MCI/AD) or normal cognitive level presents one of few examples of a possible link between cognitive decline and vestibular-guided postural instability (i.e. via the eyes-closed surface of confidence ellipse) by showing that AD UVH patients exhibited the most significant sway among participants (Micarelli et al., 2018). However, in my study, no notable correlations were established between the MMSE and the three posturography components (i.e. the Area 95% confidence ellipse, RMS AP and RMS L), irrespective of Sway condition (i.e. HO, HC, SO or SC). Similarly, there were no significant correlations between the ACE test and its five sub-components and the Sway tasks. Still, Sway is not a purely “overlearned” mechanistic task (Manckoundia et al., 2006) but a highly cognitive process, and a bigger cohort of patients is expected to be able to establish the currently missing correlation to cognition.

Vestibular Sway

It is the vestibular Sway condition (i.e. SC) that was the most striking in its difference among groups. Importantly, patients with $MMSE \leq 24$ showed an increased imbalance for the vestibular SC condition for all three posturography measures (i.e. 95% confidence ellipse, RMS AP and RMS L). Notably, this increased Sway remained obvious also for the VMP and patient/control divisions.

Importantly, two patients with $MMSE \leq 24$ fell (i.e. fell safely and were caught) on the “eyes-closed, soft surface” vestibular-guided posturography condition. The latter might be an indication of a (1) central vestibular processing impairment and/or (2) a failure of compensatory mechanisms to cope with the load that the brain was exposed to, as reported for AD patients with unilateral vestibular hypofunction (Micarelli et al., 2018). In the case of a failure of compensatory mechanisms, vestibular

cues would not ameliorate the already high computational burden of the diseased brain but rather impose an additional load (i.e. Hypothesis III). Lastly, a possibility exists that since (3) an excessively increased Sway happened only for the vestibular-driven condition (i.e. SC), this might indicate that compensatory mechanisms were indeed in place and contributing to a more stable performance in the other three conditions (i.e. HO, HC and SO). Even if the postural imbalance in vestibular patients can never be fully compensated by other systems, even after training (Carriot et al., 2015), (K. E. Cullen, 2019), either vision or proprioception could have helped to partially substitute the central vestibular system dysfunction in the other posturography conditions.

Lastly, as concurrent with previous research (Leandri et al., 2009), for the posturography test, my cohort of memory and (balance) patients showed a slightly increased vestibular Sway in the antero-posterior plane (RMS AP) as compared to lateral Sway (RMS L). This was clearly notable for a patient/control and MMSE-based division.

Vestibular Sway – VMP

When concentrating specifically on VMP division for Sway, I note that the difference within patients was most prominent for the SC condition. Still, Fig. 32 showed no statistically meaningful correlation between vestibular motion perception and vestibular-driven Sway performance, possibly because of small sample size.

However, it suggested more vestibular-mediated postural impairment than VMP impairment in my cohort of memory and (balance) patients. Thus, it supported the idea that some general balance deterioration might start before spatial deterioration but remains unnoticed as a feature that shows low specificity and is relatively common in older age (Chepishcheva, 2023). Still, even if postural instability and subsequent falls present a great risk for patients with cognitive decline, such as the Alzheimer's population, scientists reveal that out of 801 Alzheimer's patients at a tertiary AD referral centre, only 48 were sent to a general physical therapist and only 5 (i.e. 0.62%) – for a vestibular physical therapy (Gandhi et al., 2020). Therefore, a significant change in this highly 'non-vestibular strategy' is needed for people with memory impairment to be more adequately supported.

In summary, research discusses that patients with memory impairment might exhibit not only spatial deterioration (Wei et al., 2017), (Wei et al., 2018), (Agrawal et al., 2019) but also decreased postural control, especially when cognitively challenged (Camicioli et al., 1997), (Mesbah et al., 2016), (Montero-Odasso, Manuel et al., 2017). However, balance and spatial orientation, two ecologically important modalities, are seldomly linked. In this Chapter, a putative link through the central vestibular system was suggested between vestibular-driven postural stability- cognition - the vestibular motion perception test, the latter an example of basic spatial orientation under vestibular guidance. Whereas here, the statistically supported data for this link were sparse, I continue to investigate this link further in my research.

Chapter V

Vestibular spatial navigation - Memory and (balance) patients - a pilot study

A. HEALTHY CONTROLS

1. Introduction

Spatial navigation is an essential skill that we require throughout our life for survival. Allocentric and egocentric spatial strategies are a crucial part of our navigation, but they do not develop simultaneously. Egocentrism is found across the whole life span, starting from infancy, whereas allocentrism develops around the age of 7 years (Piaget & Inhelder, 1948). However, with increasing age, healthy elderly show a greater tendency towards an egocentric navigational strategy (Moffat, 2009), (Harris & Wolbers, 2013), (Lester et al., 2017) as they start to use their allocentric skills less. This way, the process of strategy selection resembles an inverted U curve (Ruggiero et al., 2016), with childhood and old age relying primarily on egocentric skills and adolescents and adults – on allocentric.

A progressive loss of spatial navigational abilities has been observed with increasing age (Wilkniss et al., 1997), (Moffat et al., 2001), (Iaria et al., 2009), (Moffat, 2009), (Lester et al., 2017), (Fernandez-Baizan et al., 2019), along with spatial working memory decline (Holden & Gilbert, 2012). Age-related differences have been observed in brain regions crucial for spatial navigation, i.e. the hippocampus, parahippocampal gyrus, retrosplenial cortex and, more generally, the temporo-parietal regions.

Empirical data as up to date recognise navigation as an aspect of cognitive function that is at risk during healthy ageing (Moffat, 2009). However, spatial performance in the elderly does not show only decline (Meade et al., 2019). Interestingly, when able to suppress the activity in the default mode network (DMN), as the younger adults did on the more demanding spatial fMRI tasks, the older adults' performance also improved (Park, 2010).

However, a lack of understanding about these mechanisms is still present even though research has made great advances in the field of spatial navigation during healthy ageing. One possible reason might be the frequent omission of a crucial part of the spatial navigational process - the vestibular signal, which plays a central role in rotational movements, especially in the dark (Kaski et al., 2016). Cognitive decline and peripheral vestibular dysfunction have shown their effects on spatial navigation also in healthy elderly (Bigelow & Agrawal, 2015), contributing to their decreased activity of daily living (Semenov et al., 2015). While a possible connection between vestibular loss and (1) decreased topographical memory (Previc et al., 2014) and (2) visuo-spatial abilities is also reported (Bigelow et al., 2015), additional research is needed to shed light on the link between spatial, cognitive and vestibular processing (peripheral and central) as we age.

Interestingly, in a recent study, healthy elderly (mean age = 77y) were examined for their peripheral vestibular function and invited to participate in a spatial task in a rotation chair. The results demonstrate that HE with bilaterally low horizontal VOR or bilaterally absent utricular function were less accurate than those with intact vestibular peripheries (Anson et al., 2021). Considering the often-seen difference

between the results of the video head impulse test and the calorics test, researchers suggest that either the bilateral horizontal semicircular canals or the utricles might contribute to the spatial angular orientation (Anson et al., 2021). This study is one of only a few available examples where results could warrant a data-based discussion about the central vestibular processing in HE (Chepishcheva, 2023). However, as presented, the experimental design of the spatial rotation test warrants further clarifications concerning the rotational movements themselves/their timing and the presentation of the allocentric cues. Thus, ambiguity about the results made it impossible to gain further knowledge about central vestibular-guided navigation of healthy elderly.

In summary, while much is known about non-vestibular and a fair amount about peripheral vestibular spatial processing, much is ahead to be discovered regarding central vestibular spatial processing and its contribution to our everyday activities during healthy ageing. In this sub-Chapter, I tested the feasibility of a three-step central vestibular spatial model (i.e. Hypothesis II) by inviting three groups of healthy controls (< 40yrs, <(40-60)>yrs and >60yrs) and observing the changes in their vestibular-guided egocentric and allocentric (egocentric+) spatial orientation with increasing age. My objectives were as follows:

1. To investigate if it was feasible to look at the vestibular-guided spatial navigation as a three-step process testing healthy controls from three age groups?
2. To investigate how the computational burden, we expose the brain to affected our spatial orientation under vestibular guidance during healthy aging?

2. Materials and Methods

2.1. Healthy controls – Recruitment

I tested 60 healthy controls, which I separated into three groups based on age: (<40yrs, age range 18-39, n = 30), (between 40 – 60yrs, n = 14) and (> 60yrs, age range 61-88, n = 16). Importantly, not all participants managed to participate in all tasks (i.e. JOYSTICK and/or MOUNTAIN task) based on their availability. A complete list of healthy participants for the JOYSTICK and MOUNTAIN task and their descriptive statistics are available in Appendix.

2.2. Methodology

To address my hypothesis and its objectives, in this section I looked at the feasibility of a three-step spatial model under vestibular guidance testing healthy controls from three age groups. This was an important step in ensuring that subsequent patient testing was possible and reasonable. Later (in the second part of this Chapter V), I take the three-step model a step further by inviting patients with memory complaints to take part in my study and thus address the second part of my Hypothesis II.

The hypothesised three-step spatial model under vestibular guidance consists of three tasks (Fig.33),

with increasing difficulty: (1) vestibular motion perception task (VMP), (2) vestibular egocentric task and (3) vestibular allocentric (egocentric+) task.

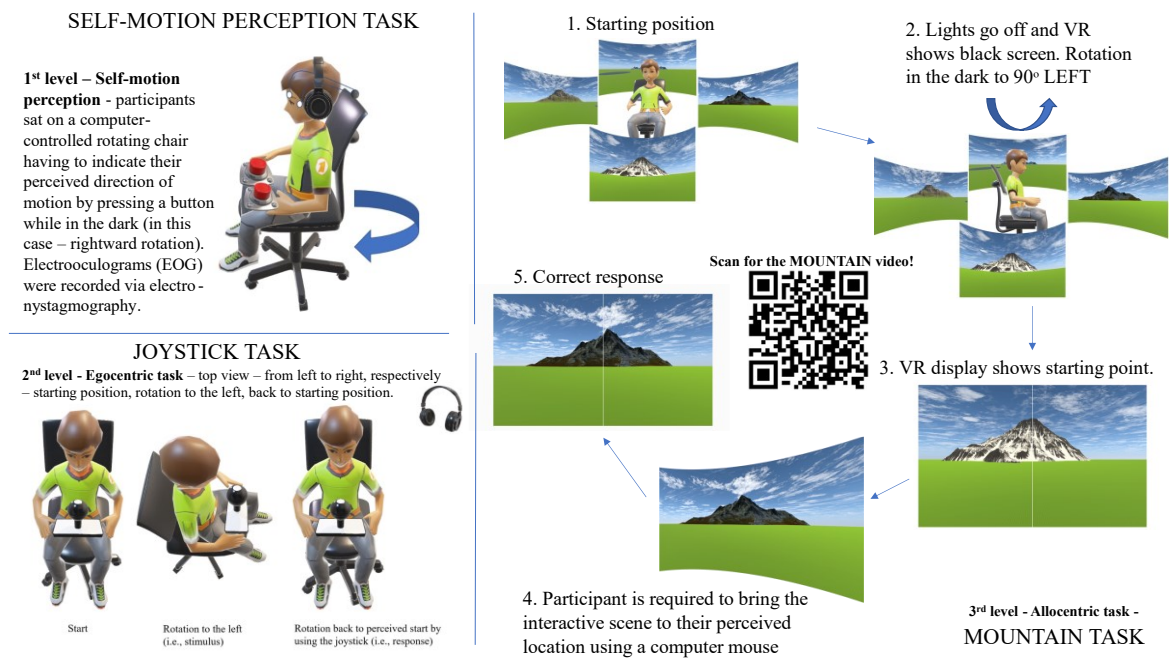


Figure.33. The three-step spatial model. Please scan the QR code for a video.

Whereas the VMP task is a less-known spatial task in the non-vestibular research community, it is a well-established task for vestibular psychophysics. In our vestibular-based group, we previously tested the feasibility of the vestibular motion perception test with the same testing equipment and established “normal range” performance to be with acceleration $\alpha \leq 2.02 \text{ }^\circ/\text{sec}^2$ (i.e. controls’ average of $0.77 \text{ }^\circ/\text{sec}^2 + 3\text{SD}$) for controls with mean age = 40.78yrs $\pm$ 14.75 (Calzolari and Chepishcheva et al., 2021). Thus, whereas the validity of the VMP task, in the same version as used in my study, was already established in previous research (Seemungal et al., 2004), (Kaski et al., 2016), (Calzolari and Chepishcheva et al., 2021) both scientifically and clinically, the feasibility of the newly adapted egocentric (i.e. JOYSTICK) task and newly developed for this study allocentric (i.e. MOUNTAIN) task, was still to be established. Importantly, whereas the JOYSTICK task did not require significant developmental changes and went only through two phases, adapted from (Brevern et al., 1997), the MOUNTAIN task went through five stages of developmental improvement as a newly developed task, and the relevant results for all phases of development are presented in Appendix. From here onwards, when discussing the JOYSTICK and MOUNTAIN tasks, I shall report only about the participants and their data from the last approved phase of the task, i.e. phase II (JOYSTICK task) and phase V (MOUNTAIN task), based on which I established the baseline of healthy individuals’ performance.

Based on the inclusion criteria for an intact peripheral vestibular system, all controls underwent a peripheral vestibular system examination, either via the video head impulse test (vHiT) or via the VMP

task itself, through the electrooculogram (EOG). As all my healthy participants performed within a normal range of this established threshold, their results present no further interest other than that “they were eligible to remain in the study as presenting with an intact peripheral vestibular function”. Thus, after establishing a normally functioning peripheral vestibular system, my healthy participants were ready to participate in the 2nd (egocentric) and 3rd (allocentric (egocentric +)) level of the three-model spatial task.

Please refer to Chapter II for a detailed explanation of the tasks used in this Chapter (Fig. 33), alongside inclusion criteria for the healthy participants recruited.

2.3. Statistical analysis

The small sample size and the Shapiro-Wilk test confirmed the use of non-parametric statistics. For all analyses, the alpha-level was set at 0.05. Results are presented as median + IQR.

In the spatial analysis to follow, I present the same datasets from two different perspectives, i.e. (1) angle-based, and (2) %Error, to ensure results, even if from a small cohort, are correctly interpreted and consistent between analyses. In addition, in Appendix, I present Slope-based analysis, R^2 , absolute Error, absolute GAIN plots, alongside Joystick and Mountain task performance with respect to AGE and separately a comparison between Joystick/Mountain slopes.

JOYSTICK task:

A detailed investigation of the performance of the three age-groups was conducted for the vestibular egocentric task.

A group-level comparison between the six tested angles (i.e. 30°, 60°, 90°, 120°, 150° and 180°) for the three age groups was performed. First, I investigated the difference in Right- and Left-sided rotations, irrespective of angle using the Wilcoxon signed-rank test. In case of a significant difference, further investigation was performed by Friedman’s test and a subsequent Conover’s test with Bonferroni corrections by dividing the results based on the beep delay (i.e. 1.5s or 6.5s).

For all age groups, the difference in some specific angles was further analysed with a ‘between groups analysis’ (using the Kruskal-Wallis test) or ‘within groups analysis’ (using the Wilcoxon signed-rank test between two angles).

Next, I performed %Error analysis. First, within group %Error difference of beep delay was estimated using the Wilcoxon signed-rank test. Then, %Error analyses (irrespective of beep delay) were performed between groups using the Kruskal-Wallis test and subsequent Dunn’s Post Hoc with Bonferroni corrections. It was followed by a more in-depth investigation via Friedman’s test based on beep delay (i.e. 1.5s or 6.5s) among the three age groups and completed by Conover’s Post Hoc.

The JOYSTICK performance of the healthy controls > 60yrs informed the baseline for ‘normal JOYSTICK performance’ in the analysis of memory patients presented in section B of this Chapter V.

MOUNTAIN task:

A detailed investigation of the performance of the three age-groups for the vestibular allocentric (egocentric+) task was conducted.

A group-level comparison between the six tested angles (i.e. 30°, 60°, 90°, 120°, 150° and 180°) for the three age groups was performed. First, I investigated the difference in Right- and Left-sided rotations, irrespective of angle using the Wilcoxon signed-rank test.

Further, %Error analysis was performed. First, within group %Error difference of beep delay was estimated using the Wilcoxon signed-rank test. Then, %Error analyses (irrespective of beep delay) were performed between groups using the Kruskal-Wallis test.

The MOUNTAIN performance of the healthy controls > 60yrs informed the baseline for ‘normal MOUNTAIN performance’ in the analysis of memory patients presented in section B of this Chapter V.

3. Results

3.1. JOYSTICK task

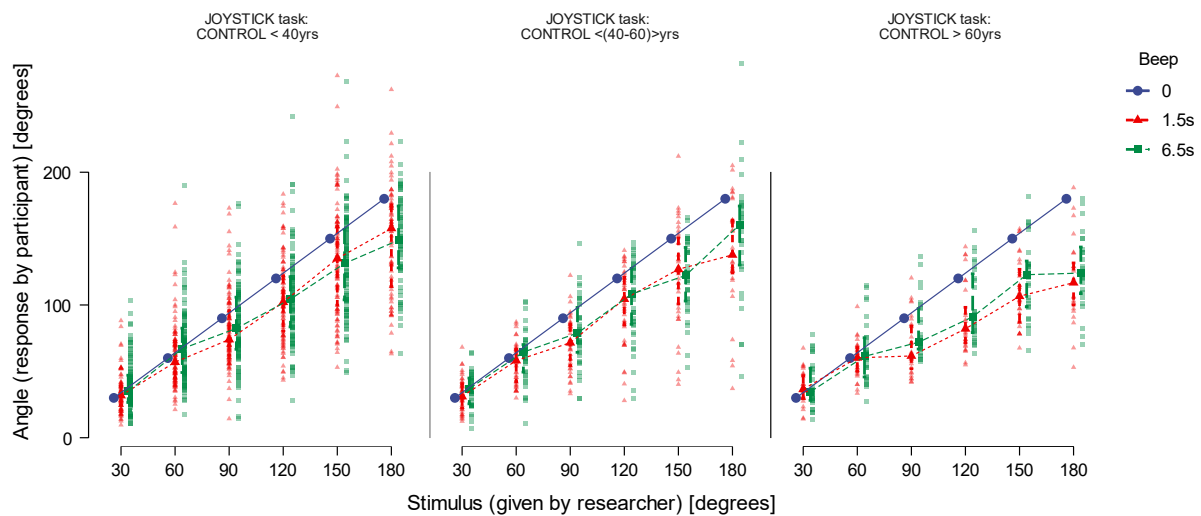


Figure.34. Healthy controls age groups (<40yrs, <(40-60)>yrs, >60yrs) – Individual and Group JOYSTICK task performance. The X-axis displays the possible angles of rotation given as stimulus – (30° – 180°), in steps of 30°, whereas the Y-axis – the response given by the participant as a result of the stimulus. On the plot, with blue colour, exactly at 45°, is the ideal Slope of 1 with respect to which the participants' performance is estimated. The plot presents individual performance based on the delay of the beep tone, either 1.5s or 6.5s, with the small green quadrats and red triangles being individual performances. Group performance is displayed with medians and IQR.

Figure 34. displays the performance of the healthy controls divided into three groups (<40yrs, <(40-60)>yrs, >60yrs), irrespective of the direction of rotation, i.e. Right and Left rotations are combined. In addition, performance is divided by beep tone delay of 1.5s and 6.5s. Interestingly, Right- and Left-sided rotations (please check Appendix) were not statistically different for healthy controls <40yrs and <(40-60)>yrs, with the Wilcoxon signed rank showing ($W = 13$, $p = 0.68$) and ($W = 4$, $p = 0.21$), respectively. However, for the controls >60yrs, the comparison between Right- and Left-sided rotations

was notable ($W = 0.00$, $p = 0.03^*$), with a notable Friedman's test ($\chi^2(3) = 10.2$, $p = 0.01^*$, Kendall's $W = 0.97$), but subsequent insignificant Conover's Post Hoc investigation.

The control group <40yrs in Fig. 34. displayed the closest to the Slope of '1' group performance compared to the other two age groups, although individual performance was varied, with hypometric and hypermetric responses being present. The control group <(40-60)>yrs displayed similar group performance as the <40yrs group, but individual variation in performance did not vary as much on the hypermetric side as it did on the hypometric side. In contrast to the controls mentioned until now, controls >60yrs showed a distinct hypometric group and individual preference, with angles above 120° showing a tendency for hypometricity.

Attention is drawn to 180°, which visually differed among the three age groups but not statistically, with a Kruskal-Wallis test being insignificant $\chi^2(2) = 5.11$, $p = 0.07$. In addition, a “within group” comparison for the 150° and 180° for controls >60yrs group was conducted, and the Wilcoxon test ($W = 1$, $p = 0.06$) revealed no statistical difference between the two angles, both when beep delays were combined and when they were separated in 1.5s and 6.5s. (Friedman's test $\chi^2(3) = 3.2$, $p = 0.36$).

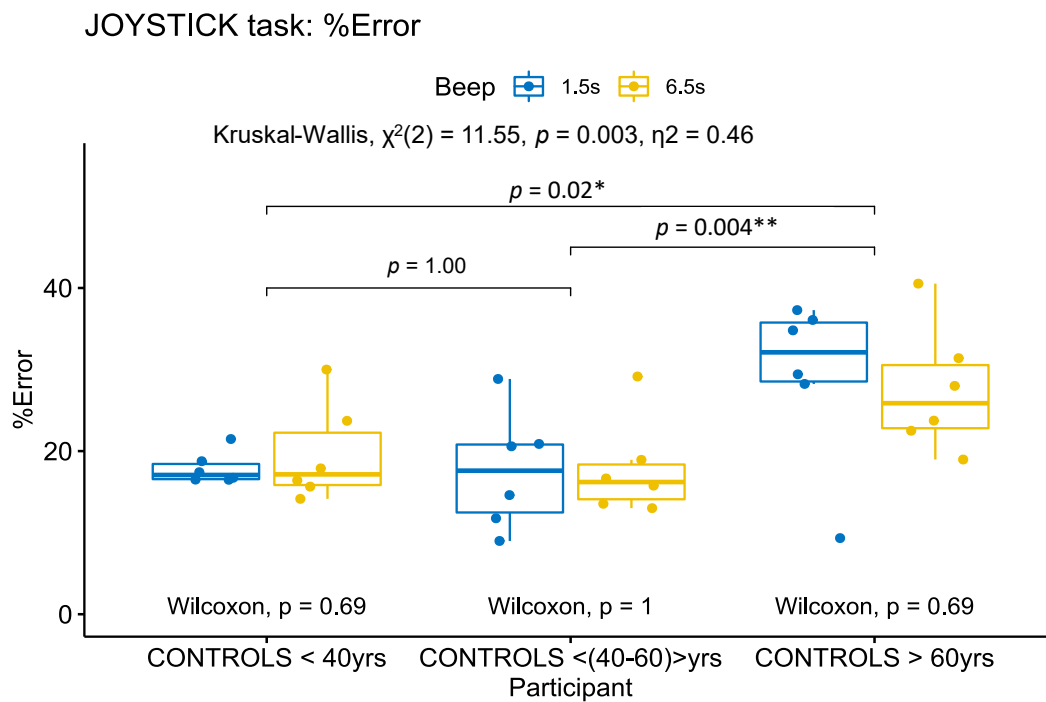


Figure.35. Healthy controls age groups (<40yrs, <(40-60)>yrs, >60yrs) - Group JOYSTICK task performance based on %Error (%error = [(response angle – stimulus)/stimulus] * 100). The X-axis displays the participant type, i.e. the three control groups, whereas the Y-axis – the %error derived from their performance. The boxplots are further divided by the delay in beep tone, i.e. 1.5s or 6.5s. A Kruskal-Wallis test result between the three control groups is displayed on top of the graph, whereas below it are the results from the multiple comparison analysis. Lastly, within group Wilcoxon tests were calculated and displayed at the bottom of each control group.

Further, the %Error analysis showed to be another meaningful way to present this small dataset (Fig. 8.4). Percentage Error is calculated based on the following formula: (% error = [(response angle – stimulus)/stimulus] * 100)]. Based on the data presented in Fig.34, it was expected that controls >60yrs would show the most significant %Error compared to the other participants, with 1.5s angular

movements displaying a more considerable group %Error than 6.5s. Still, they achieved no significant within-group results, as demonstrated by the Wilcoxon test in Fig. 35.

Further to Fig. 35, a Kruskal – Wallis test between the three groups showed a significant main effect of group ($\chi^2(2) = 11.55, p = 0.003^{**}, \eta^2 = 0.46$). The latter was driven by the difference with controls >60yrs group and showed that these results remain significant after multiple comparisons (Fig.35).

To further investigate the statistical relationships among the age groups %Error, this analysis was concluded with a significant Friedman’s test looking into repeated measures of 1.5s and 6.5s across %Error: ($\chi^2(5) = 16.19, p = 0.006^{**}, \text{Kendall's } W = 0.34$) and a subsequent Conover’s Post Hoc test (table in Appendix). The Conover’s test revealed several significant comparisons between “<40yrs (1.5s) and >60yrs (6.5s)”, and several for “<(40-60)>yrs and >60yrs”, which, however, did not remain statistically notable after Bonferroni corrections.

3.2. MOUNTAIN task

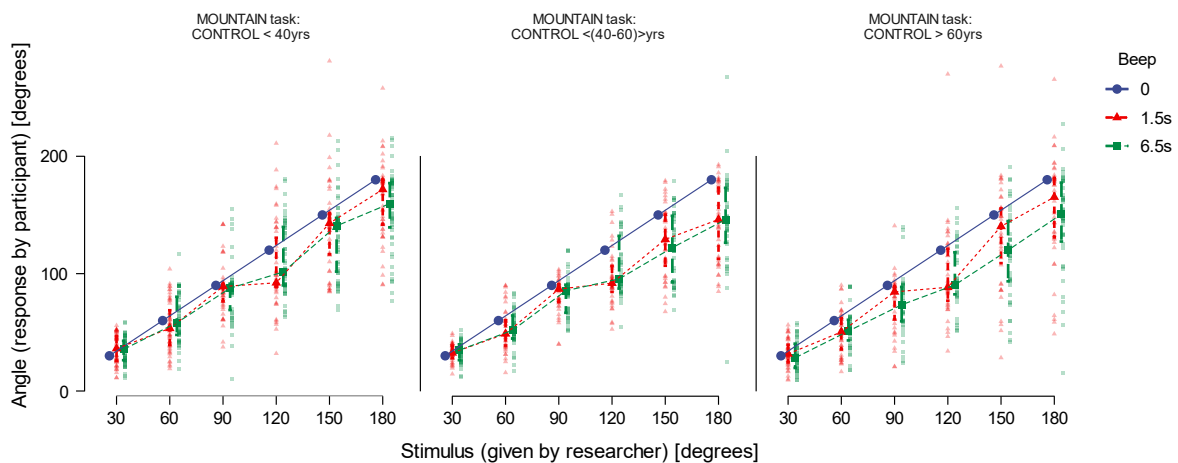


Figure.36. Healthy controls age groups (<40yrs, <(40-60)>yrs, >60yrs) – Individual and Group MOUNTAIN task performance. The X-axis displays the possible angles of rotation given as stimulus – (30° – 180°), in steps of 30°, whereas the Y-axis – the response provided by the participant as a result of the stimulus. On the plot, with blue colour, exactly at 45°, is the ideal Slope of 1 with respect to which the participants' performance is estimated. The plot presents individual performance based on the delay of the beep tone, either 1.5s or 6.5s, with the small green quadrats and red triangles being individual performances. Group performance is displayed with medians and IQR.

After discussing the healthy controls’ egocentric performance, here, I discuss their allocentric (egocentric+) performance for the MOUNTAIN task. The Wilcoxon signed rank test did not reveal any statistical difference between Right- and Left-sided allocentric rotations for either of the three groups of controls, i.e. controls <40yrs ($W = 6, p = 0.43$), controls <(40-60)>yrs ($W = 3, p = 0.15$) or controls >60yrs ($W = 5, p = 0.31$).

Figure 36. displays a combined Right- and Left-sided rotation performance of the healthy controls divided by age groups (<40yrs, <(40-60)>yrs, >60yrs) for the MOUNTAIN task. In addition, performance is divided by beep tone delay of 1.5s and 6.5s. *By observation*, all three groups displayed

similar performance up to 120°, whereas for 150° and 180°, the control groups <40yrs and >60yrs showed a more accurate estimation of angular movements and allocation of position than <(40-60)>yrs group, although the difference was not statistically significant. Still, it is of note that the 1.5s performance showed a slight tendency for more accurate responses as compared to 6.5s. beep tone delay, which was nevertheless not statistically notable. In addition, healthy controls >60yrs no longer showed a hypometric performance (as for the JOYSTICK task) compared to the other control groups. No further statistical difference analysis between angles between groups (e.g. 150° - 150° - 150°) was conducted as performance was homogenous.

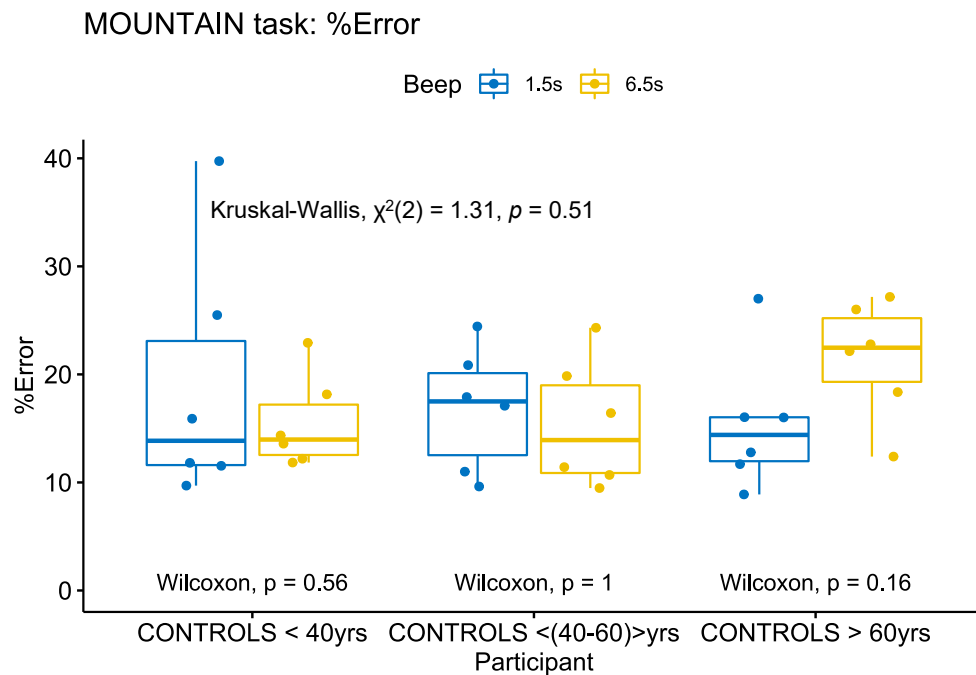


Figure.37. Healthy controls age groups (<40yrs, <(40-60)>yrs, >60yrs) – Group MOUNTAIN task performance based on % Error (%error = [(response angle – stimulus)/stimulus] * 100). The X-axis displays the participant type, i.e. the three control groups, whereas the Y-axis – the %error derived from their performance. The boxplots are further divided by the delay in beep tone, i.e. 1.5s or 6.5s. A Kruskal-Wallis test result between the three control groups is displayed on top of the graph. Lastly, within groups Wilcoxon tests were calculated and displayed at the bottom of each control group.

Next, I present the %Error analysis (Fig. 37) (%error = [(response angle – stimulus)/stimulus] * 100). The difference between the three groups was minimal, as analysis has shown so far, and a Kruskal – Wallis test between the three groups confirmed no statistical difference ($\chi^2(2) = 1.31, p = 0.51$). Examining the difference within groups via the Wilcoxon signed rank test resulted in no statistical difference between delays of beep tone (i.e. 1.5s or 6.5s) for the three age groups, as shown in Fig.37.

4. Discussion

In this pilot study, I presented a three-step model of vestibular spatial orientation, comprising three tasks with increasing difficulty: (1) vestibular motion perception task (VMP), (2) egocentric (JOYSTICK) task and (3) allocentric (egocentric+) (MOUNTAIN) task. The feasibility of the VMP test was already

established in previous studies (Seemungal et al., 2004), (Kaski et al., 2016), (Calzolari and Chepishcheva et al., 2021) and was not further discussed here. However, to test the feasibility of the egocentric and allocentric level of the three-step model, I first started testing healthy participants that I divided into three groups based on their age: <40yrs, <(40-60)>yrs and >60yrs.

JOYSTICK task

The egocentric task is a form of an uncalibrated task, performed without any visual help while in complete darkness. When investigating the difference between Right- and Left-sided rotations, only the healthy controls >60yrs showed a significant difference between directions of rotations, indicating that their spatial processing might differ compared to their younger counterparts.

The three age groups demonstrated distinct egocentric behaviour based on the angle graphs. Participants <40yrs and <(40-60)>yrs showed a close to Slope = 1 (i.e. highly precise) group estimate for angular movements of 30° and 60°, irrespective of the time delay of the beep tone, i.e. 1.5s. or 6.5s. Still, at the same time, they showed a group-level tendency towards hypometricity after that (i.e. 90°-180°). Further, the variability of individual angular rotation responses, i.e. hypometric or hypermetric, is noted, especially for the younger adults <40yrs, while more hypometricity was seen for the <(40-60)>yrs group. In contrast, the healthy elderly adults >60yrs showed a marked hypometric performance for angles bigger than 90°, thus greatly underestimating the amount of travelled distance. This concurred with previous research indicating a general hypometricity tendency for bigger angles (Petzschner & Glasauer, 2011) and especially for healthy elderly up to 65yrs of age who experienced perceptual decrease for angular movements between 120°-180° (Brevern et al., 1997). Interestingly, even if not statistically notable, there was a tendency for the temporal delay of 6.5s to lead to less hypometricity in the rotational responses of the elderly >60yrs than a temporal delay of 1.5s. This might indicate (1) a longer processing time needed to correctly estimate the travelled distance or (2) that events closer in time were less distinct and thus recalled less precisely because of possible interference. The latter would possibly indicate that temporal representations themselves did not decay over time, but rather were less easily accessible because of this interference with neighbouring events in time, as discussed in (Manohar et al., 2017).

While it is unclear which might be the contributor to the temporal delay performance, a general tendency for a decline in the spatial navigational abilities in healthy elderly, as also observed in the JOYSTICK task, is what studies exploring navigation in human healthy ageing have reported (Wilkniss et al., 1997), (Moffat et al., 2001), (Iaria et al., 2009), (Lester et al., 2017), (Fernandez-Baizan et al., 2019). Interestingly, I further investigated the relationship between angles of 150° and 180° within the controls >60yrs to find that they were not statistically different, which might suggest that they might be perceived equally by the healthy elderly. Another possibility was that a bigger sample size of the cohort would be able to make this difference notable.

Such a reduction in perceived angular rotations was not unexpected, mainly due to the start of some possible decrease in the semicircular canal functioning. Interestingly, a study discussing an active navigational task in healthy ageing (mean age + SD = 69.8yrs + 13.6) suggested a statistically notable link between the decrease in saccular function (otoliths) and an impaired angular and distance perception in the Triangle Completion test (Anson et al., 2019). This was not an expected result, given that the otolith impairment is not directly linked to angular perception, especially when the authors reported no link between semicircular canal function and heading errors. Even if (1) "saccular stimulation leads to widespread cortical activation, including the posterior insular cortex, the inferior parietal cortex, the intraparietal sulcus, and temporo-parietal junction", as discussed in (Harun et al., 2016) and even if (2) vertical movements/gravitational cues are indeed a crucial part of our spatial navigation, the result of the study was unclear. This is especially true when considering that the task they used, did not involve any vertical exercises but was the standard triangle completion task in the horizontal plane. Thus, the implication of the saccular function alone in this "complex outcome" warrants further investigation, and the authors were cautious of overinterpretation by suggesting that this link was not causal and might be due to visuospatial cognitive impairment and a possible reduction of multisensory perception that could be in place (Anson et al., 2019).

Some further scientific efforts from the same research group stressed a link between saccular impairment and hippocampal volume loss in healthy ageing (Kamil et al., 2018). In addition, a detailed investigation of the volume and shape of vestibular-related regions showed a reduced volume of the hippocampus and the entorhinal cortex corresponding to a decreased saccular function in the elderly (A. Jacob et al., 2020). Even if these results prove to be of interest, further studies are needed to establish such a central role for the saccule in the elderly, primarily horizontal navigation, where little climbing (mainly limited to climbing the stairs) or little extreme vertical (up-down) activities are performed.

It is of note that in my study, the cVemps test for saccular function was not a part of my testing battery. Nevertheless, my healthy elderly cohort displayed a within-normal range peripheral vestibular functioning via the horizontal video head impulse test (vHiT) or the vestibular motion perception test (combined with an EOG recording). As passive chair rotations around the body axis involve horizontal movements in the yaw plane, I mainly concentrated on investigating the integrity of the peripheral vestibular system via the lateral (horizontal) semicircular canal. In addition, "the vestibular nuclei combine semicircular canals and otoliths afferents with an importance that is frequency dependent – canals inputs are more heavily weighted at low frequencies" and the otoliths – at higher frequencies (K. E. Cullen, 2019). Therefore, using this specific raised cosine chair rotation algorithm with relatively low-frequency chair rotations, I considered it an appropriate way to approach the testing of the peripheral vestibular system integrity in my healthy volunteer cohort/my study. However, considering saccular integrity is reported to remain stable only up to the age of 50-60yrs (Ji & Zhai, 2018), some might argue that the testing of the saccular function might be helpful and serve as a timely indicator.

Still, older adults' cVemps (saccular testing) might not always be present (Piker et al., 2013), thus limiting its ability to reveal a potential vestibular dysfunction.

Nevertheless, research is yet ambiguous about the exact reason for the spatial decline in healthy elderly, with a recent study suggesting that with ageing, the source of path integration errors might be more due to noise accumulating in the velocity input and not so much because of noise in the velocity integrator itself (Stangl et al., 2020). Still, path integration errors might also differ based on whether they are purely encoding errors (regardless of the required response) or they are execution of response errors (Chrastil & Warren, 2017). What is more, scientists suggest looking even higher up in the central vestibular processing as “often the deterioration in vestibular functioning relates to how the signal is processed by the brain circuits rather than an impairment in the sensory transduction process” (Arshad & Seemungal, 2016).

The last part of my egocentric (i.e. JOYSTICK) analysis, the %Error analysis, also discriminated on a statistically significant level between controls >60yrs and the other two control groups. In addition, R^2 showed that JOYSTICK data across all three control groups fit well a linear regression model and were not statistically different (plot in Appendix). Interestingly, %Error Dunn's test revealed a more significant difference between healthy controls >60yrs and the other two age groups, i.e. the <(40-60)>yrs and the <40yrs. This way, I suggest that the egocentric task is a sensitive task to discriminate between healthy controls' age groups, especially as compared to the healthy elderly >60yrs. By doing so, it differentiates younger adults from the elderly, as the level it covers (i.e. egocentric) in the spatial navigational process might be where diversion/deterioration in spatial performance starts.

MOUNTAIN task

After having summarised the egocentric performance, I now discuss the allocentric (egocentric+) spatial performance, which research has shown to be especially dependent on hippocampal and parahippocampal structures. Still, age-related differences in the brain have been observed not only in the hippocampus and the parahippocampal gyrus but also in other regions involved in spatial navigation— the retrosplenial cortex and, more generally, the temporo-parietal regions. However, as the vestibular system has been shown to contribute to spatial navigation via the hippocampus, entorhinal cortex and the cerebellum, its suggested decline in both the semicircular canals and otoliths with increasing age (Agrawal et al., 2009), (Ji & Zhai, 2018) is expected to further contribute to an even higher degree of spatial disorientation.

Still, in this study, the allocentric task seemed to be unable to discriminate between healthy controls' age groups, with healthy elderly >60yrs performing similarly to the rest of the age groups, i.e. controls <40yrs and <(40-60)>yrs. These results were confirmed via the %Error and angle-based analyses. Thus, even if the load, i.e. cognitive and spatial processing, for this task was greater than for the egocentric task, this did not allow it to discriminate between cognitively intact individuals, such as those that

participated in my study, irrespective of their age. One possible reason might be that my allocentric task was not a pure allocentric task, but a combination of egocentric and allocentric modalities. Thus, the egocentric component in combination with the allocentric component might have become a source of additional spatial cues that the healthy and cognitively intact brain of my participants was able to use in an advantageous way to achieve a better performance. Thus, as the ageing peripheral vestibular system is also a factor to be taken into account, at this point, I considered that age and the vestibular system were two independent factors contributing to spatial orientation, similar to (Xie et al., 2017).

Therefore, when comparing the egocentric and allocentric tasks, only the egocentric task managed to discriminate between healthy elderly > 60yrs and the other two groups of participants. Thus, my results were similar to a previously published study about healthy elderly subjects that were divided into three age groups (62-66yrs, 67-74yrs and 75-81yrs) (Fernandez-Baizan et al., 2019). There, only the egocentric task could discriminate among the three groups, but not the allocentric (Fernandez-Baizan et al., 2019), suggesting the egocentric level examination was a more sensitive task, especially for the elderly participants. Possibly, my allocentric task (i.e. MOUNTAIN task) is able to be a sensitive task only in cognitively impaired participants.

Research often discusses decreased visuospatial abilities as an important factor contributing to the spatial performance in the elderly (Bigelow et al., 2015). Still, this pattern varies among the elderly, and for my healthy elderly participants >60yrs, visual landmarks had potentially contributed to the more precise updating of internally derived angular displacement perception. Thus, while they turned vision into a possible contributor to the improved allocentric performance compared to their highly hypometric egocentric performance, other factors should not be excluded.

However, healthy elderly often show highly accurate spatial performance, as many of their functions are still preserved, and it is not always that they perform abnormally compared to younger adults. A study reported that if healthy elderly were given the chance to actively navigate during training instead of passively encoding while seated in a chair in front of a computer screen, they actually showed a significant improvement when re-tracing the learned virtual route (Meade et al., 2019). Even if the authors did not discuss the vestibular system as a possible contributor to this improvement of results, it is worth mentioning that the natural exploration of the environment contributed to the generation of multiple sensory cues, among which also vestibular cues, which in turn might have helped re-trace the virtual route. Thus, compensatory mechanisms are evidently in place to keep normally ageing individuals able of successful navigation. This stresses the great flexibility and plasticity of the human brain, even during the process of ageing. Similarly, in my study, some possible contributors to the allocentric healthy elderly's performance managed to mask some minimal allocentric impairment. In contrast, these contributors seemed unavailable at the egocentric level, and thus a slight abnormality via the hypometric behaviour started to be evident.

Still, it is essential to note that studies also report about (1) healthy elderly showing a greater preference

for egocentric skills as compared to allocentric during navigation, possibly because of their allocentric skills being partially impaired. Further, there is also (2) some suggested allocentric skills impairment compared to egocentric skills and an impaired transition between the two strategies (Harris & Wolbers, 2013), (Colombo et al., 2017). The latter might be due to dysfunction in the prefrontal-noradrenergic network that is responsible for coordinating switching behaviour (Harris & Wolbers, 2013). Consequently, based on different study reports, spatial behaviour interpretation in healthy ageing might be ambiguous, but differences with the younger populations are usually noted.

Thus, the reasons for the decline in spatial navigation are various, and it does not seem appropriate when researchers discuss it as a purely cognitively related decline. Spatial navigation has proven its complex nature and its involvement in various modalities, which allow for multiple compensatory mechanisms to be in place to keep normally ageing and cognitively intact elderly individuals able of successful navigation.

In summary, the three-step spatial model showed its feasibility to be used as a test in healthy controls across different age groups and suggested its potential to be a possible test also in patients with central affections of the nervous system. Next, I look at the implementation of this model in patients with memory and (balance) complaints who visited a general Neurology clinic or a Memory clinic because of their medical issues.

B. MEMORY and (BALANCE) PATIENTS

1. Introduction

Whereas non-vestibular spatial research in AD patients is abundant, vestibular-driven studies are rather sparse. Still, as discussed in detail in (Chepishcheva, 2021), research has shown that vestibular dysfunction is associated with hippocampal damage (P. Smith, 2017), and subsequent spatial impairment is to be expected. This makes vestibular-guided spatial studies especially valuable for our better comprehension of the general model under which spatial orientation deteriorates in patients with cognitive decline.

In one of the few vestibular studies in Alzheimer's patients, researchers examined saccular, utricular and semicircular canal function (i.e. the peripheral vestibular system) in MCI and AD patients. They observed more expressed impairment in the AD patients in the otoliths (i.e. saccule and utricle) and not in the semicircular canals when compared to healthy elderly (Harun et al., 2016). In addition, AD patients showed more significant peripheral vestibular impairment (in the otoliths only) than MCI (Harun et al., 2016). Further, a more recent study (Wei et al., 2018) suggested yet once more that saccular vestibular loss may contribute to spatial deterioration in AD patients, irrespective of whether a general cognitive decline is already present or not. Thus, as research has shown that AD patients with vestibular loss (most probably authors meant "peripheral" vestibular loss) have "disproportionate levels

of spatial cognitive impairment relative to AD patients without vestibular loss” (Agrawal et al., 2019), it was suggested that vestibular dysfunction might lead to a “spatial” subtype of AD (Wei et al., 2018), (Agrawal et al., 2019). Still, considering the measuring of the saccular function via the cVemps is an indirect measure of otolith activity (Ji & Zhai, 2018), the results in these already rare vestibular studies must be interpreted with caution (Chepysheva, 2022).

In a very recent and the first of its kind study (Coughlan et al., 2022), “at genetic risk” AD participants ($\epsilon 3\epsilon 4$ carriers) and $\epsilon 3\epsilon 3$ carrier controls (ϵ classification based on saliva samples) were tested in a type of vestibular-based spatial task (i.e. path integration) on a rotatory chair, while in complete darkness. The discrepancies in the participants’ vestibular-derived performance were enough for an automated algorithm to differentiate between them with a 65%-79% accuracy. Thus, the authors hope that early identification of vestibular dysfunction might give better chances for “at genetic risk” individuals to receive targeted treatment (Coughlan et al., 2022). Even if an interesting candidate for “central vestibular system” research, the study leaves an unclear message about its vestibular results. Briefly, the researchers (1) do not report for peripheral or central vestibular testing to have taken place for the cohort aged 50-75yrs. Consequently, it becomes unclear if the nature of the reported vestibular disadvantage for the $\epsilon 3\epsilon 4$ carriers is of peripheral or central aetiology, which would lead to different conclusions and intervention procedures. (2) The testing procedure warrants further detail regarding the vestibular stimulus itself, e.g. the range and duration of angular rotations, the consistency in the way the vestibular stimulus was produced, the peak velocity (Brevern et al., 1997), (Seemungal et al., 2004), (Bronstein et al., 2008), (Yoder & Taube, 2009). Thus, unclarities about the results made it impossible to gain further knowledge about central vestibular dysfunction in the navigation of AD patients.

Despite the significant advances in the knowledge of spatial orientation in AD patients, further understanding is needed for the better management and support of these patients with spatial disabilities. A key challenge is to define the link between disease aetiology and the consequent cascade of spatial deteriorating events. However, this can only happen if taking into consideration all components of spatial processing, including the central vestibular system. The latter is often given too little attention. In this sub-Chapter, I particularly concentrated on the central vestibular signal by hypothesising that vestibular-guided spatial orientation comprises three vestibular spatial processes (i.e. vestibular self-motion perception, egocentric and allocentric (egocentric+) navigation) (i.e. Hypothesis II). I discuss this model in great detail in the following sections while observing the different levels of vestibular-guided spatial performance and the effect of the stepwise increasing cognitive burden on patients with memory and (balance) complaints (i.e. Hypothesis III). My objectives were:

1. To investigate how vestibular spatial navigation (i.e. the three-step model) was affected during passive rotations in patients with memory impairment?
2. To investigate the link between cognitive dysfunction (using the MMSE/ACE III-R tests) and vestibular-mediated spatial navigation (i.e. the three-step spatial model)?

2. Materials and Methods

2.1. Recruitment of memory and (balance) patients

As previously mentioned, the memory and (balance) patients of this pilot study represented a natural continuum from possible prodromal to possible early AD. Therefore, I tested this patients' group as a single group and separated them into two groups based on their cognitive performance score (using the MMSE test), rather than on an existing or lacking cognitive/neurodegenerative diagnosis. Please refer to Chapter II for the inclusion/exclusion criteria of this study and to Chapter IV for more details about recruitment of patients and additional behavioural testing.

2.2. Methodology

To specifically address my hypotheses and their objectives, I used the three-step spatial model to learn more about the spatial navigation in patients with memory impairment from a central vestibular system point of view. The hypothesised three-step spatial model consists of three tasks (Fig.33): (1) vestibular motion perception task (VMP), (2) vestibular egocentric task and (3) vestibular allocentric (vestibular egocentric+) task. Each step of the model incorporates in itself the previous one. Thus, this is a continuous and cognitively involved model where each level presents an increased demand in comparison to the previous one. Therefore, the last step of each spatial analysis under vestibular guidance was to look for a link to patients' cognitive performance as based on the two tests applied for this study (i.e. the MMSE and ACE III-R).

Please refer to Chapter II. for a detailed explanation of the three tasks used in this Chapter (a quick reference is also available at the beginning of Chapter V, Fig. 33).

JOYSTICK task (initial analysis):

For the egocentric task, several levels of correction of the data were needed before I was confident the results were realistic from a vestibular system perspective. This analysis is called "initial" as it was performed before the secondary type of analysis, which I call "main" analysis.

First, I looked at the participants' raw data by conducting (1) angle-based, (2) Slope-based and (3) R^2 analyses. These analyses were performed on three levels: (1) before any corrections of the data were done (called 'BEFORE CORRECTIONS'), (2) after wrong directions were eliminated (called 'PARTIAL CORRECTIONS'), and (3) after I corrected for the role of the vestibular system by eliminating all responses that, considering constant speed, lasted more than 7s (called 'AFTER ALL CORRECTIONS'). From a neurophysiological point, the optimal velocity profile of the semicircular canals is a raised cosine velocity motion, which was also used to develop the JOYSTICK task. With such a raised cosine profile, the canal dynamics is frequency dependent (for reference Fig. 2, page 505 from R. Mayne Chapter from the Handbook of sensory Physiology (Mayne, 1974)). The bode plot presented there displays the optimal canal transduction range (in Hz) of angular rotations and confirms

that 7s (corresponding to 0.1944Hz) is within the optimal transduction range. Notably, the falloff in stimulus-response gain with increasing periods of rotation is not abrupt, which would potentially allow for a few more seconds optimal range above 7s. Still, to ensure accuracy and reliable vestibular signal, a cut-off of 7s was discussed and agreed upon.

The next step I took was to classify the data based on two criteria: (a) vestibular motion perception performance (VMP) and (b) MMSE score performance. Based on the already discussed criteria and the side of rotation (i.e. Right and Left) and beep tone delay (i.e. 1.5s and 6.5s), I prepared 8 panels for this initial exploration of the data. This was an essential step in my JOYSTICK analysis, helping me to better understand the data. The analysis and the above-mentioned panels, alongside a plot displaying the type of errors participants performed during the task, are presented in Appendix.

2.3. Statistical analysis

For the patients with memory and (balance) impairment, I use two types of division: (1) based on MMSE (i.e. $MMSE \leq 24$ and $MMSE > 24$), and (2) VMP division (i.e. into normal VMP/abnormal VMP performance). In this Chapter, I present the MMSE division analysis as MMSE is a well validated test for clinical use in patients with memory impairment. On the other hand, the VMP division analysis was rather an exploratory analysis, which I attach in Appendix.

In the spatial analysis to follow, I present the JOYSTICK and MOUNTAIN datasets from several different perspectives (1) angle-based, (2) Slope, (3) R^2 and (4)%Error analyses, to ensure results, even if from a small cohort, are correctly interpreted and consistent between analyses. In addition, I present absolute Error and absolute GAIN plots based on VMP and MMSE division in Appendix. There, I also attach the initial Joystick analysis panels, effect size, sample size and Bayesian estimates (for JOYSTICK and MOUNTAIN tasks), followed by K-means, Hierarchical clustering and PCA analyses for the MOUNTAIN task.

The small sample size and the Shapiro-Wilk test confirmed the use of non-parametric statistics. For all analyses, the alpha-level was set at 0.05. Results are presented as median + IQR.

Vestibular motion perception:

Detailed VMP analysis for the memory and (balance) patients was presented in Chapter IV. Here, I stressed the lack of difference between Right-sided VMP and Left-sided VMP thresholds (performed with the Wilcoxon signed-rank test) and the significant Kruskal Wallis test between $MMSE \leq 24/MMSE > 24$ /controls. Lastly, using the Spearman's test, I assessed the correlation between VMP and MMSE/ACE total and its subcomponents.

JOYSTICK task (main analysis):

A detailed investigation of the performance of the memory patients was conducted for the vestibular egocentric task.

First, I investigated the difference in Right- and Left-sided rotations, irrespective of angle using the Wilcoxon signed-rank test. Next, a group-level comparison between the six tested angles (i.e. 30°, 60°, 90°, 120°, 150° and 180°) for the MMSE ≤ 24/MMSE > 24/controls was performed.

Further, Slope-based, R², %Error analyses were performed between groups using the Kruskal-Wallis test and the subsequent Dunn's Post Hoc with Bonferroni corrections. In addition, a Wilcoxon signed-rank test was used to examine 'within group' difference between beep delays.

Lastly, a Spearman correlation between the JOYSTICK task and the MMSE/ACE and its subcomponents was performed to investigate for a possible link between vestibular egocentric and cognitive performance.

MOUNTAIN task:

A detailed investigation of the performance of the memory patients for the vestibular allocentric (egocentric+) task was conducted.

First, I investigated the difference in Right- and Left-sided rotations, irrespective of angle using the Wilcoxon signed-rank test. A significant difference was further investigated by Friedman's test and a subsequent Conover's test with Bonferroni corrections by dividing the results based on the beep delay (i.e. 1.5s or 6.5s).

Next, a group-level comparison between the six tested angles (i.e. 30°, 60°, 90°, 120°, 150° and 180°) for the MMSE ≤ 24/MMSE > 24/controls was performed.

Further, Slope-based, R², %Error analyses were performed between groups using the Kruskal-Wallis test and the subsequent Dunn's Post Hoc with Bonferroni corrections. In addition, a Wilcoxon signed-rank test was used to examine 'within group' difference between beep delays.

Lastly, a Spearman correlation between the MOUNTAIN task and the MMSE/ACE and its subcomponents was performed to look for a link between the cognitively demanding vestibular allocentric task and the two cognitive tests.

3. Results

3.1. Vestibular motion perception task

The VMP test is the first step of the three-step model, and in this section, I briefly report the results that my patients achieved during the test. Detailed information about the VMP performance of the 15 memory and (balance) patients is available in Chapter IV. There were 7 patients out of 15 who achieved abnormal vestibular motion perception, while 8 patients – retained within normal range performance. No significant difference was found between Right-sided and Left-sided vestibular-guided self-motion perception ($W = 70, p = 0.59$).

The VMP test (Fig. 31) showed to be sensitive in discriminating not only between healthy controls and patients, but also among patients themselves. Healthy controls >60yrs (mean

VMP threshold, $\alpha = 0.9^\circ/s^2$) performed approximately 6.4 times better than patients with $MMSE \leq 24$ ($n = 4$, average age = 80.5yrs, vestibular thresholds $\alpha = 5.77^\circ/s^2$). Still, healthy elderly >60yrs showed performance close to patients with $MMSE > 24$ ($n = 11$, average age 73.3yrs, vestibular thresholds $\alpha = 1.16^\circ/s^2$). However, it is to be noted that the average age of patients with $MMSE \leq 24$ is the highest compared to the rest of the patients and the healthy elderly >60yrs.

A Kruskal-Wallis test showed a significant main effect of group ($\chi^2(2) = 10.35$, $p = 0.006^{**}$), which was driven by the difference between patients with $MMSE \leq 24$ and (1) the controls > 60yrs ($p_{(bonf)} = 0.002^{**}$) or (2) the $MMSE > 24$ patients ($p_{(bonf)} = 0.02^*$) (Fig.31).

Lastly, the VMP task (patients only) correlated stronger with MMSE ($\rho = -0.78$, $p = 0.002^{**}$) than with ACE TOTAL ($\rho = -0.49$, $p = 0.12$) or its five components. Still, there was a tendency for a significant correlation with ACE attention ($\rho = -0.59$, $p = 0.05$).

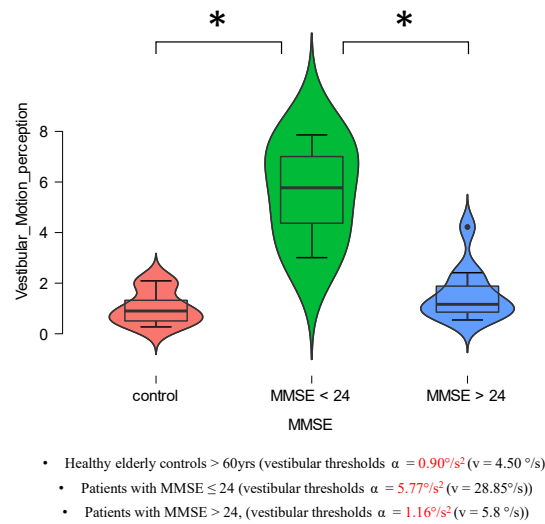


Figure.31. (Duplicate from Chapter IV) Memory and (balance) patients – Mean VMP test – GROUP results for memory and (balance) patients (divided based on their MMSE score performance) and healthy controls > 60yrs of age (median + IQR). In addition, results in acceleration (α) and velocity(v)) for each group are presented.

3.2. MAIN JOYSTICK analysis

After completing the initial JOYSTICK analysis for the patients, here I present the main JOYSTICK analysis, based on data after ALL corrections, i.e. the third and last level of correction where in addition to the exclusion of wrong directions, I also considered the contribution of the vestibular system.

In Figure 38, I present the individual JOYSTICK performance. While some of the patients exhibited a restricted range of response rotations, remaining relatively hypometric, others - spanned through a wide range of hypermetric responses (Left-sided (from “0” to “-400”) and Right-sided (from “0” to “300”)). The Wilcoxon signed rank test did not show any notable difference between Left-sided and Right-sided rotations in either of the two patients’ groups, i.e. $MMSE \leq 24$ ($W = 16$, $p = 0.31$) and $MMSE > 24$ ($W = 6$, $p = 0.43$).

Figure. 39 displays the angular responses of patients (divided based on their MMSE score, i.e. $MMSE \leq 24$ and $MMSE > 24$) and healthy elderly controls >60yrs. The plot shows combined Right- and Left-

sided angular movements in addition to performance being divided by beep tone delay of 1.5s and 6.5s. Figure 39 suggests that healthy elderly controls and patients with $MMSE > 24$ had similar group performance, which tended to be hypometric. Still, healthy elderly experienced a more condensed range of angle responses, whereas the $MMSE > 24$ showed a higher variability of individual responses than controls. In contrast, patients with $MMSE \leq 24$ tended to show a close-to-ideal performance due to the counterbalance of their hypermetric and hypometric individual responses. As the number of participants in this $MMSE \leq 24$ subgroup was 3, as I excluded 1 participant after the vestibular level corrections, here I refrained from investigating any ‘between groups’ or within $MMSE \leq 24$ group angle comparisons as results would not be realistic. Still, it is important to note that both patients’ groups showed some tendency towards forming a plateau in their angle responses - the $MMSE \leq 24$ showed such a tendency for both delays of beep tone for the $90^\circ - 150^\circ$ angle range, whereas the $MMSE > 24$ presented with a non-varying highly hypometric behaviour for $90^\circ - 180^\circ$.

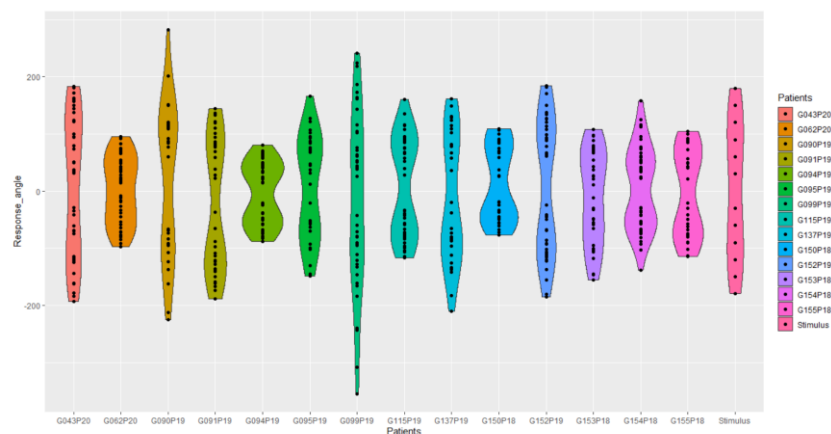


Figure.38. Memory and (balance) patients – Individual JOYSTICK task performance. The X-axis displays the individual patients with their specific study numbers (e.g. G043P20), whereas the Y-axis displays their response angle range in degrees. The rightmost part of the plot contains the stimulus spanning from $(-180^\circ, -150^\circ \dots -30^\circ, 30^\circ \dots 150^\circ, 180^\circ)$ to allow for comparison with the patients’ response angles/performance. Responses from $0 - [200^\circ]$ indicate rotation to the Right, whereas $0 - [-200^\circ]$ – to the Left.

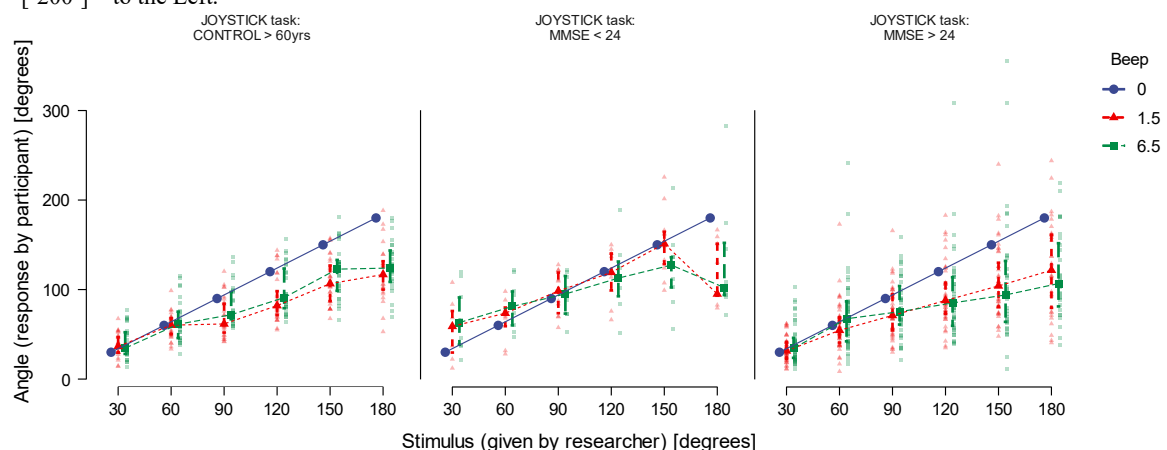


Figure.39. Memory and (balance) patients ($MMSE > 24$ and $MMSE \leq 24$) and healthy controls over 60yrs – Individual and Group JOYSTICK task performance. The X-axis displays the possible angles of rotation given as stimulus – $(30^\circ - 180^\circ)$, in steps of 30° , whereas the Y-axis – the response provided by the participant as a result of the stimulus. On the plot, with blue colour, exactly at 45° , is the ideal Slope of 1 with respect to which the participants’ performance is estimated. The plot presents individual performance based on the delay of the beep tone, either 1.5s or 6.5s, with the small green quadrats and red triangles being individual performances. Group performance is displayed with medians and IQR.

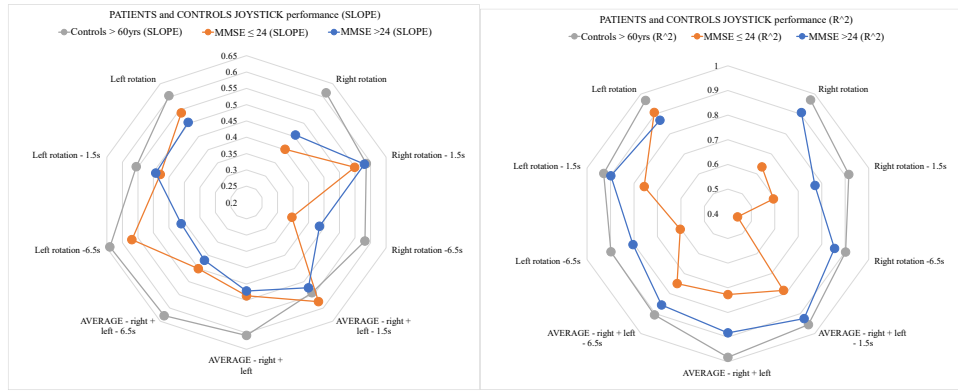


Figure.40. Memory and (balance) patients (MMSE > 24 and MMSE ≤ 24) and healthy controls over 60yrs – Group JOYSTICK task performance based on SLOPE (Left panel) and R² (Right panel). The plots display group performance for the side of rotation – Right, Left and combined (i.e. AVERAGE = Right + Left), while also taking into consideration the delay of the beep tone – Right, Left, and combined for 1.5s and Right, Left, and combined rotations for 6.5s.

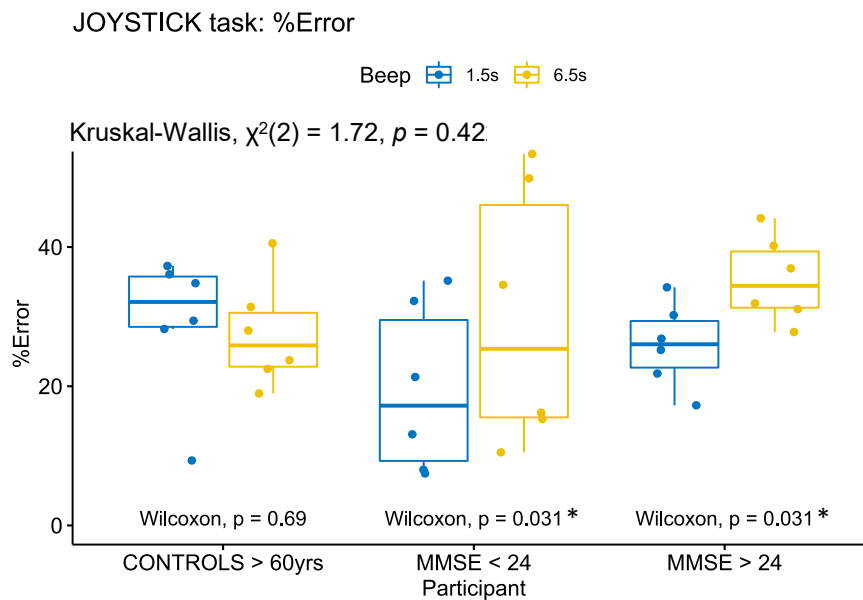


Figure.41. Memory and (balance) patients (MMSE > 24 and MMSE ≤ 24) and healthy controls over 60yrs - Group JOYSTICK task performance based on %Error (%error = [(response angle – stimulus)/stimulus] * 100). The X-axis displays the participant type, i.e. the three participants' groups, whereas the Y-axis – the %error derived from their performance. The boxplots are further divided by the delay in beep tone, i.e. 1.5s or 6.5s. A Kruskal- Wallis test result between the three groups is displayed on top of the graph. Lastly, within groups Wilcoxon tests were calculated and displayed at the bottom of each control group.

While the angle-based plot (Fig. 39) did not display a distinct difference for patients and controls, the Slope-based plot (Fig.40, Left panel) managed to discriminate between them more clearly. A Kruskal-Wallis test was significant ($\chi^2(2) = 14.61, p = 0.0006^{***}, \eta^2 = 0.56$), and the suggested difference was driven by the difference between the healthy controls >60yrs group and (a) MMSE ≤ 24, $p_{(bonf)} = 0.005^{**}$ and (b) MMSE > 24, $p_{(bonf)} = 0.001^{**}$.

For this analysis, also R² (Fig. 40, Right panel) showed a statistical difference among groups (Kruskal-Wallis, $\chi^2(2) = 17.04, p = 0.0001^{***}, \eta^2 = 0.65$) and a Dunn's Post Hoc analysis informed that only healthy controls > 60yrs - MMSE ≤ 24, $p_{(bonf)} = 0.0001^{***}$ remained significant after multiple comparisons.

Next, I looked at the %Error analysis (Fig. 41), which statistically showed no significant result (Kruskal-Wallis test: $\chi^2(2) = 1.72, p = 0.42$). Examining the difference within groups via the Wilcoxon signed rank test resulted in a statistical difference between delays of beep tone (i.e. 1.5s or 6.5s) for the two patients' groups, as displayed in Fig. 41.

Lastly, the JOYSTICK task (patients only) correlated neither with MMSE ($\rho = 0.07, p = 0.83$) nor with ACE TOTAL ($\rho = -0.01, p = 0.97$) or its five components.

3.3. MOUNTAIN task

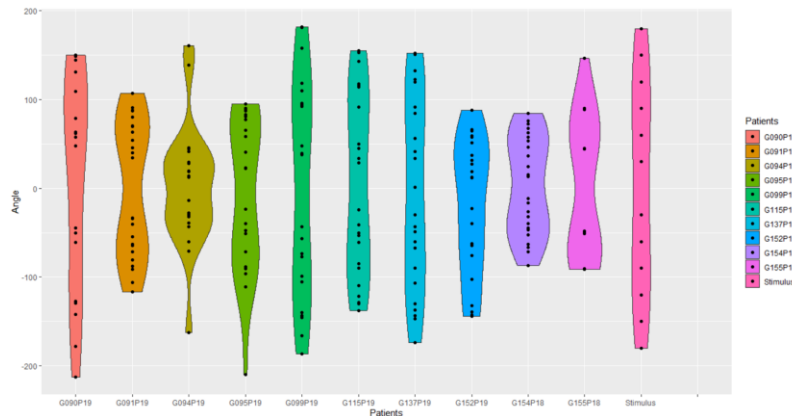


Figure.42. Memory and (balance) patients – Individual MOUNTAIN task performance. The X-axis displays the individual patients with their specific study numbers (e.g. G090XX), whereas the Y-axis displays their response angle range in degrees. The right-most part of the plot contains the stimulus spanning from (-180°, -150°...-30°, 30° ...150°, 180°) to allow for comparison with the patients' response angles. Responses from 0 – [200°] indicate rotation to the Right, whereas 0 – [-200°] – to the Left.

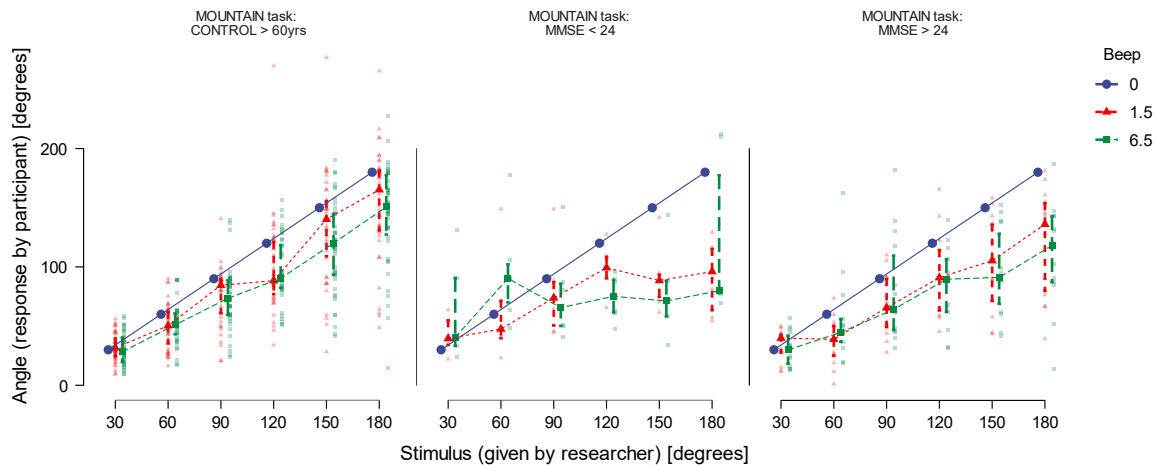


Figure.43. Memory and (balance) patients (MMSE > 24 and MMSE ≤ 24) and healthy controls over 60yrs – Individual and Group MOUNTAIN task performance. The X-axis displays the possible angles of rotation given as stimulus – (30° – 180°), in steps of 30°, whereas the Y-axis – the response provided by the participant as a result of the stimulus. On the plot, with blue colour, exactly at 45°, is the ideal Slope of 1 with respect to which the participants' performance is estimated. The plot presents individual performance based on the delay of the beep tone, either 1.5s or 6.5s, with the small green quadrats and red triangles being individual performances. Group performance is displayed with medians and IQR.

In this last section of the RESULTS, I display the allocentric (egocentric+) performance of the memory and (balance) patients with Fig.42. demonstrating their individual performance. Patients' performance

was diverse, and while some concentrated their responses around the small angles, others had wider distribution across the angle range.

Interestingly, for the allocentric task, patients with $MMSE \leq 24$ displayed that their Left-sided rotations were more varied within the angle range, whereas the Right-sided rotations were more condensed but are the ones that later drove the group Slope towards a horizontal plateau. Still, mainly because of the small numbers in the $MMSE \leq 24$, there was no statistically significant difference between Right- and Left-sided rotations ($W = 12, p = 0.84$). On the other side, a Wilcoxon signed test between Right- and Left-sided rotations for patients with $MMSE > 24$ was significant ($W = 21, p = 0.03^*$). The latter result was further investigated via a notable Friedman's test ($\chi^2(3) = 8.4, p = 0.03^*$, Kendall's $W = 0.95$), followed by an insignificant Conover's Post Hoc.

Figure 43. shows the individual performance based on angles, with combined Right- and Left-sided angular responses. In addition, performance is divided by beep tone delay of 1.5s and 6.5s. Notably, the $MMSE > 24$ group displayed a pronounced hypometric performance compared to the healthy controls >60 yrs, with this trend being stronger after 120° angles. A very interesting performance was observed in the $MMSE \leq 24$ group, which tended to form a horizontal plateau between 90° - 180°. Thus, at least *by observation*, there seemed to be no difference within $MMSE \leq 24$ for 90° - 180° angles. Due to the small sample size, further investigation via Friedman's test (for combined or separated delays of 1.5s and 6.5s) was not attempted as results would not be realistic.

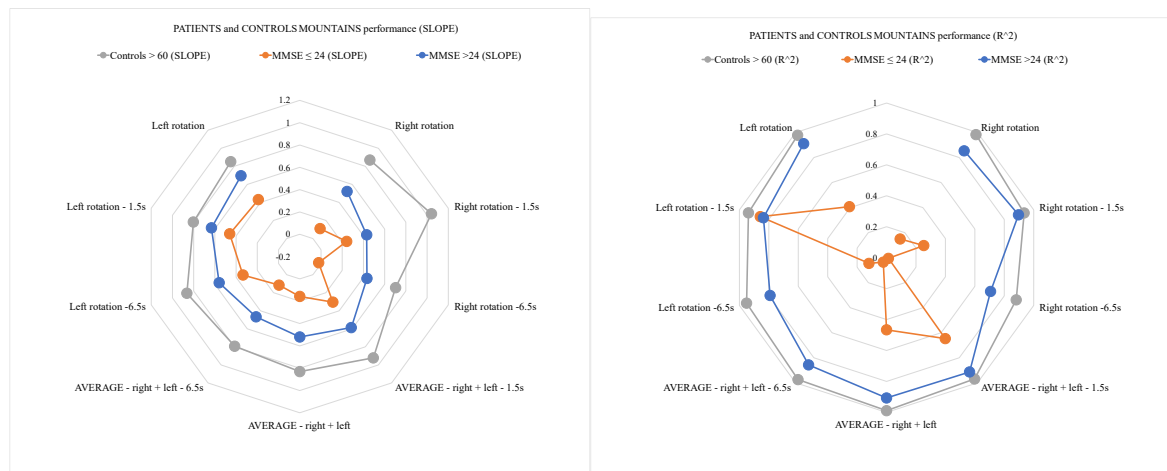


Figure 44. Memory and (balance) patients ($MMSE > 24$ and $MMSE \leq 24$) and healthy controls > 60 yrs – Group MOUNTAIN performance based on SLOPE (Left panel) and R^2 (Right panel). The plots display group performance for side of rotation – Right, Left and combined (i.e. AVERAGE = Right + Left), while also taking into consideration the delay of the beep tone – Right, Left, and combined for 1.5s and Right, Left, and combined rotations for 6.5s.

Next, I looked at Slope-based performance for the allocentric task (Fig. 44, Left panel). A Kruskal-Wallis test showed a significant difference between the three groups ($\chi^2(2) = 22.31, p = 0.00001^{***}, \eta^2 = 0.85$) and a Dunn's Post Hoc suggested a notable difference between controls > 60 yrs and (a) $MMSE \leq 24, p_{(bonf)} = 0.000007^{***}$ and (b) $MMSE > 24, p_{(bonf)} = 0.03^*$.

Consistent with the angle plot (Fig. 43), the R^2 (Fig. 44, Right panel) showed a good fit to the regression model for healthy controls >60 yrs and even for patients with $MMSE > 24$. However, the result for

MMSE ≤ 24 was abnormal, and a linear regression model in the latter case was inappropriate. As expected, Kruskal-Wallis revealed a significant difference between groups ($\chi^2(2) = 20.64$, $p = 0.00003^{***}$, $\eta^2 = 0.79$) and a Dunn's test showed the driver of this significance, i.e. controls > 60 yrs - MMSE ≤ 24 , $p_{(bonf)} = 0.00001^{***}$.

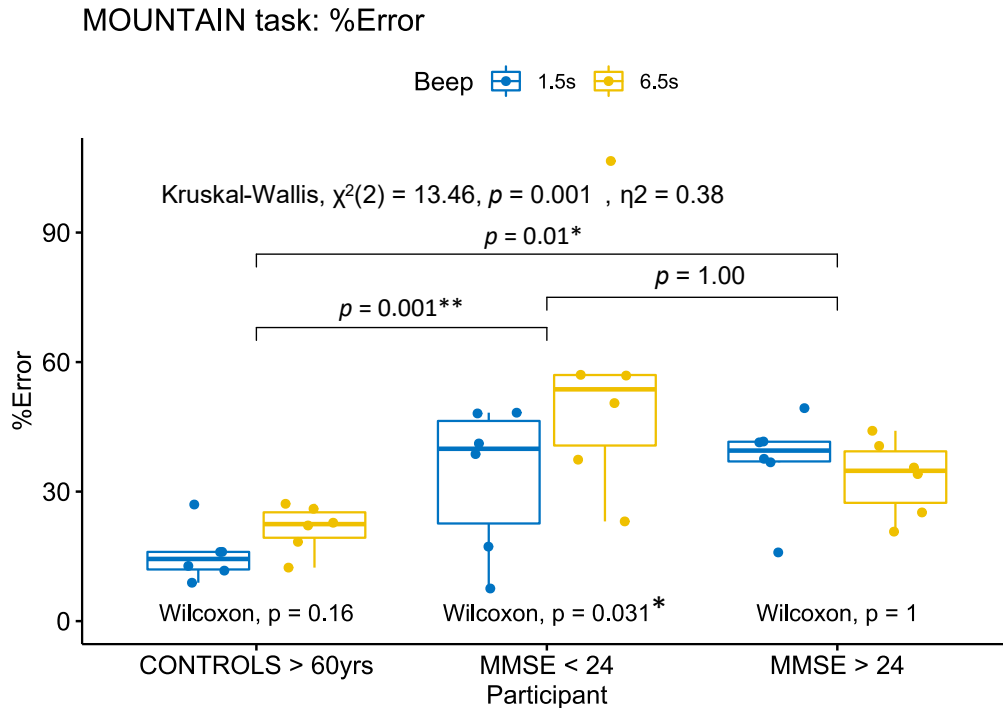


Figure.45. Memory and (balance) patients (MMSE > 24 and MMSE ≤ 24) and healthy controls over 60yrs – Group MOUNTAIN task performance based on %Error (%error = [(response angle – stimulus)/stimulus] * 100)]. The X-axis displays the participant type, i.e. the three participants' groups, whereas the Y-axis – the %error derived from their performance. The boxplots are further divided by the delay in beep tone, i.e. 1.5s or 6.5s. A Kruskal-Wallis test result between the three groups is displayed on top of the graph, whereas below it are the results from the multiple comparison analysis. Lastly, within groups Wilcoxon tests were calculated and displayed at the bottom of each control group.

Further, the %Error analysis for the allocentric task also managed to clearly present the difference between patients and controls (Fig. 45). The within-group Wilcoxon signed rank test showed no statistical difference for healthy controls and MMSE > 24 , but for patients with MMSE ≤ 24 (Fig. 45). A Kruskal-Wallis test between the three participants' groups was significant ($\chi^2(2) = 13.46$, $p = 0.001^{**}$, $\eta^2 = 0.38$), and a Dunn's Post Hoc test showed that the significance was driven by the difference between healthy controls > 60 yrs group and (a) MMSE ≤ 24 , $p_{(bonf)} = 0.001^{**}$ and (b) MMSE > 24 , $p_{(bonf)} = 0.01^*$. Lastly, a subsequent Friedman's test looking into repeated measures of 1.5s and 6.5s across %Error was significant ($\chi^2(5) = 14.66$, $p = 0.01^*$, Kendall's W = 0.21), and the Conover's Post Hoc test revealed a significant comparison only between controls > 60 yrs (1.5s) and MMSE ≤ 24 for 6.5s ($p_{(bonf)} = 0.03^*$).

What is more, the MOUNTAIN task (patients only) correlated significantly with MMSE ($\rho = 0.69$, $p = 0.03^*$) but not with ACE TOTAL ($\rho = 0.63$, $p = 0.07$). When looking at ACE sub-components, the MOUNTAIN task showed significant results for ACE attention ($\rho = 0.66$, $p = 0.05$) and ACE memory ($\rho = 0.86$, $p = 0.005^{**}$).

4. Discussion

4.1. INITIAL JOYSTICK analysis

The initial JOYSTICK analysis was a helpful way for me to (1) explore the dataset itself, (2) observe the way that other, i.e. non-vestibular, researchers usually see egocentric spatial data of patients with memory impairment, and (3) turn these data into a vestibular system – controlled dataset.

As previously noted, it was the participants with decreased cognitive performance whose spatial performance changed mostly after the three levels of corrections. On the other hand, patients with MMSE > 24 showed less varied behaviour among levels of corrections, and their spatial performance BEFORE, after PARTIAL and after ALL modifications remained relatively stable. Some possible reasons for the latter might be linked to patients with MMSE > 24 (1) picking up a strategy and having the cognitive ability to adhere to it, even if they do not have an entirely working vestibular self-motion perception signal. Another option was that they might (2) have a normal VMP and thus performed correctly, or (3) it might be connected to chance performance and/or other confounding factors. Consequently, vestibular system driven correction seemed to play a significant role in the overall analysis of patients with MMSE $\leq$ 24 but did not show such an effect on patients performing within normal cognitive range (i.e. MMSE > 24) as these participants did not tend to make a high number of errors, especially vestibular-driven errors. Thus, the vestibular-based corrections confirmed the importance they might play in the further and more precise interpretation of the data.

The spatial orientation system is a highly adaptive but, at the same time, rigorous system that does not seem to mix between the strategies available for orientation, especially for older healthy participants. Therefore, in healthy controls >60yrs and patients with performance ‘within normal cognitive range’, I did not observe modulated responses but rather a linear and logical pattern that applied to all responses in a specific test. That is to say, if someone showed a hypometric response, they would usually rather keep that type of response throughout all angles or show a stepwise hypometric pattern. Still, I consider that this linearity in responses was linked to the low-frequency movements and head rotational velocity that participants usually exhibit in laboratory-based experiments, where frequencies/velocities are considered lower than what is normally present in the real world (K. E. Cullen, 2019). On the other hand, my patients with poor cognitive skills tended to perform in a stochastic way, making the group performance widely range. Thus, while possibly looking for compensatory mechanisms from the whole-brain network, they often relied on different strategies, i.e. both modulated and linear.

Nevertheless, an implication in my study arose from the inability of patients with MMSE $\leq$ 24 to reliably perceive angular rotations of bigger angles and thus be able to reproduce them later. The inability to correctly perceive the bigger angles could be connected to (1) decreased velocity storage function that did not correctly reflect the angular movement and the consequent perception of angular motion. Further, also potentially linked to velocity storage dysfunction, it might have been due to a (2) damaged velocity integrator unable to properly store the perception and trigger a vestibular memory for longer

angular movements, i.e. partial encoding in which the signal was perceived correctly but could not be stored over time and thus executed correctly. Still, a possibility existed that (3) it was pure execution of a response error. Lastly, the partial loss of 150° and 180° angles for some of the patients in my analysis could also be due to (4) the velocity restriction I had imposed on the joystick tool itself. This aspect I discuss further in “Possible Limitations of the study”.

4.2. MAIN analysis (VMP, JOYSTICK and MOUNTAIN task)

This was the first study to explore vestibular motion perception in patients with memory and (balance) complaints. In addition, my pilot study was the first to investigate a comprehensive three-step spatial model from a vestibular system point of view. I hypothesised that vestibular-guided spatial orientation performance was mediated by three stages involving: (1) vestibular self-motion perception, (2) conversion to uncalibrated space (egocentric level) and (3) mapping to calibrated external space (allocentric (egocentric+)level). This model (Fig. 46) presented as not only novel for healthy controls but even more so for patients with central affections of the nervous system due to memory impairment. Before taking a more holistic approach and considering the results from the perspective of the whole three-step model, next, I summarise the group results for each of the three tasks of the model separately.

1. The Vestibular Motion Perception test

The *vestibular self-motion perception* task is designed to trigger the working of the peripheral vestibular system and, more precisely, of the horizontal semicircular canals that have a special sensory detector called cristae ampullaris. This detector provides information about rotational head acceleration. At this stage, the processing is still at the inner ear level, i.e. the peripheral vestibular system through the cristae ampullaris provides the crucial signal of angular head acceleration and its calculation to angular head velocity in the brain. However, before reaching the cerebral cortex, the velocity signal is not yet a conscious perception. Once the cerebral cortex, via the central vestibular pathway passing through the thalamus, is reached, the velocity signal becomes consciously perceived. However, if there is a lesion in the central vestibular processing, this velocity perception is expected to be impaired, and consequently, participants would experience abnormal vestibular self-motion.

If considering a healthy individual, the conscious perception of velocity helps to detect the minimal acceleration threshold of self-motion during passive rotations in the dark, thus triggering a response by the subject as soon as they have perceived their motion. However, research has shown that some pathological individuals can experience a decreased perception of self-motion or none. For instance, traumatic brain injury patients might present with a condition called “vestibular agnosia” (Calzolari and Chepishcheva et al., 2021), which occurs when their VMP is variably (mildly to severely) decreased due to an acute (or possibly even chronic) brain lesion. Thus, they cannot timely detect lower accelerations

Spatial Navigation = “am I moving?” + “how much have I moved?” + “where am I?” + other factors
 (Level 1) (Level 2) (Level 3)

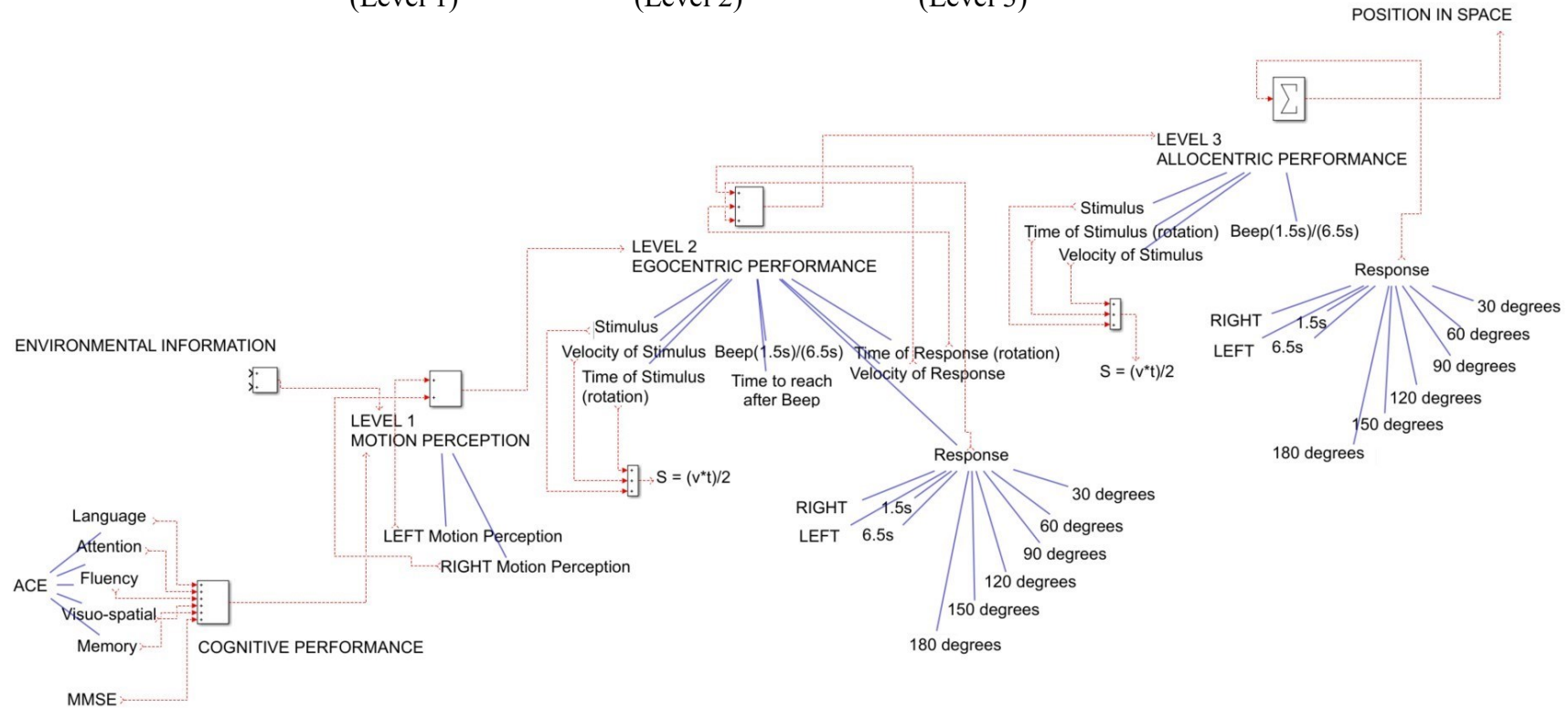


Figure.46. The continuous three-step model. Information from the environment enters the peripheral vestibular system. Together with the individual’s cognitive capacity (tested via the ACE and MMSE), they contribute to the formation of the acceleration signal during the vestibular self-motion perception task. At this level, the questions to answer are “am I moving?” and “In which direction am I moving?”. Considering that the peripheral vestibular system is intact, at this level, a subject would benefit from a normally working vestibular self-motion signal, and attention, which is important as drowsiness or sleep can impair the final perception result. Left- and Right-sided motion perception contribute to how the subject performs on the next level, i.e. the egocentric level. In addition, there the certain stimulus itself, its timing, its velocity and the beep tone delay affect the egocentric response. At this level, the questions to answer are “how much have I moved” or “how much of a distance have I travelled/covered?”. Additionally, temporal, spatial and vestibular memory are needed to perform at this egocentric level. Further, when going to the allocentric (egocentric+) level, the Right- and Left- sided vestibular motion perception from the 1st level and the response accuracy, the timing of the response and the velocity of the response during the egocentric task, i.e. all of them, affect how the participant performs on the allocentric level. Here, the question that needs to be answered is “where am I exactly?” and apart from temporal, spatial and vestibular memory, also visual memory is required in order to map the amount of travelled distance to the remembered visual scene.

of the rotating chair, and it might take time before they press the response button at a moment when the chair already moves much quicker. However, pressing the button at “some point”, later in the course of the rotation, might not always give an answer to whether the participant finally “felt” the rotation, or they just “know” that at some point they “have to press the button” and since no motion perception was felt by them, they just do so. This could lead to a “chance performance” due to reasons such as a genuine desire “to just perform well in front of the researcher”. Exactly, to exclude such a bias, all participants in the TBI study (presented in Chapters III, VI, VII) and also here in my three-step spatial study (presented in Chapters IV and V) were instructed to press the button only *“if”* they feel a chair rotation, not being assured that there will always *“be”* a rotation indeed.

Importantly, it is to be noted that not all pathological individuals with lesions in spatially involved regions are expected to experience self-motion abnormalities, possibly because the specific vestibular pathways were not damaged. Thus, a study discussed that while patients with lesions in the temporo-parietal junction (TPJ) showed impaired angular travelled distance for leftward (contralateral to their stroke) as compared to rightward (ipsilateral to their stroke) rotations (Kaski et al., 2016), their VMP estimate was not affected (Kaski et al., 2016). Still, VMP has not yet been explored in patients with neurodegenerative disease, and especially in those with Alzheimer’s dementia.

At this stage of the spatial orientation processing (Fig.46), two main components are essential for successful completion of the self-motion task: (1) an intact peripheral vestibular system to know whether one is moving or not and if so, in which direction (i.e. Right or Left) and (2) a capability to keep concentrated on the task and not fall asleep while in the dark or in other words, the cognitive ability to perceive the signal of self-motion. Thus, the involvement of the prefrontal and parietal brain regions is needed. In the case where a participant is not able to remain awake or concentrated, their performance for the perceptual threshold is going to be poor. More importantly for this study, however, would be the case in which the participant could not answer the question if they were moving, considering they were fully alert (which was the case for all my participants monitored via a camera during the testing). In this latter scenario, damage would suggest being in the central vestibular processing since an intact peripheral vestibular system was an obligatory inclusion criterion for the study.

The results of the study showed that the *vestibular motion perception test* possesses high sensitivity in discriminating not only between healthy controls >60yrs and patients but also among patients themselves. Healthy controls >60yrs (vestibular thresholds $\alpha = 0.9^\circ/\text{s}^2$) performed around 6.4 times more accurately than patients with MMSE ≤ 24 (vestibular thresholds $\alpha = 5.77^\circ/\text{s}^2$), but still close to patients with MMSE > 24 (vestibular thresholds $\alpha = 1.16^\circ/\text{s}^2$). However, MMSE > 24 performed almost 5 times more accurately than MMSE ≤ 24 . Thus, decreased cognitive abilities might have negatively affected the general self-motion perception and, from there, also the whole spatial orientation processing, as based on the three-step spatial model. Importantly, however, is that patients with MMSE ≤ 24 are the oldest compared to the rest of the patients and the healthy elderly controls, and age, among other confounding factors, needs to be considered. Nevertheless, the Spearman correlation between

AGE and VMP was not significant ($p = 0.354$, $p = 0.195$). Still, causation could also have occurred without correlation, especially in small samples. Thus, the contribution of age could not be excluded. When examining the relationship between VMP and MMSE score performance, I note that there was a significant negative Spearman correlation ($\rho = -0.78$, $p = 0.002^{**}$). This significance remained even if I separated the vestibular motion perception into Right- and Left-sided VMP, with Left-sided threshold having a slightly stronger link to MMSE. The latter reminds of the suggested right-sided hemispheric dominance for spatial orientation/vestibular system (Blanke et al., 2000), (Dieterich et al., 2003) but is not enough to imply it.

2. JOYSTICK (egocentric) task

Although the initial acceleration signal comes from the cristae ampullaris in the inner ear (i.e. peripheral vestibular system), the more complicated calculation of the ‘amount of travelled distance’ needed for the *egocentric task* is supposed to happen in the central vestibular system. The processing of the central vestibular signal is thought to be “highly convergent and strongly multimodal” (Angelaki & Cullen, 2008). Therefore, this calculation depends on (1) the ability to perceive head angular movements via head angular acceleration (and in this study - minimal whole body rotations considering participants were passively moved in a chair and instructed to remain still) and (2) the capacity to update our position in space while relying on self-motion cues. Indeed, it is the integration of the vestibular and non-vestibular self-motion cues that allow for the constant tracking of our position in space while we are moving (Stangl et al., 2020).

Consequently, egocentric navigation and, specifically - path integration enables us to know in which direction our home is after we depart from it while using different updating mechanisms (Chrastil & Warren, 2017). These mechanisms might be more successful on a continuous basis, or on the contrary - constant updates would merely contribute to a more significant error accumulation because of the acquisition of too much information and thus leading to disorientation. It is equally possible that these mechanisms might be more successful on a configural basis, i.e. by remembering the shape of the outbound path and updating our path only when required and not continuously (Wiener et al., 2011), (Stangl et al., 2020). Research demonstrates that while continuous updating provides quicker responses, the configural mechanism is more accurate, and people tend to themselves choose their preferred strategy (Wiener et al., 2011), (Stangl et al., 2020). Irrespective, the ability to perform these tasks varies even among healthy individuals and is meant to deteriorate with age and, especially, in disease.

The main region implicated with egocentric navigation is the posterior parietal cortex (PPC), and research shows that chronic posterior parietal lesions (Farrell & Robertson, 2000) or repetitive transcranial magnetic stimulation (rTMS) to the PPC (Seemungal et al., 2008) impair the perception of travelled distance/egocentric navigation. In the latter study, authors recorded decreased vestibular spatial perception of angular position for contralateral rotations only (i.e. perception of travelled distance was impaired) but unaffected self-motion perception. This led them to assume that PPC might

be embroiled in contralateral angular movements and thus path integration, but not in vestibular self-motion or velocity perception (Seemungal et al., 2008), (Seemungal et al., 2009). Thus, the link between vestibular egocentric and PPC was suggested. It follows that patients with impaired egocentric navigational skills can still experience a normal perception of self-motion or vice versa, which applies to the hypothesised and later observed patients' performance based on the continuous three-step model (Fig. 48).

Importantly, we must consider that the longer the travelled distance and the time we spent in such a rotation mode while in the dark, the greater the chance our estimation of accuracy would decrease. Thus, temporal and spatial memory components are essential to the egocentric calculation of the amount of travelled distance. While some studies suggest no hippocampal and entorhinal involvement in path integration (Shrager et al., 2008), other lesion studies have demonstrated the importance of the medial temporal lobe for path integration, as discussed in (Wiener et al., 2011). For instance, a study with stroke patients with right temporo-parietal junction (TPJ) lesions showed that these patients underestimated the amount of travelled distance and the length of the motion duration (for rotations contralateral to their lesion) but were not impaired in their estimate of vestibular self-motion perception (Kaski et al., 2016). Hence, it was proposed that the cerebral cortical regions for vestibular self-motion and vestibular-spatial perception are two different places (Kaski et al., 2016). Evolutionarily, the separation of cortical areas implicated in spatial processing suggests that they have different weighting and gives the brain a higher chance of successful navigation in case of a lesion. Another interesting point from the latter study (Kaski et al., 2016) is the mutual underestimation of time and travelled distance only by the patients with TPJ lesions. The authors suggest that this might indicate a link between these deficits and a possible role of the TPJ as a cortical integrator for self-motion velocity over time to derive the amount of travelled distance, which would assume that any damage to timing would inevitably cause spatial abnormalities.

Consequently, the skills that would be required for the JOYSTICK task at this stage of the navigational process involve not only our ability to know whether we are currently moving but also the calculation of this motion perception to “a consciously travelled amount of distance”. In addition, (1) the peak velocity of the stimulus, (2) the stimulus duration, (3) temporal, (4) spatial and (5) vestibular short-term memory also affect the final estimate of travelled distance (Fig. 46).

My statistical analysis for the egocentric angle-based plots showed that healthy elderly controls > 60 yrs and patients with MMSE > 24 had similar group performance, which tended to be hypometric. Still, the variation in angle responses for the control group > 60 yrs was less than the variation for MMSE > 24 . It is of note that both patients' groups (MMSE ≤ 24 and MMSE > 24) showed a tendency to form a plateau, but healthy elderly refrained from it at this point. Thus, the egocentric task showed a good level of sensitivity towards discriminating between patients and age-matched controls. Still, even if there was some tendency towards discrimination based on the angle-based plots, they did not manage to make the clear contrast that Slope-based plots achieved. There, the difference among the three groups of

participants became more evident with the difference between the healthy elderly controls >60yrs versus both patients' groups driving the significance.

Both patients with MMSE > 24 and healthy controls > 60yrs achieved a higher R^2 than MMSE $\leq$ 24. Further to the R^2 analysis, I note the statistically significant difference between the controls > 60yrs as compared to MMSE $\leq$ 24.

Lastly, %Error analysis for the egocentric task did not achieve a statistical difference among groups, although "within groups examination" of %Error based on a temporal beep delay of 1.5s and 6.5s showed statical importance within both patients' groups.

In summary, even if the main JOYSTICK analysis managed to discriminate between healthy control groups (section A, Chapter V), it does not seem as sensitive as to distinguish clearly between patients. Still, based on data from the initial JOYSTICK analysis, I note that there, the discrimination was also possible between patients. This indicates that the JOYSTICK task needs to be improved as to be able not only to produce "vestibular system – controlled dataset", but also to be sensitive enough to discriminate among patients.

3. MOUNTAIN (allocentric (egocentric+)) task

The ability to link the amount of travelled distance to a visual map is a complex task requiring the proper working of many higher-order association areas. Thus, the last stage of the continuous three-step model (Fig.46), the *allocentric* (egocentric+) task, would combine all skills used so far and add a certain number of additional skills that could lead to the successful completion of the task. Such skills are connected to (1) the spontaneous exploration of new environments and novel objects, (2) shape recognition, (3) colour perception, (4) visual feature extraction, (5) exploring topographical scene stimuli such as landscapes and (6) visual memory (Fig. 46 and Table.A4 from Appendix). At this stage, we aim to answer a misleadingly easy question behind whose answer lie various complex calculations: "where am I exactly?". To address this question, we need different aspects of our short-term memory – (1) visual, (2) temporal, (3) vestibular and (4) spatial, and also (5) attention and (6) concentration. The neural basis of attention lies in the reticular activating system (brainstem and the thalamic nuclei) and multimodal association areas (prefrontal, posterior parietal, and temporal lobes). However, considering that the pathology of Alzheimer's disease starts in the locus coeruleus (located in the brainstem) and all the projections it sends to a huge part of the brain, it is to be expected that attention in these patients is also affected. Still, without adequately attending to the task, we can neither successfully encode it nor retrieve it later. In addition, the literature suggests that successful encoding and retrieval require the transition between egocentric and allocentric skills. This transition is mediated by the posterior parietal cortex (PPC) and the retrosplenial cortex (RC) and the "use of head direction representations in Papez's circuit" (Byrne et al., 2007). Thus, as the transferring of the velocity to position information is at the base of our understanding of how all these processes are linked and function together, further vestibular-

guided research is needed to shed more light on the neural mechanisms involved in the spatial navigation of brain-impaired patients.

The hippocampus has long been implicated in allocentric spatial orientation, along with memory over short and long time delays (Olson et al., 2006). What is more, since the 1960's scientists have theorised on the vestibular system contributing to the spatial navigational processing via this core spatial structure - the hippocampus (P. Smith, 1997) and later also via the entorhinal cortex (EC) (P. Jacob et al., 2014). Interestingly, neuroimaging studies in humans have demonstrated that the lateral EC is “preferentially selective for object identity information” (i.e. ‘what’) (Montchal et al., 2019), whereas the medial EC is “preferentially selective for spatial locations” (i.e. ‘where’) (Montchal et al., 2019), (Reagh & Yassa, 2014), thus showing their essential role for the estimation of the surrounding environment. Further, peripheral vestibular damage in animal studies has been demonstrated to lead to abnormalities in the functioning of the hippocampal place cells and the entorhinal HD cells (Stackman et al., 2002), (Angelaki & Cullen, 2008), (Yoder & Taube, 2009), (P. Smith & Zheng, 2013), (P. Smith, 2019). Taken together, this afresh shows how tightly implicated the vestibular system is in the whole spatial processing and what a critical input it represents towards generating the spatial cognitive map.

Another important aspect of my egocentric and allocentric tasks is the temporal delay of the beep tone, with which I impose ‘vestibular memory related’ testing. Hippocampal time cells (located in CA1 and medial EC) offer a suitable mechanism for short timescales in the range of milliseconds to seconds to be encoded and indicate that “the medial temporal lobe (MTL) may employ similar mechanisms and shared circuitry to encode both space and time” (Montchal et al., 2019), along the hippocampal place cells (Umbach et al., 2020). However, this idea is not new, as we discussed that the TPJ (Kaski et al., 2016), as part of the medial temporal lobe, might also be a location where time and space are mutually encoded. Thus, “time cells provide an additional dimension that is integrated with spatial mapping” (Eichenbaum, 2014).

The allocentric (egocentric+) task in my study, i.e. the MOUNTAIN task, displayed a very different behaviour among the three groups ($MMSE \leq 24$, $MMSE > 24$ and healthy controls > 60 yrs). Importantly, regarding the side of rotation, $MMSE \leq 24$ patients exhibited a higher variation in their Left-sided rotations and more condensed Right-sided rotations. The latter, however, contributed to the generation of an almost horizontal slope for the $MMSE \leq 24$ group analysis. This indicated a possible re-weighting of sensory dependence for patients with decreased cognitive skills. Interestingly, a study about the vestibular modulation of spatial perception via GVS discussed that healthy volunteers showed a pattern for Leftward bias in near space, along with a Rightward bias in far space (Ferrè et al., 2013). This reminds us of the egocentric-allocentric performance of my patients with $MMSE \leq 24$, although it is ambiguous whether I can consider the egocentric task in the dark as a “near space” and the allocentric task “as a far space”. Still, some consideration might be possible. Indeed, my patients with $MMSE \leq 24$ demonstrated a higher tendency towards Left-sided rotational deterioration during the egocentric task,

while for the allocentric task, the Right-sided angular movement affected more the overall spatial performance.

Further, the patients with MMSE > 24 showed more expressed hypometricity for Right-sided averaged rotations. Importantly, asymmetry in the perception of angular head motion during whole-body rotations is not atypical for vestibular-guided spatial performance in pathological individuals. A study in two patients with unilateral vestibular failure (UVF) and severe atrophy in the posterior insula, hippocampus, putamen and thalamus showed that the patient with Right hemispheric damage showed hypermetric ipsilateral and hypometric contralateral performance (Philbeck et al., 2006). On the other hand, the Left hemispheric lesion patient exhibited bilateral hypometric performance (considered as in the low-normal range by the authors of the study) for whole-body rotations (25°–125°) in the yaw axis (Philbeck et al., 2006). Interestingly, the results from (Philbeck et al., 2006) and, more importantly, my allocentric task results for MMSE ≤ 24 and MMSE > 24 patient groups could also be explained by the fact that Right- and Left-sided rotational signals of velocity storage are coded by neurons located on both sides of the vestibular nuclei of the brainstem. In addition, their interaction is considered crucial as a potential lesion of the interconnections abolishes the velocity storage function (Katz et al., 1991). As velocity storage is essential for the way the brain “stores”/“memorizes” its position in space over time (P. Smith, 2019), velocity storage is important for patients with vestibular damage not only from the perspective of spatial orientation but also with regard to postural stability. This becomes an important consideration for my patients, some of whom exhibited both spatial and postural abnormalities (as seen in Chapter IV), following a cerebellum-related damage, as per their clinically available MRI reports.

Previously in the controls’ section Discussion (section A), I noted that controls > 60yrs managed to improve their allocentric performance compared to their highly hypometric egocentric performance when compared to the other healthy controls’ groups. Here, when compared to patients’ performance, they displayed a close to slope = 1 spatial group allocentric behaviour (i.e. highly accurate) that is only marginally hypometric. As suggested, this improvement from egocentric → allocentric performance might be due to the visual system and its overall contribution to the spatial orientation process. In addition, vision is important for developing the velocity storage, and the lack of it might modulate it (Seemungal et al., 2007). However, in AD dementia, decreased visual abilities are often a contributing factor to the impaired spatial performance (Tetewsky & Duffy, 1999), (O’Brien, 2001).

Further, the contribution of cognitive skills to allocentric performance should not be underestimated as it is another major driving factor, likewise tightly connected to the vestibular system. Still, even if cognitively intact, patients with MMSE > 24 did not manage to perform as accurately as the controls >60yrs. Thus, a certain difference existed between the two groups. In comparison to the controls >60yrs, patients with MMSE > 24 showed a more expressed hypometric behaviour, with some individual variability being present. Interestingly, the individual variability for the egocentric task for MMSE > 24 was greater than for the allocentric task (with vision being a possible contributor for the allocentric

task), whereas the trend of the group performance for the egocentric task was more stable than the trend for the group allocentric performance. Thus, undoubtedly, the visual system involvement during the MOUNTAIN task showed its crucial weight also for these patients' spatial navigation. Therefore, when research indicates visual impairment in Alzheimer's dementia patients, this inevitably leads to an even more significant deterioration in their navigation. Spatial planning (Passini et al., 1995) and route learning impairment (Allison et al., 2016) are just a few examples of how visuospatial deterioration can manifest during early Alzheimer's dementia.

An interesting trend was seen for patients with $MMSE \leq 24$, who formed an almost perfectly horizontal plateau of angular responses between 90° - 180° . Although this was the performance of only 3 patients (the 4th being excluded for both JOYSTICK and MOUNTAIN tasks), a trend towards a particular behaviour was shown – patients with decreased cognitive skills, all of whom also had an abnormal VMP, had remarkably decreased perception of vestibular-guided angular movements which even vision could not compensate for. Thus, research suggests that impaired allocentric spatial orientation in Alzheimer's disease is not the result of a memory deterioration alone, but rather a complex process, and more precisely - the patients' inability to link “recognised scenes with locations in the environment” (Monacelli et al., 2003). Indeed, Alzheimer's patients rely mostly on intact egocentric path integration strategies when moving in familiar environments. However, when surrounded by an unfamiliar environment, this strategy is no longer appropriate, and the success of their navigation relies on the possible combination of various sensational (i.e. visual, vestibular, tactile, olfactory) inputs.

Slope-based analysis discriminated significantly between controls and the two patients' groups, whereas R^2 analysis revealed a notable difference only between the controls and $MMSE \leq 24$. Lastly, the allocentric %Error analysis revealed a notable difference between the healthy elderly >60 yrs versus the two patients' groups, but not between the two patients' groups themselves. Still, the clear discrimination between healthy elderly controls and patients showed a good overall sensitivity of the MOUNTAIN task and a realistic chance for this sensitivity to be further improved to achieve discrimination between patient groups as well.

5. Extended Discussion

In this extended discussion section, I provided additional information and interpretations of my results. Section 5.3. and section 5.4. are available in Appendix.

5.1. Vestibular-guided Spatial performance prediction based on a continuous three-step model

Considering a continuous model of spatial vestibular information flow, I hypothesise on patients' performance during the proposed three-step spatial model. I look at two possible scenarios that patients

might exhibit (Fig. 47), although other strategies are also possible, as I discuss later when putting actual results from the study in this diagram.

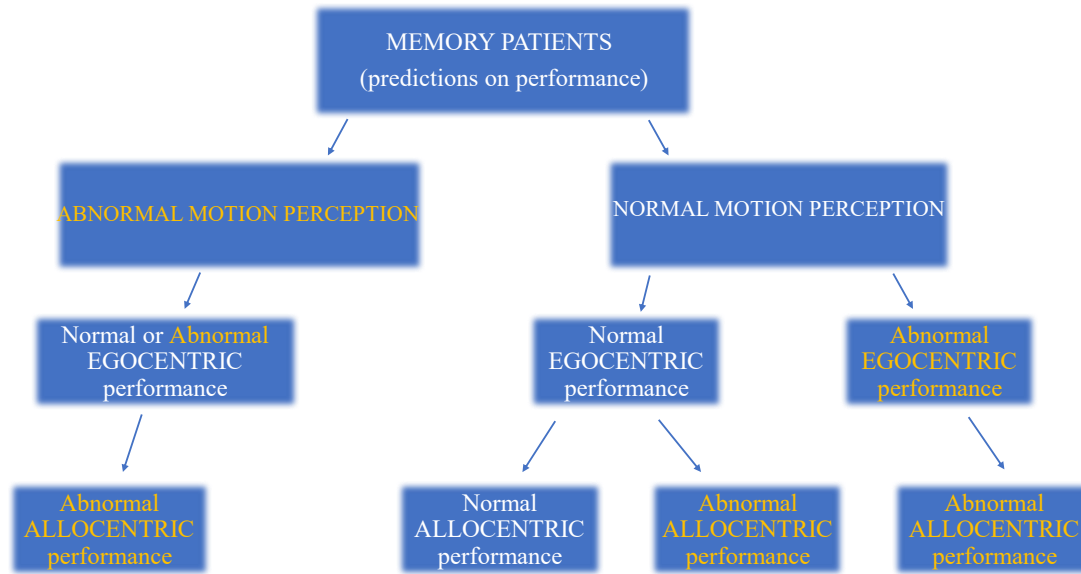


Figure. 47. Spatial performance prediction based on a continuous three-step model.

Scenario 1:

Scenario 1 describes only the situation when the VMP of a participant is within the normal range, with “normal” defined as vestibular motion perception performance with angular acceleration $\alpha \leq 2.02^\circ/\text{sec}^2$ (Calzolari and Chepishcheva et al., 2021). Thus, here I discuss the right portion of Fig. 47. Having a normal perception of self-motion, a participant can have either normal or abnormal performance on the uncalibrated, i.e. the egocentric task. In the former case, the participant accurately estimates the distance spent travelling with a specific velocity while being passively rotated in the dark and consequently appropriately updates their self-motion cues with respect to their travelled distance. However, abnormal egocentric performance is also possible and is discussed in *Scenario 2*.

Further, I look at the allocentric (egocentric+) task in a similar manner: whereas abnormal egocentric performance most probably leads only to abnormal allocentric performance, normal egocentric skills can yield normal or abnormal allocentric performance. If the latter case is true, i.e. normal egocentric performance leads to abnormal allocentric performance, this can mean that this participant has a commenced process of spatial deterioration (top-down), which, if able to remain as it is, can at least secure accurate egocentric level performance. However, if the decline continues, then the participant can be expected to show impaired egocentric skills in the future.

Lastly, abnormal allocentric performance based on abnormal egocentric performance can be due to (1) hypometric or (2) hypermetric performance even if the visual memory is properly working and the participant can remember the landmarks of the virtual environment. However, the opposite situation is also possible in which a patient can have a very precise feeling of the amount of rotation but cannot map it correctly because of memory gaps or inability to specifically map the virtual world to the rotations happening in the real world.

Scenario 2:

In this situation, the vestibular motion perception is outside the established normal range (Calzolari and Chepishcheva et al., 2021). The reason why patients could fail to accurately assess the amount of travelled distance, i.e. egocentric navigation, is mostly due to decreased sensation of self-motion, which prevents them from perceiving the amount of distance they have covered while travelling with the chair. Consequently, if the participant has an abnormal self-motion perception, they are not able to detect certain rotations that are gentler and slower (i.e. lower frequency angular movements) but might need a more robust move (i.e. a higher frequency rotation) to be able to appreciate that they are currently moving.

In general, this has serious implications for their independent spatial orientation as part of their ADL, as it would affect their ability to timely detect situations when posture needs to be corrected in order to retain balance. This can not only lead to falls but also disorientation while not being able to estimate the distance to an object and its position in space with respect to the self, thus leading to an unexpected collision with this object. This group of patients is expected to either show slight deterioration in their egocentric task or a more advanced impairment based on how severe their vestibular damage is. This leads to a situation where participants do not fully perceive the outgoing passive rotation, i.e. the stimulus in the egocentric task, especially if it is with a lower velocity or lasts longer (up to a maximum of 4 seconds in my study). Later, when they have to give their account of the amount of travelled distance, they reflect only on a brief moment they felt as a rotation and so perform in a hypometric fashion. Alternatively, they start pushing the joystick mounted on the chair, and as they do not feel that the chair is actually moving, they end up generating excessively hypermetric responses. A hypometric performance suggests that although unable to perceive vestibular self-motion, patients are still capable of some sensation and, therefore, some part of the given stimulus is perceived. On the other hand, hypermetric performance would more closely indicate a system that is incapable of receiving any signal and relies more often on a guess. Still, normal egocentric performance after abnormal VMP should not be excluded entirely, remembering that the neural correlates for vestibular self-motion and travelled distance might be distinct (Kaski et al., 2016). Lastly, considering abnormal egocentric skills, the allocentric performance is also expected to be deteriorated.

5.2. The continuous three-step model - performance prediction based on the results achieved in this study

In my study, I recruited 15 patients with memory and (balance) complaints, 7 of whom performed abnormally for the VMP task (among whom 4 patients with $MMSE \leq 24$ and 3 patients with $MMSE > 24$) and 8 patients – who had a within normal range vestibular motion perception (all patients with $MMSE > 24$). Summarised data are displayed in Table 9 and Figure 8.48.

Following Fig. 48, I report that out of the 7 patients with abnormal motion perception (*Left side of the*

diagram), only 2 performed abnormally for the egocentric task (both patients with MMSE ≤ 24), while 5 managed to show within normal range egocentric performance (2 patients with MMSE ≤ 24 and 3 patients with MMSE > 24). In my hypothesised model, I did not account for the fact that more than half of the patients with abnormal vestibular motion perception would still manage to show an intact egocentric performance. This indicates that the VMP test might have a very high sensitivity and detect patients whose impairment is still masked on an egocentric level but can potentially be observed on an allocentric level. In addition, other factors, such as compensatory mechanisms, might be in place.

Participant	MMSE score	Motion Perception ($^{\circ}/\text{sec}^2$)	JOYSTICK (average slope)	MOUNTAINS (average slope)
subject_1	MMSE ≤ 24	6.71	0.40	0.07
subject_3	MMSE ≤ 24	3.00	0.52	0.15
subject_2	MMSE ≤ 24	7.86	0.48	0.35
subject_6	MMSE ≤ 24	4.82	not analysable	not analysable
subject_5	MMSE > 24	1.05	0.30	0.02
subject_12	MMSE > 24	1.16	0.47	not analysable
subject_13	MMSE > 24	2.41	0.64	not performed
subject_8	MMSE > 24	0.89	0.41	0.41
subject_9	MMSE > 24	0.81	0.46	0.43
subject_15	MMSE > 24	0.74	0.41	ophthalmological issue
subject_4	MMSE > 24	2.19	0.81	0.68
subject_7	MMSE > 24	1.41	0.46	0.74
subject_10	MMSE > 24	0.54	0.55	0.83
subject_11	MMSE > 24	1.57	0.59	0.52
subject_14	MMSE > 24	4.22	0.86	not performed

Table. 9. Spatial performance of PATIENTS from the three-step model. MMSE score and Motion Perception columns display the division of memory and (balance) patients (with a red colour, I display outside of normal range results for MMSE, Motion Perception (abnormal is considered $> 2.02 \text{ }^{\circ}/\text{sec}^2$, egocentric and allocentric navigation). The JOYSTICK and MOUNTAIN task columns show the performance of the patients based on their averaged Slope result. As there is no established “normal”/“abnormal” performance for the JOYSTICK and MOUNTAIN tasks, I use the results from healthy elderly controls $> 60\text{yrs}$ as a reference and assume that results that are below ‘healthy elderly controls $> 60\text{yrs}$ group result $- 1 \text{ SD}$ ’ are abnormal (**for reference:** Controls $> 60\text{yrs}$ (Slope J) = 0.5838 ± 0.1226) and (for reference: Controls $> 60\text{yrs}$ (Slope M) = 0.7844 ± 0.1867).

Indeed, 2 out of these 5 patients with normal egocentric performance did not achieve within normal range results for the allocentric (egocentric+) task. Importantly, these patients had ‘white matter abnormalities in both hemispheres and possible SVD’ and ‘volume loss of the hippocampal heads’, respectively on their scan reports. The patient who achieved an abnormal vestibular motion perception but consequently performed normally for both the egocentric and allocentric task was someone with VMP only slightly higher (i.e. $\alpha = 2.19^{\circ}/\text{sec}^2$) than the used by our group established threshold of $\alpha = 2.02 \text{ }^{\circ}/\text{sec}^2$ for healthy controls with mean age = $40.78\text{yrs} \pm 14.75$ (Calzolari and Chepishcheva et al., 2021). Notably, the smaller cohort of healthy controls $> 60\text{yrs}$ had a “mean value + 3SD” = $3.06 \text{ }^{\circ}/\text{sec}^2$ which indicates a possibility that since my patient was 84yrs old at the time of testing, this slight increase in their self-motion perception result was still acceptable and was within the normal range for VMP concerning their age. Still, as the cohort of healthy controls $> 60\text{yrs}$ was smaller and the VMP threshold is not an established measure (as it highly depends on the equipment used), I decided to take into account the more robustly calculated value by the $n = 37$ healthy controls (Calzolari and Chepishcheva et al., 2021), even if their mean age was lower (age range 18yrs – 65yrs). Considering that this was an

exploratory analysis and I was also observing patients' performance on an individual basis, I believed this to be acceptable. Lastly, in case a higher threshold for VMP was considered, then instead of 7 abnormal vs 8 normal performing patients, I would have had 4 abnormal and 11 normal VMP performing patients, which would almost coincide with the division of patients based on MMSE (4 vs 11). A plot displaying this alternative division for VMP, alongside an alternative figure of Fig.32 reflecting this new VMP threshold, are presented in Appendix.

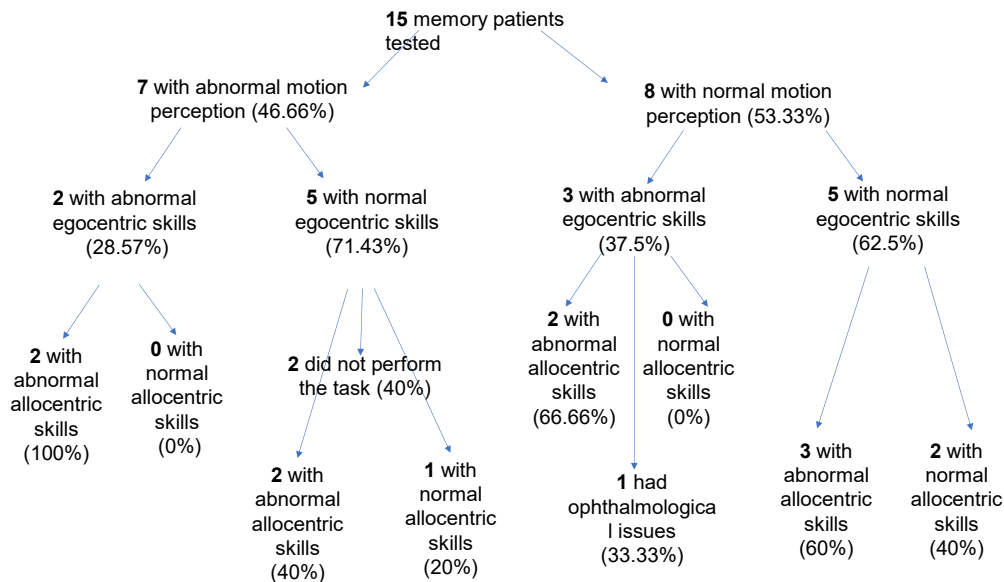


Figure. 48. Spatial performance prediction based on the results from the three-step model.

Interestingly, the two patients with abnormal vestibular motion perception (79yrs old, mean VMP acceleration $\alpha = 6.71^\circ/\text{sec}^2$ and 93yrs old, $\alpha = 4.82^\circ/\text{sec}^2$) displayed both egocentric and allocentric (egocentric+) skill abnormalities. Importantly, despite having a decreased cognitive score (MMSE ≤ 24), both patients were capable of normal communication during the testing session and are socially active members of the community, living with their families. Based on their clinically available MRI scan, the first patient had volume loss in the Right hippocampus and had Right cerebellar infarction. Irrespective of their spatial impairment, this patient with a probable Alzheimer's disease diagnosis showed an intact peripheral vestibular system (based on EOG and ENG recordings, posturography, expert neurologist clinical examination and the horizontal vHiT gain = 1). Still, their central vestibular system was no longer intact, with mean vestibular motion perception threshold of $6.71^\circ/\text{sec}^2$. In addition, a Right hippocampal volume loss was already present, which alone was a distinct feature for deterioration in spatial performance. Also, cerebellar infarction was noted, with the cerebellum implicated in one of the four vestibular pathways responsible for correcting the posture, while also recently established as a region involved in spatial orientation.

While this patient's balance was stable, even in the eyes-closed condition on a foamy surface, their orientation impairment could no longer remain masked. In 2013, Prof. Fred Previc discussed a "vestibular hypothesis" and made a strong case suggesting that peripheral vestibular loss needs to be

more critically reviewed as it might be linked to the neurodegenerative decline in Alzheimer's disease (Previc, 2013). In short, he discussed that the wide-spread vestibular network is strongly represented in the medial temporal lobe (a crucial region for AD pathology) and that multiple risk factors for Alzheimer's disease are also accompanied by vestibular impairment. In addition, numerous cholinergic fibres link the hippocampus and the vestibular system (Wei et al., 2018). A subsequent commentary to Prof. Previc's article by Prof. Paul Smith (Smith, 2013) gave a clear explanation that a patient diagnosed with AD might experience spatial navigational deficits and memory decline but still show a preserved VOR as the vestibular pathways contributing are different. Although more recent studies have already revealed that no association between VOR and cognitive impairment was found (Harun et al., 2016), I think that my patient presents the example Prof. Previc and Prof. Smith were looking for.

The second patient (93yrs old, $\alpha = 4.82^\circ/\text{sec}^2$) with abnormal egocentric and allocentric (egocentric+) performance had Left restricted striatocapsular diffusion, a mature lacunar infarction in the Left anterior thalamus and above and below tentorium volume loss. Importantly, this patient's performance for both the egocentric and allocentric tasks led to his exclusion from those analyses: (1) egocentric performance was with too many over the optimal with respect to the vestibular physiology rotations and (2) allocentric data were practically not analysable. This patient had no official diagnosis mentioned in his clinical record, although his memory issues were noted by neurologists who had seen the patient in the clinic. This patient' thalamic infarction might have also had profound implications considering the function of the thalamus as a relay station for the brain. The thalamus is possibly also implicated in the integration of information across cortical networks (Hwang et al., 2017), and the lack of transfer of the vestibular spatial information through it would result not only in spatial disorientation (and possibly also postural impairment) but also in the lack of conscious awareness of the vestibular signal involved. In addition, the volume loss in the region of the tentorium this 93yrs old patient exhibited, might reflect a cerebellar connection to the balance and spatial issues he showed. The latter follows from research suggesting the cerebellum might be involved in the vestibular-mediated perception of self-motion (Kleinschmidt et al., 2002), (Bronstein et al., 2008) and as such cerebellar networks contributing to velocity storage are expected to project to vestibular-cortical brain regions (Bronstein et al., 2008).

The Right side of the diagram (Fig. 48) presents the participants' performance within the normal vestibular motion perception range. Their behaviour fits my prediction model better as performance followed a more logical path. Two of the patients who experienced abnormal egocentric performance also exhibited a subsequent deterioration in their allocentric (egocentric+) skills. Notably, one of them showed mild bilateral hippocampal volume loss and mild angiopathic disease on their MRI scan, while the other had a mild SVD. The third patient had light congenital blindness of the right eye, and as their allocentric (egocentric+) performance was highly abnormal, I decided to exclude this patient from the analysis in order to consider their ophthalmological issue.

The last part of the diagram (the rightmost part) displays the patients with normal vestibular motion perception and normal egocentric performance. Two of these patients retained their normal allocentric

(egocentric+) performance, and it is important to note that these were patients considered by the clinical neurologists as “MCI patients”. However, no official “mild cognitive impairment diagnosis” existed for them. On the other hand, the rest of the patients, i.e. the three patients who exhibited abnormal allocentric (egocentric+) performance also showed some specifications on their MRI scans. The first patient had a ‘mature damage (maybe ischaemic) in the Right parietal lobe, microangiopathic disease and mild parietal volume loss’, while the second had ‘foci in supratentorial WM and mild microangiopathic ischaemic change, along with general cerebral volume loss’. The third patient did not have a clinically available scan.

Although it was helpful to observe real patients' spatial behaviour along with their MRI scans, a fine-grained analysis of MRI scans was complicated, and no generalisations could be made, considering all these individual medical histories and their specificities. Still, I note that as some of my patients were at quite advanced age, I often saw SVD being mentioned as part of their imaging reports. However, as SVD is an umbrella term for multiple pathologies, I could not draw any conclusions, as all possible spatial performance scenarios were available in my patients' performance (normal/abnormal motion perception, normal/abnormal egocentric and normal/abnormal allocentric (egocentric+) skills). Nevertheless, I note that both patients with explicit Right hippocampal volume loss and bilateral hippocampal volume loss, respectively, experienced abnormal egocentric and allocentric (egocentric+) skills (in addition to having a probable Alzheimer's diagnosis). On the other hand, ‘parietal volume loss’ and ‘not specified general cerebral volume loss’ patients experienced abnormal allocentric (egocentric+) skills only at this stage. The former patient (with ‘parietal volume loss’) had a probable AD diagnosis, while the latter (with ‘not specified general cerebral volume loss’) had performed within the normal range for all cognitive tests on a specialised cognitive examination outside of my study.

Interestingly, during testing, I had the chance to test twice the egocentric skills of one of the patients participating in my current analysis. This was a patient with a probable AD diagnosis (with minor SVD on their MRI scan) whose performance on the JOYSTICK task changed from almost perfect and slightly hypometric to extremely hypometric when the patient came visiting after 1 year and 3 months. Their average Slope result decreased from 0.86 to 0.44, and if looking at the beep delay, then for 1.5s – from 0.71 to 0.47 and for 6.5s – from 1.02 to 0.41. In contrast, their self-motion perception remained stable and within the normal range ($\alpha = 0.9043^\circ/\text{sec}^2$ and $\alpha = 0.8949^\circ/\text{sec}^2$, respectively).

5.3. VMP is not an accepted way to divide patients in groups but shows its potential.

5.4. The anatomical correlates of vestibular-guided spatial disorientation in Alzheimer's disease.

IV. Conclusion (section A and B)

In this Chapter V, I explored the feasibility of the idea that vestibular-guided spatial navigational comprised three tasks with stepwise increasing cognitive demand. These tasks I presented as part of a behavioural testing battery, first to (a) healthy volunteers separated into three age groups and then to (b) patients with memory and (balance) complaints.

My main findings were that **(1)** patients with decreased cognitive skills displayed an abnormal motion perception performance and **(2)** poor spatial behaviour during both the egocentric and the allocentric (egocentric+) tasks. This suggested that motion perception over a certain point might no longer be perceivable. **(3)** Patients with cognitive decline formed a plateau of angular responses for the allocentric (egocentric+) task, which might suggest place and grid-cells-like representation damage preventing the formation of a spatial map. **(4)** Two out of these three patients forming the plateau had hippocampal volume loss, and the third “might” have had communicating hydrocephalus, as based on their clinically available MRI scans. In addition, **(5)** two out of the three patients fell on the “soft surface, eyes-closed” (SC) vestibular-guided posturography condition (data in Chapter IV). Furthermore, as previously discussed, these cognitively impaired patients (i.e. $MMSE \leq 24$) were more affected by the corrections of the JOYSTICK results from a vestibular system point of view. In comparison, **(6)** patients with preserved vestibular motion perception (and in this case also preserved cognitive skills, $MMSE > 24$) had a less varied and more predictable behaviour.

Correlation analysis revealed **(7)** a more considerable number of significant correlations between the MMSE and ACE’s components with the allocentric (egocentric+) task, and **(8)** no significant correlations with the egocentric task, stressing the cognitive load the allocentric (egocentric+) task must have had posed.

Whereas **(9)** the JOYSTICK task turned out to be the better task to distinguish between the three controls groups (<40yrs, <(40-60)yrs, >60yrs), it was **(10)** the MOUNTAIN task that better differentiated between patients and controls >60yrs. Still, the MOUNTAIN task did not manage to discriminate statistically, but only *by observation* within patients (i.e. $MMSE \leq 24$ and $MMSE > 24$), possibly because of the small number of participants. I note that **(11)** often, patients with preserved cognitive skills (i.e. $MMSE > 24$) and healthy controls >60yrs showed a similar trend in their spatial behaviour, although their egocentric performance was more alike than their allocentric (egocentric+) performance. Still, they managed to show a gradual and logical process of spatial navigational performance and its negative development from health to early disease.

Lastly, **(12)** the vestibular self-motion perception showed a significant negative correlation with MMSE and emerged as an acceptable way to divide patients into groups as an alternative to cognitive tests such as the MMSE. Still, vestibular motion perception and MMSE did not show a complete match, i.e. abnormal self-motion did not always equal the decreased MMSE score.

Chapter VI

Diffusion tensor imaging - TBI study

A. DTI WHOLE-BRAIN ANALYSIS

1. Introduction

Animal and human-based studies have shown that traumatic brain injury (TBI) is a dynamic insult, triggering a sequence of secondary processes, with often unexpected complications (Werner & Engelhard, 2007), (Jolly, 2020). Atrophy after TBI is not limited to grey matter (GM) damage alone but, in fact, is even more often and at greater rates observed in white matter (WM) (Cole et al., 2015), (Jolly, 2020). Traumatic brain injury is often followed by axonal lesions that damage long-distance white matter connections (Johnson et al., 2013), (Fagerholm et al., 2015). Still, even if diffuse axonal injury (DAI) “plays a fundamental role in the pathophysiology of TBI” (Jolly, 2020), it is difficult to measure in the clinic (Jolly, 2020), (Bourke et al., 2021).

One possible reason is that standard clinical imaging, such as computed tomography (CT) that is performed acutely at the emergency room, can miss subtle WM damage or microscopic lesions after TBI (Mac Donald et al., 2007), (Kinnunen et al., 2011), (Sharp et al., 2014), (Jolly, 2020), (Bourke et al., 2021). To address this limitation, a more advanced imaging technique, such as diffusion tensor imaging (DTI), can be used. It can quantitatively observe the subtle abnormalities and allow for a high-quality *in vivo* measure able to detect changes in WM disruption thanks to its diffusion-derived metrics (Mac Donald et al., 2007), (Kinnunen et al., 2011). Studies have shown that even mild TBI damage can reliably be detected and assessed by DTI (Kraus et al., 2007). What is more, diffusion tensor imaging was able to detect white matter atrophy also in scans that were otherwise reported as unremarkable (Hellström et al., 2017), (Jolly, 2020), thus giving TBI patients a better chance for recovery.

However, if not properly diagnosed and thus not properly treated, patients can be left with long-term disabilities, showing among others a significant dependence on activities such as spatial orientation and/or the maintenance of proper balance. Research in acute TBI/concussion shows that patients exhibit a decreased cognitive ability to learn their orientation during active locomotion (McFarlane et al., 2020) alongside increased body sway and are thus more prone to falls up to six months into their chronic state (Akin & Murnane, 2011).

TBI is considered a leading cause of long-term disability (Langlois et al., 2006) not only in the elderly but also in young adults (Calzolari and Chepishcheva et al., 2021), preventing them from returning to their normal daily routine. In fact, while 75% of mild TBI survivors without any vestibular features (e.g. dizziness) (mean age $31.6\text{yrs} \pm 12.3$) were likely to return to work after six months post-injury, only 33% of those with accompanying vestibular dysfunction (mean age $33.6\text{yrs} \pm 11.6$) were able to do so (Chamelian & Feinstein, 2004), (Calzolari and Chepishcheva et al., 2021).

However, despite its importance in the recovery from traumatic brain injury, vestibular dysfunction and its neural mechanisms underlying spatial and postural impairment after TBI are poorly understood (Calzolari and Chepishcheva et al., 2021). Some possible reasons for this lie in the fact that there are (1)

no acute vestibular TBI data in the literature that can help to better understand the aetiology of brain damage and the long-term consequences after TBI (Marcus et al., 2019). In addition, there are (2) no TBI prospective studies (with a bigger sample size) examining the spatial and postural processing under central vestibular guidance. Therefore, in this Chapter VI, I performed a whole-brain DTI analysis looking at the effect of acute TBI on vestibular-guided spatial and postural processing (i.e. Hypotheses I and III). My objectives were:

1. To investigate how the brain mechanisms of vestibular spatial orientation or vestibular balance were affected during acute TBI and what WM regions were implicated based on DTI analysis?
2. To investigate if vestibular-guided spatial and postural modalities shared a common neuronal network and where these network regions were located?

2. Materials and Methods

2.1. Recruitment of patients

Please refer to Chapter II for the inclusion/exclusion criteria of this study and to Chapter III for more detailed information about acute TBI patients and their demographics. Importantly, only 30 acute TBI patients and 36 healthy controls completed the imaging part of this study.

2.2. Methodology

This PhD study was a multi neuroimaging initiative comprising two types of analysis - DTI and VBM whole brain and ROI analyses. Specifically, in this section “A” of Chapter VI, I concentrated on a whole-brain DTI analysis. In a subsequent section “B”, I looked in more depth into the statistical relations of the white matter tracts that proved notable or showed a tendency towards significance during my initial vestibular-based whole-brain DTI analysis.

Using DTI whole brain analysis, I investigated the WM microstructure in acute TBI patients by calculating four DTI-derived parameters - fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). Please refer to Fig. 18. (Chapter II) for a schematic overview of the DTI pipeline and the statistical analysis conducted after the tract-based spatial statistics (TBSS). After TBSS, I was able to perform whole-brain statistical analysis based on mean value DTI parameters’ measures derived from TBSS (Behrens et al., 2003), and later - whole-brain voxelwise statistical calculation via FSL GLM. I used FSL GLM to set contrast and design matrices with the parameters of interest.

I used two FSL incorporated atlases to estimate the brain regions involved in each of the contrasts: (1) JHU ICBM-DTI-81 white-matter labels atlas (Mori et al., 2008) and (2) JHU white-matter tractography atlas (Hua et al., 2008). I always present the images overlaid on the mean FA skeleton mask (derived during the DTI analysis) and upon a standard MNI 152 T1 brain. In addition, I report the complete MNI

coordinates of the maximum intensity voxel and the brain regions it involved based on the FSL atlases – MNI coordinates as per [X, Y, Z] with X for the sagittal plane, Y for the coronal plane and Z for the axial plane coordinates. All imaging analysis was conducted on Ubuntu Debian and Jupyter. Please refer to Chapter II. for a detailed explanation of the behavioural tasks (i.e. the VMP, Sway and EOG) used in this Chapter.

FRACTIONAL ANISOTROPY

A table with the main voxelwise contrasts consisting of correlations and t-tests (i.e. comparisons) that were reported for FA is presented in Table.10. The contrasts of interest are in yellow.

<i>Voxelwise Correlations</i>	<i>Voxelwise Comparisons (t-tests)</i>
ABNORMAL* patients to TASK (positive test)	ABNORMAL patients FA < NORMAL patients FA (positive test)
ABNORMAL patients to TASK (negative test)	ABNORMAL patients FA > NORMAL patients FA (negative test)
NORMAL* patients to TASK (positive test)	ABNORMAL patients FA < Controls (positive test)
NORMAL patients to TASK (negative test)	ABNORMAL patients FA > Controls (negative test)
Controls to TASK (positive test)	NORMAL patients FA < Controls (positive test)
Controls to TASK (negative test)	NORMAL patients FA > Controls (negative test)

Table. 10. Voxelwise correlations and Voxelwise t-tests for Fractional anisotropy (FA) – general scheme. Legend: **ABNORMAL* patients perform abnormally for Vestibular Motion perception or Sway 95% confidence ellipse SC (task is specified). **NORMAL* patients perform normally for Vestibular Motion perception or Sway 95% confidence ellipse SC (task is specified). In yellow colour, I specified the contrasts of interest for the FA analysis as based on the relationship between the VMP/Sway data and FA parameter.

Whereas the meaning of the t-tests contrasts in Table.10. seem straightforward, an example of the correlations is presented. For instance, I take “ABNORMAL patients to TASK” (negative test) and use FA and VMP (as TASK) as examples. This way, “ABNORMAL patients to TASK” (negative test) becomes “What was the correlation between the FA of the abnormally performing VMP patients AND their own VMP results”. I also mention that it was a negative test, as the correlation between FA and the VMP test was expected to be opposite – FA decreased with TBI damage, whereas the VMP threshold increased (i.e. worsened) with damage.

For the t-test (comparisons), positive and negative tests had a similar meaning - it was to be expected that the ABNORMAL VMP patients FA < NORMAL VMP patients FA. Therefore, this was a “positive test” and the remaining one – was negative.

MEAN DIFFUSIVITY, AXIAL DIFFUSIVITY and RADIAL DIFFUSIVITY

A table with the main voxelwise contrasts consisting of correlations and t-tests (comparisons) that were reported for MD is presented in Table.11. The same scheme applied also to AD and RD.

The relationship that MD held with the VMP/Sway/EOG tests was the opposite of what the relationship of FA was, i.e. the increase of MD correlated positively with the increased (i.e. worsened) VMP result, Sway and EOG.

<i>Voxelwise Correlations</i>	<i>Voxelwise Comparisons (t-tests)</i>
ABNORMAL* patients to TASK (positive test)	ABNORMAL patients MD < NORMAL patients FA (positive test)
ABNORMAL patients to TASK (negative test)	ABNORMAL patients MD > NORMAL patients FA (negative test)
NORMAL* patients to TASK (positive test)	ABNORMAL patients MD < Controls (positive test)
NORMAL patients to TASK (negative test)	ABNORMAL patients MD > Controls (negative test)
Controls to TASK (positive test)	NORMAL patients MD < Controls (positive test)
Controls to TASK (negative test)	NORMAL patients MD > Controls (negative test)

Table. 11. Voxelwise correlations and Voxelwise t-tests for Mean Diffusivity (MD) – general scheme. Legend: **ABNORMAL* patients perform abnormally for Vestibular Motion perception or Sway 95% confidence ellipse SC (task is specified). **NORMAL* patients perform normally for Vestibular Motion perception or Sway 95% confidence ellipse SC (task is specified). In yellow are the contrasts of interest.

If taking the VMP task as an example (Table.11), “ABNORMAL patients to TASK” (positive test) becomes “What was the correlation between the MD of the abnormally performing VMP patients AND their own VMP results”. I also mention that it was a positive test, as the correlation between MD and the VMP test was expected to be positive – MD increased with TBI damage and also did the VMP threshold (i.e. it worsened) with damage.

For the t-test, I used the same list of conditions for the contrasts as for FA, but here I took the negative test, which in the case of MD was the logical choice if following the previously established order.

2.3. Statistical analysis

For my analysis, I use three types of division: (1) patient/control, (2) based on their vestibular motion perception performance (VMP) (i.e. into normal/abnormal performance), and (3) based on their Sway 95% confidence ellipse/posturography performance in the eyes-closed condition on a foamy surface, i.e. vestibular-driven posturography condition (similarly, into normal/abnormal performance).

The Shapiro-Wilk test informed the use of parametric statistics. For all analyses, the alpha-level was set at 0.05.

DTI – mean value analysis:

A group-level comparison between acute TBI patients and controls was performed for mean value FA, MD, AD and RD using the independent sample t-test. To quantify the effects reported, t-statistics data were included.

One-way ANOVA was performed for the four DTI measures to assess the difference between abnormal VMP/normal VMP/control or abnormal Sway/normal Sway/control groups. To quantify the effects reported, eta squared values for F-tests were included. All significant results were further investigated with a Post Hoc with Bonferroni corrections. ANCOVA analysis with AGE and GENDER as covariates is available in Appendix.

Lastly, a ‘patient only’ correlation analysis using the Pearson’s test informed about the potential link between VMP/Sway tests and the four DTI parameters. In addition, the DTI parameters were also analysed with the Pearson’s test for a correlation to more of the behavioural tests used in Chapter III.

DTI – voxelwise analysis:

This DTI analysis presented only contrasts corrected for multiple hypothesis testing at a threshold of 0.05 via fsl randomise (Winkler et al., 2014) with 10,000 permutations for each contrast. The contrasts were the primary findings of this analysis and, as such, were displayed in the following images. It is of note that the output of the voxelwise contrast was a value that, when subtracted from “1.0” provided the p -value of this contrast.

Importantly, I report not only statistically significant contrasts (i.e. contrast value ≥ 0.95), but also something I called “tendencies”. They had contrast values between [0.9 – 0.949], and their corresponding p -values were between [0.1 and 0.051]. Tendencies were an essential component of my vestibular-driven observation analysis in all of the imaging chapters. Even if caution must be taken with their overinterpretation, such “tendencies” might become an important “target” in a longitudinal TBI research and/or in a bigger sample size of possibly more severe TBI patients.

Lastly, even if my analysis concentrated on statistically significant results and tendencies, around 400 DTI images are available for contrasts between 0.7-0.9, presenting sagittal, coronal, and axial planes. In addition, exploratory voxelwise analysis was performed for all of the tests discussed in Chapter III, with no specific notable results to report (all these data are available upon request).

3. Results

I. DTI MEAN WHOLE-BRAIN VALUE ANALYSIS

3.1. Analysis of variance

A mean whole-brain value analysis of DTI-derived parameters was performed between acute TBI patients and healthy individuals. Figure. 49. shows a statistically notable distinction between the acute TBI patients and controls for three out of the four DTI parameters: FA ($t(64) = 2.32, p = 0.02^*$), MD ($t(64) = -2.01, p = 0.04^*$) and RD ($t(64) = -2.36, p = 0.02^*$), but not for AD, where the data were similar between groups, ($t(64) = -0.24, p = 0.80$).

For Fractional Anisotropy (Fig. 50.), the analysis showed a clear difference among groups, with controls displaying the highest mean FA values > normally performing patients FA > abnormally performing patients FA for the VMP and Sway task. However, ANOVA did not show any effect of group for VMP division ($F[2,63] = 2.92, p = 0.06$), even if a close tendency was present. Still, ANOVA showed a statistical significance for vestibular Sway-based sub-groups ($F[2, 63] = 4.17, p = 0.02^*, \eta^2 = 0.11$), and a Post Hoc revealed that it is the “*control – elevated (abnormal) Sway patients*” that contributed to this main effect – $p_{(bonf)} = 0.01^*$.

Next, Mean diffusivity (MD) measures are presented in Fig. 51. For both behavioural tasks (i.e. VMP and Sway), the elevated (i.e. abnormally performing) patients showed the highest MD values, followed

by the normally performing patients and lastly, by controls (sometimes controls and normally performing patients were identical in their MD measures). Statistical analysis showed no effect of group for VMP ($F[2, 63] = 2.20, p = 0.11$). However, similar to FA analysis, also for MD analysis, only vestibular Sway-based division showed an effect of group - ($F[2, 63] = 4.01, p = 0.02^*, \eta^2 = 0.11$), which was due to the “*control – elevated (abnormal) Sway patients*” – $p_{(bonf)} = 0.01^*$.

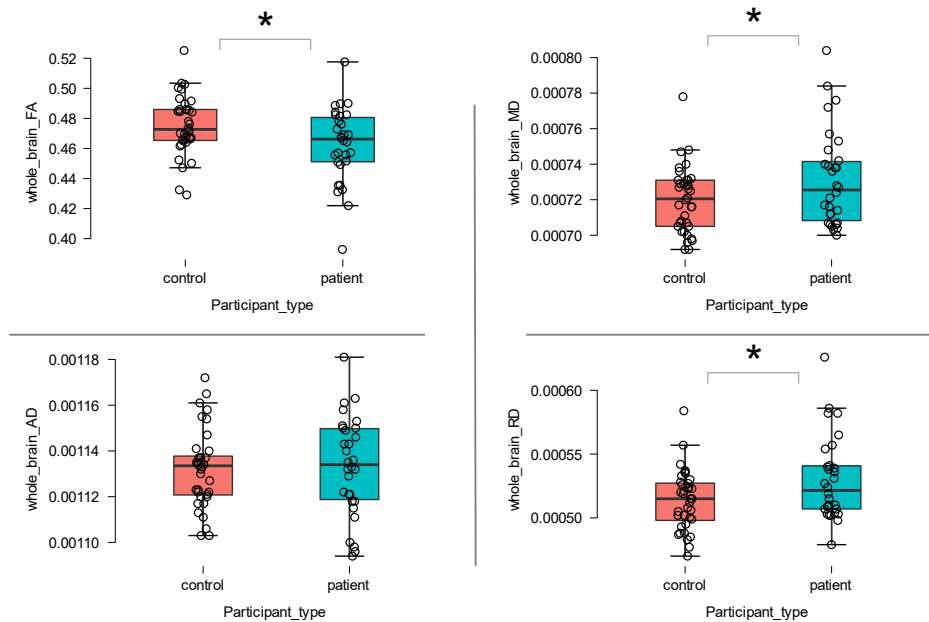


Figure.49. Comparison between patient/controls for FA, MD, AD and RD (median + IQR).

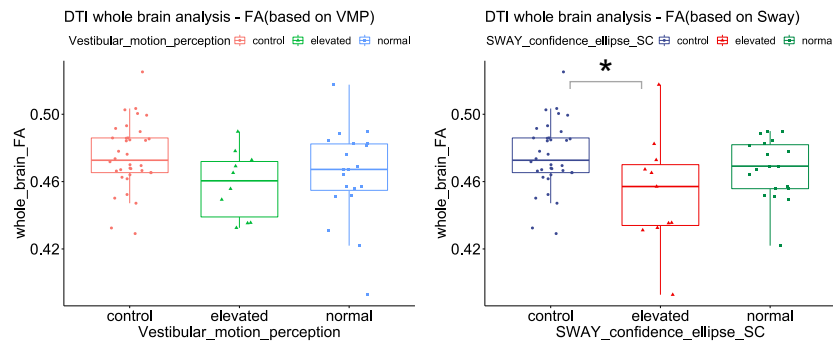


Figure. 50. DTI Mean whole-brain analysis for Fractional anisotropy (FA) based on VMP (left) and Sway (right) division (median + IQR).

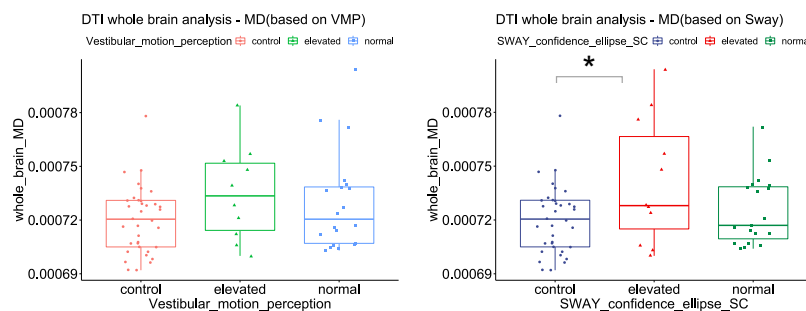


Figure. 51. DTI Mean whole-brain analysis for Mean Diffusivity (MD) based on VMP (left) and Sway (right) division (median + IQR).

Whole-brain Axial Diffusivity (AD) displayed only a small difference among sub-groups for the three division methods (Fig. 52). Thus, ANOVA did not show any effect of sub-group: VMP ($F[2, 63] = 0.04, p = 0.95$), Sway ($F[2, 63] = 0.65, p = 0.52$).

Lastly, Radial Diffusivity (RD) (Fig. 53.) showed a consistently clear difference among groups with controls $RD < \text{normally performing patients } RD < \text{abnormally performing patients } RD$ for the two behavioural tasks. Still, ANOVA did not show an effect of group for VMP division, although there was a close tendency towards significance ($F[2, 63] = 3.02, p = 0.056$). Further, vestibular Sway-based division achieved an effect of group ($F[2, 63] = 4.83, p = 0.01^*, \eta^2 = 0.13$), which a Post Hoc revealed to be driven by the “*control – elevated (abnormal) Sway patients*” – $p_{(bonf)} = 0.009^{**}$.

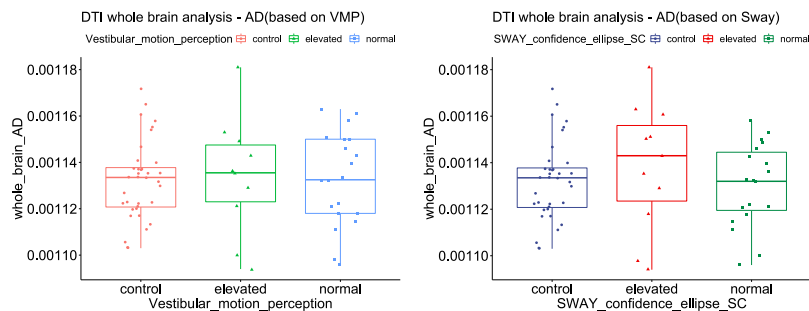


Figure. 52. DTI Mean whole-brain analysis for Axial Diffusivity (AD) based on VMP (left) and Sway (right) division (median + IQR).

An exploration of mean whole-brain DTI parameters analysis for VMP and vestibular Sway based on AGE and GENDER as covariates is available in Appendix, alongside similar analysis about the effect of normal ageing within controls data.

My next step was to perform a correlation analysis for ‘*patients only*’ DTI-derived parameters and their VMP and vestibular Sway tests. No correlation was observed with the VMP or vestibular Sway tasks. Further, no statistically important results were noted when looking for a correlation between “all patients” as one group’ and the behavioural, neuropsychological, neurophysiological or psychophysics tests discussed in Chapter III and the whole-brain DTI parameters presented in this Chapter VI. The results were similar when taking only the patients with elevated VMP or poor balance – no correlations worth mentioning.

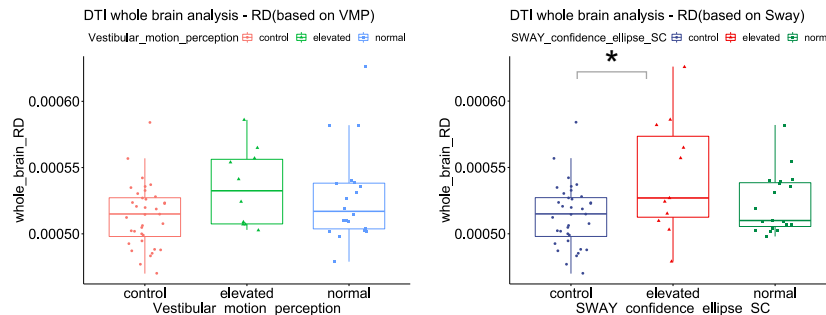


Figure. 53. DTI Mean whole-brain analysis for Radial Diffusivity (RD) based on VMP (left) and Sway (right) division (median + IQR).

Further, no correlation was found between DTI parameters and GCS (Glasgow Coma Scale) score, and PTA (Post-Traumatic amnesia). However, ‘GCS at scene – PTA (in days)’ and ‘lowest GCS – PTA (in days)’ showed a statistically notable Pearson’s $r = -0.63, p < 0.001^{***}$ and $r = -0.70^{***}, p < 0.001^{***}$, respectively. Lastly, I investigated for a correlation between “days since injury” and the DTI parameters but found no statistically notable results (irrespective if patients were taken as one group or I only looked at abnormally performing VMP/Sway patients).

II. DTI WHOLE-BRAIN VOXELWISE ANALYSIS

The following sections, A, B, C and D, present a brief summarised version of the data for this analysis, whereas a detailed report containing information about MNI coordinates of the maximum intensity voxels/cluster specifications and specific suggested brain regions for the significant and tendency results is available in Appendix.

A. FRACTIONAL ANISOTROPY (FA)

1) FA - Vestibular motion perception division

In this vestibular-guided spatial and postural study, there were 10 patients with abnormal VMP performance and 20 with normal VMP, alongside 36 healthy age-matched controls.

a) FA Voxelwise Correlations

Fractional anisotropy (FA) voxelwise correlation analysis revealed no significant correlation between “all patients to VMP data” ($p = 0.2319$). When further dividing the participants into three groups based on their VMP performance (i.e. abnormally/normally performing VMP patients and controls), I used not only VMP data as an input for possible correlations but also vestibular Sway data and EOG data. The data in Fig. 54. present a trend towards significance only for the “**abnormal VMP patients to Sway**” correlation (with an axial-plane image displayed, $p = 0.0854$), whereas “abnormal VMP patients to VMP” and “abnormal VMP patients to EOG” remained insignificant. Interestingly, when dividing VMP into Right-sided and Left-sided performance, no statistical significance was achieved either – Right-sided threshold ($p = 0.1204$) and Left-sided threshold ($p = 0.8404$).

b) FA Voxelwise Comparisons (t-tests)

Fractional anisotropy (FA) voxelwise t-test analysis revealed a significant difference between patients and controls FA (i.e. “**patients FA < controls FA**”, $p = 0.0035^{**}$).

Further, when dividing the patients into their VMP performance (Fig. 55.), there were two significant comparisons - “**abnormal VMP FA < controls FA**” ($p = 0.016^{*}$) and “**normal VMP FA < controls FA**” ($p = 0.0192^{*}$).

2) FA - Sway 95% confidence ellipse SC (Soft Closed) division

In this study, there were 11 patients with abnormal vestibular-guided Sway performance and 19 with normal vestibular-driven Sway performance, alongside 36 healthy age-matched controls.

a) FA Voxelwise Correlations

The “*all participants to Sway*” correlation revealed a statistically notable result ($p = 0.0051^{**}$). When looking into a *patient/control* division, I note that “*patients to Sway*” was significant (p -value = 0.0386^{*}).

Further, I divided patients based on their vestibular Sway performance into abnormally/normally performing for the Sway task and used either Sway data or VMP or EOG data as an input for the correlations (Fig. 56).

Two contrasts above 0.9 were noted - one of them was significant “*abnormal Sway patients to EOG*” ($p = 0.0214^{*}$), and the other “*abnormal Sway patients to VMP*” showed a trend towards significance ($p = 0.0719$).

b) FA Voxelwise Comparisons (t-tests)

Fractional anisotropy (FA) voxelwise t-test analysis based on Sway performance division revealed three contrasts above 0.9 and two of them were significant (Fig. 57.). These were “*abnormal Sway patients FA < normal Sway patients FA*” ($p = 0.0359^{*}$), “*abnormal Sway patients FA < controls FA*” ($p = 0.0011^{**}$) and “*normal Sway patients FA < controls FA*” showing only a tendency ($p = 0.066$).

B. MEAN DIFFUSIVITY (MD)

1) MD - Vestibular motion perception division

a) MD Voxelwise Correlations

MD voxelwise correlation for “*all participants to VMP*” showed a significant result ($p = 0.0449^{*}$). When dividing into patients/controls subgroups, the correlation lost significance, but it was the patients and not the controls who contributed to its previously reported significant result – “*patients to VMP*” ($p = 0.0973$).

Further, when dividing the patients based on their VMP performance (Fig.58.), similar to FA analysis, a tendency towards significance was reached only for “*abnormal VMP patients to Sway*” ($p = 0.0634$).

b) MD Voxelwise Comparisons (t-tests)

The mean diffusivity t-test revealed a significant result for “*patients MD > controls MD*” ($p = 0.0443^{*}$). Further, when dividing based on the VMP test, “*abnormal VMP patients MD > controls MD*” was significant ($p = 0.0351^{*}$)(Fig. 59).

2) MD – Sway 95% confidence ellipse SC (Soft Closed) division

a) MD Voxelwise Correlations

“*All participants to Sway*” showed a significant correlation ($p = 0.015^*$), but when dividing into patients/controls subgroups, only the “*patients MD to Sway*” correlation remained notable ($p = 0.0411^*$).

Further, when dividing patients into Sway performance groups, there were two significant contrasts. Interestingly, “*abnormal Sway patients to Sway*” did not reach significance, similar to FA Sway-based analysis. However, “*abnormal Sway patients to VMP*” was statistically important ($p = 0.0486^*$).

The other significant correlation was “*abnormal Sway patients to EOG*” ($p = 0.0067^{**}$) (Fig.60).

b) MD Voxelwise Comparisons (t-tests)

Patients MD > controls MD was significant ($p = 0.0443^*$) and Sway-based division revealed the drivers of this result - “*abnormal Sway patients MD > normal Sway patients MD*” ($p = 0.0321^*$) and “*abnormal Sway patients MD > controls MD*” ($p = 0.0076^{**}$) (Fig. 61).

C. AXIAL DIFFUSIVITY (AD)

Due to the more dynamically changing profile of axial diffusivity (Sidaros et al., 2008), its relationship with the three behavioural tests (i.e. VMP, vestibular Sway and EOG) was more difficult to interpret than for FA and MD.

Close to the event (i.e. even the first few hours), axial diffusivity after TBI shows to be lower in experimental models (Mac Donald et al., 2007), which would indicate a negative correlation between the tests and the AD. However, with increasing time after TBI, axial diffusivity shows higher values in patients as compared to controls, suggesting an ongoing axonal recovery (Sidaros et al., 2008), (Kinnunen et al., 2011) and a positive correlation to the VMP/Sway/EOG test in this spatial and postural study under vestibular guidance.

Another critical factor to consider is the time of the scan and the days that have passed since the injury contributing to the stabilisation of the white matter (WM) changes. Literature suggests that scanning after the seventh day is an appropriate time to acquire good-quality FA data (FA as the proxy of white matter damage) (Edlow et al., 2016). The patients in this study were scanned on average 24 days (range [9-77days]) after the injury, thus in agreement with previous research. A last consideration for my decision was the observed slight trend towards an increase of the AD values during the mean whole-brain value analysis. Thus, I considered an ongoing axonal recovery and decided to look at the positive relationship between AD and the VMP/Sway/EOG tests. Consequently, I followed the same rules as outlined for mean diffusivity (MD) in Table.11. Still, caution must be taken so as not to overinterpret AD results, keeping in mind their dynamic profile in the acute period of TBI. Therefore, AD diffusivity analysis for the VMP and vestibular Sway division, alongside brain images are available in Appendix.

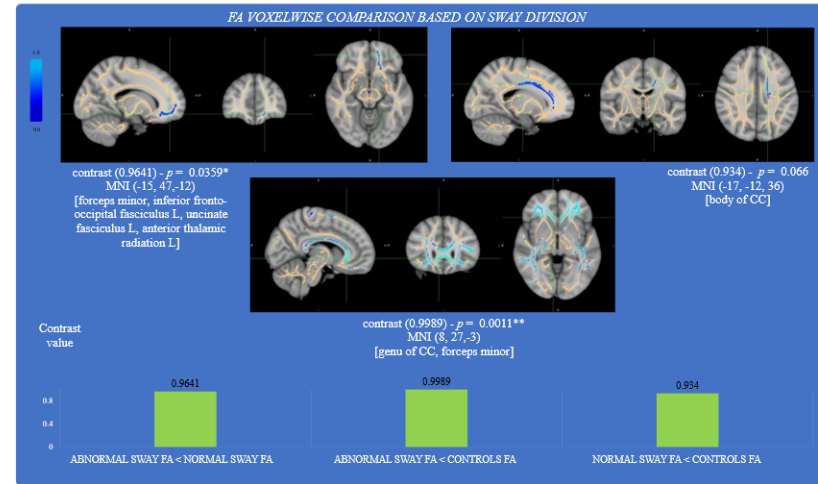
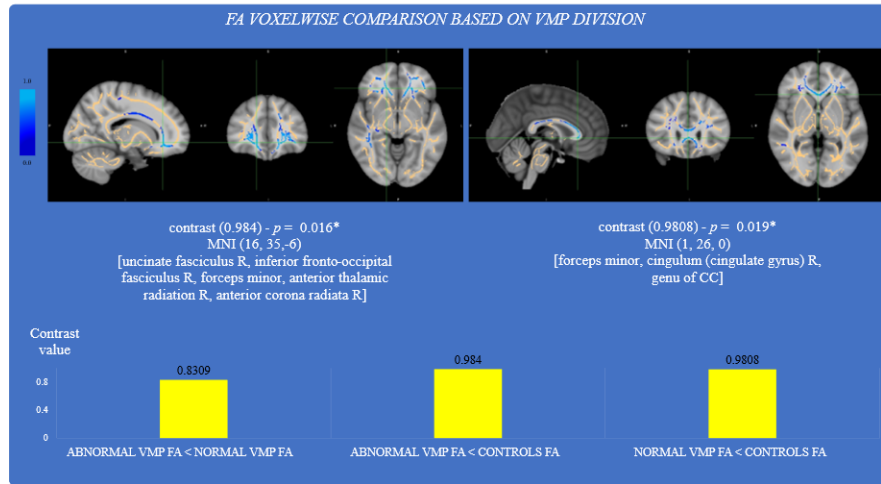
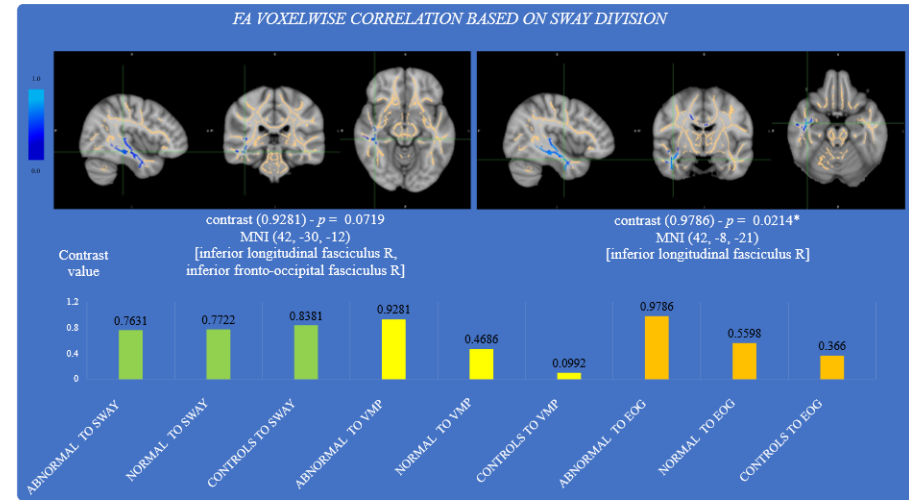
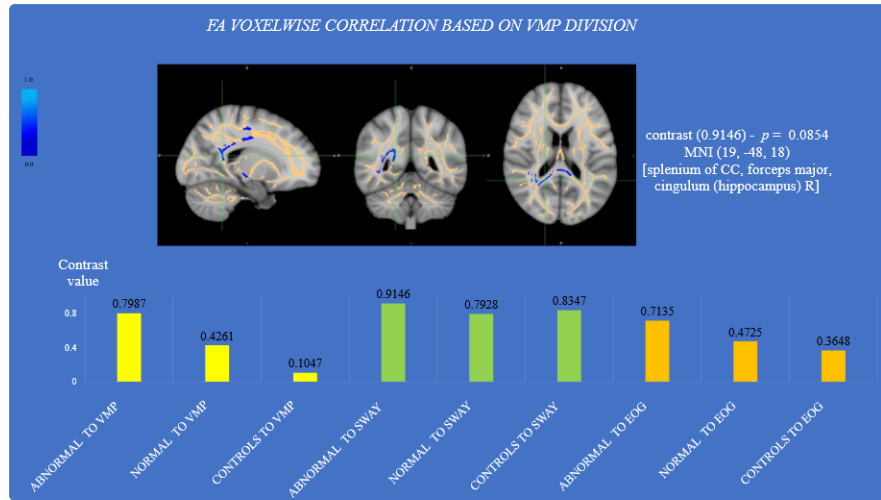


Figure.54. Fractional Anisotropy (FA) Voxelwise Correlation based on VESTIBULAR MOTION perception division (panel – top row – left).

Figure.55. Fractional Anisotropy (FA) Voxelwise Comparison based on VESTIBULAR MOTION perception division (panel – bottom row – left).

Figure.56. Fractional Anisotropy (FA) Voxelwise Correlation based on SWAY 95% confidence ellipse division (panel – top row – right).

Figure.57. Fractional Anisotropy (FA) Voxelwise Comparison based on SWAY 95% confidence ellipse division (panel – bottom row – right).

Legend to Fig. 54,55,56 and 57: *VPM – Vestibular motion perception, yellow colour – Vestibular motion perception data; green colour – Sway 95% confidence ellipse data; orange colour – EOG data; *ABNORMAL patients perform abnormally for Vestibular Motion perception/ Sway 95% confidence ellipse SC task (indicated on each panel), *NORMAL patients perform normally for Vestibular Motion perception/ Sway 95% confidence ellipse SC task (indicated on each panel). Only contrasts above 0.9 are displayed with images (in radiological orientation).

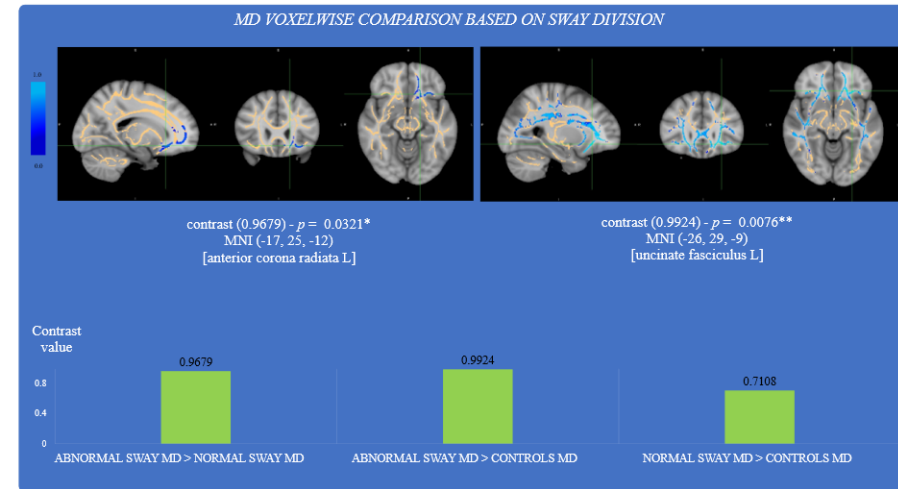
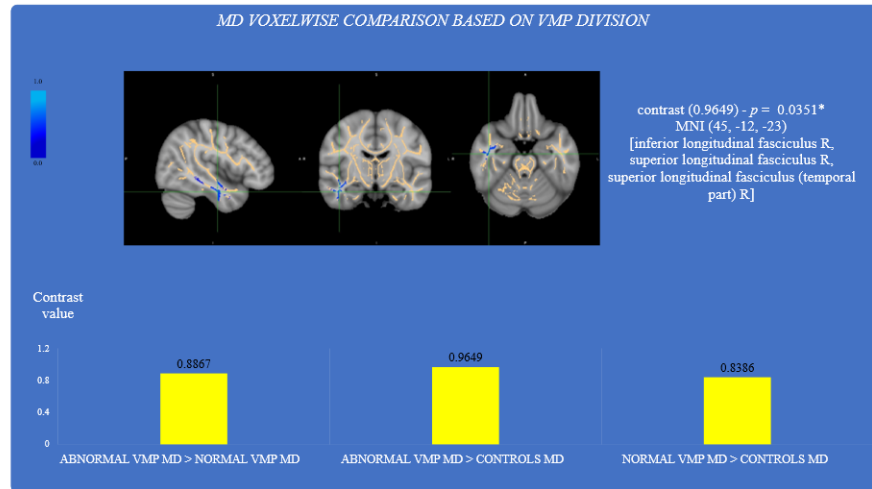
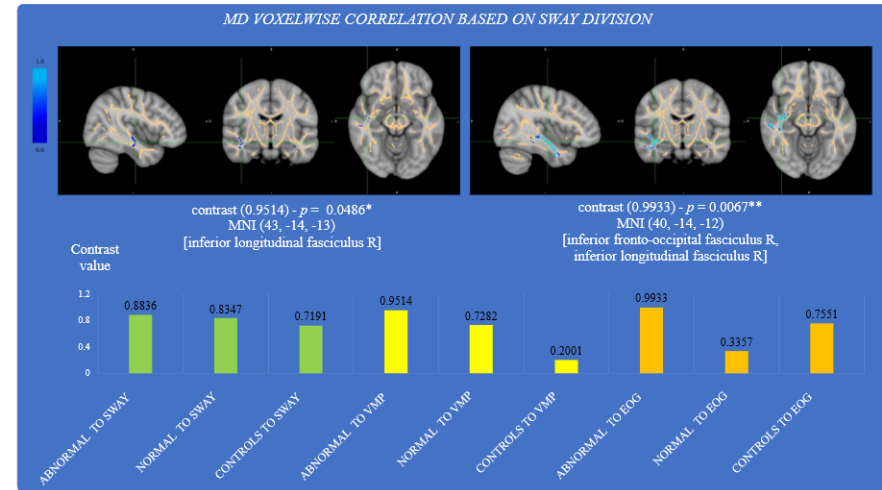
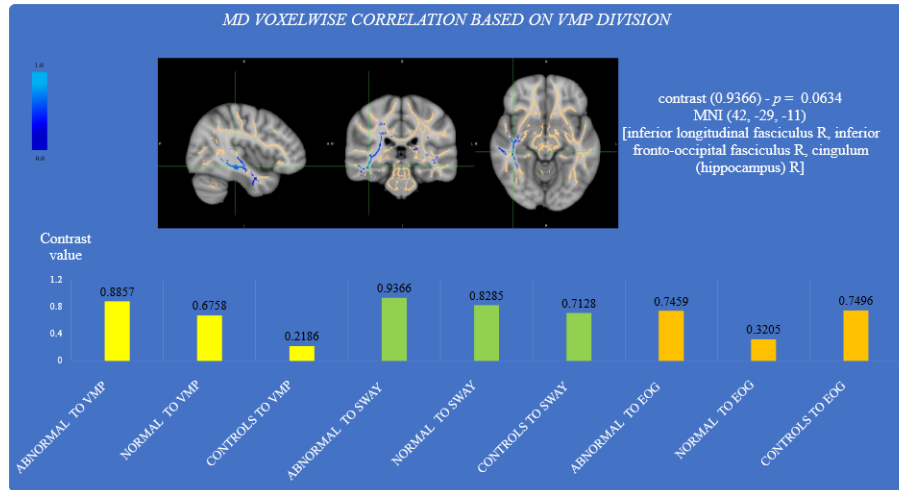


Figure.58. Mean Diffusivity (MD) Voxelwise Correlation based on VESTIBULAR MOTION perception division (panel – top row – left).

Figure.59. Mean Diffusivity (MD) Voxelwise Comparison based on VESTIBULAR MOTION perception division (panel – bottom row – left).

Figure.60. Mean Diffusivity (MD) Voxelwise Correlation based on SWAY 95% confidence ellipse division (panel – top row – right).

Figure.61. Mean diffusivity (MD) Voxelwise Comparison based on SWAY 95% confidence ellipse division (panel – bottom row – right).

Legend to Fig. 58,59,60 and 61: *VPM – Vestibular motion perception, yellow colour – Vestibular motion perception data; green colour – Sway 95% confidence ellipse data; orange colour – EOG data; *ABNORMAL patients perform abnormally for Vestibular Motion perception/ Sway 95% confidence ellipse SC task (indicated on each panel), *NORMAL patients perform normally for Vestibular Motion perception/ Sway 95% confidence ellipse SC task (indicated on each panel). Only contrasts above 0.9 are displayed with images (in radiological orientation).

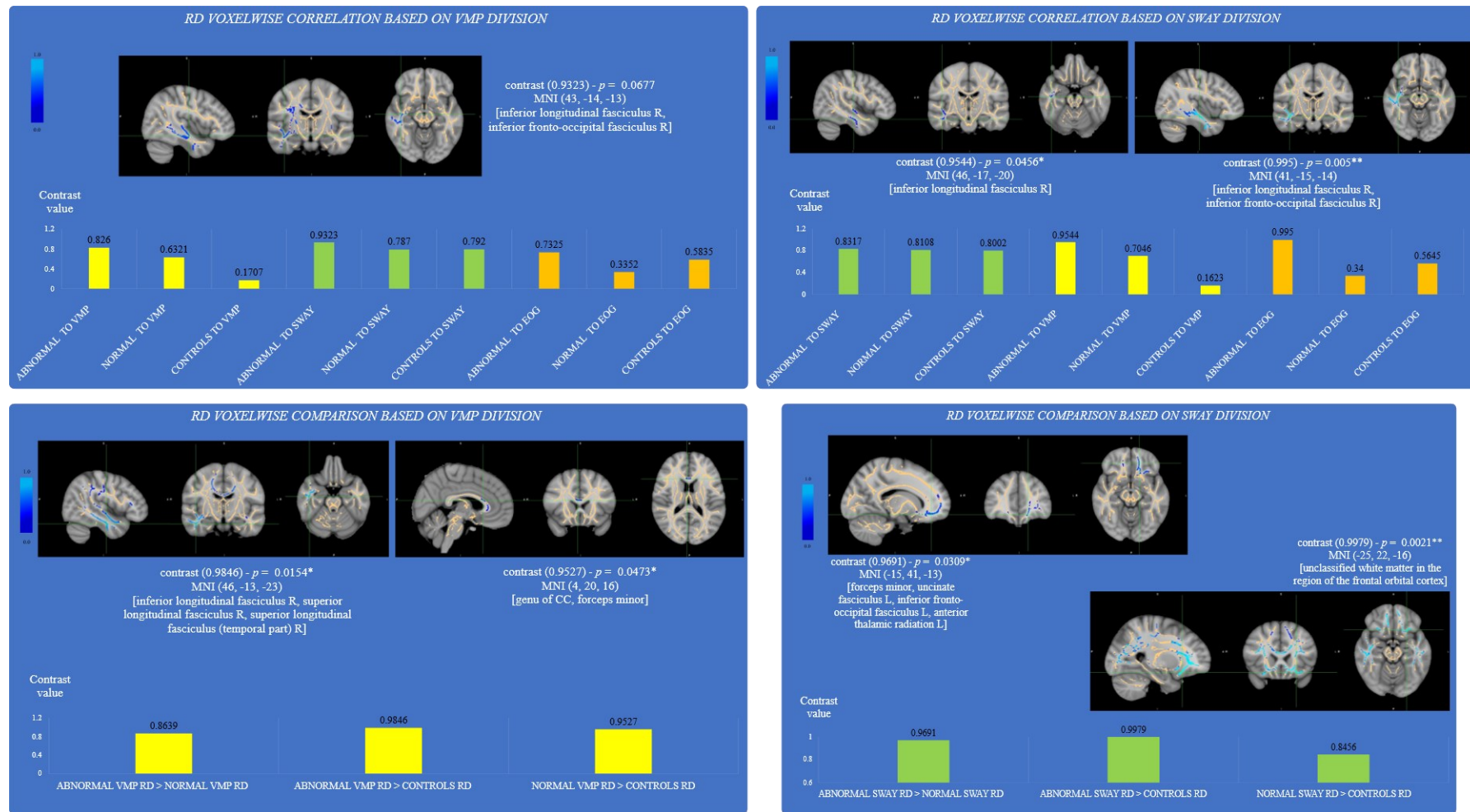


Figure. 62. Radial Diffusivity (RD) Voxelwise Correlation based on VESTIBULAR MOTION perception division (panel – top row – left).

Figure. 63. Radial Diffusivity (RD) Voxelwise Comparison based on VESTIBULAR MOTION perception division (panel – bottom row – left).

Figure. 64. Radial Diffusivity (RD) Voxelwise Correlation based on SWAY 95% confidence ellipse division (panel – top row – right).

Figure. 65. Radial Diffusivity (RD) Voxelwise Comparison based on SWAY 95% confidence ellipse division (panel – bottom row – right).

Legend to Fig.62,63,64 and 65: *VPM – Vestibular motion perception, yellow colour – Vestibular motion perception data; green colour – Sway 95% confidence ellipse data; orange colour – EOG data; *ABNORMAL patients perform abnormally for Vestibular Motion perception/ Sway 95% confidence ellipse SC task (indicated on each panel), *NORMAL patients perform normally for Vestibular Motion perception/ Sway 95% confidence ellipse SC task (indicated on each panel). Only contrasts above 0.9 are displayed with images (in radiological orientation).

D. RADIAL DIFFUSIVITY (RD)

The contrasts of interest for Radial diffusivity (RD) were the same as for MD (See Table. 11).

1) RD - Vestibular motion perception division

a) RD Voxelwise Correlations

“*All participants to VMP data*” showed a strong positive correlation ($p = 0.041^*$), but when divided into patient/control sub-groups, the “patients RD to VMP” lost this significance ($p = 0.1043$).

Division of patients into abnormal/normal VMP performance did not reveal any notable results for the VMP and EOG tests, but a tendency towards significance for “*abnormal VMP patients to Sway*” ($p = 0.0677$) (Fig. 62).

b) RD Voxelwise Comparisons (t-tests)

A voxelwise t-test “*patient RD > controls RD*” revealed a statistically meaningful difference ($p = 0.0093^{**}$). When looking into more detailed comparisons, “abnormal VMP patients RD > normal VMP patients RD” showed only a tendency towards significance ($p = 0.1361$), in contrast to “*abnormal VMP patients RD > controls RD*” that was statistically important ($p = 0.0154^*$). Lastly, “normal VMP patients RD > controls RD” was also notable ($p = 0.0473^*$)(Fig. 63).

2) RD - Sway 95% confidence ellipse SC (Soft Closed) division

a) RD Voxelwise Correlations

“*All participants RD to Sway data*” correlation was statistically important ($p = 0.0078^{**}$). Further division into patients/controls revealed that “*patients RD to Sway*” remained significant ($p = 0.0407^*$). When dividing patients into abnormal and normal Sway performance (Fig. 64), “*abnormal Sway patients to VMP*” showed a notable result ($p = 0.0456^*$). There was also a second significant correlation, “*abnormal Sway patients to EOG*” ($p = 0.005^{**}$).

b) RD Voxelwise Comparisons (t-tests)

Radial diffusivity in the abnormally performing Sway patients was significantly higher than in those with normal balance, i.e. “*abnormal Sway patients RD > normal Sway patients RD*” ($p = 0.0309^*$). Further, “*abnormal Sway patients RD > controls RD*” was also statistically meaningful ($p = 0.0021^{**}$) (Fig. 65).

4. Summary/ Discussion

A. Mean Whole-Brain value analysis

In this sub-section, I investigated the statistical relationship of the mean whole-brain values of four DTI parameters – FA, MD, AD and RD and their correlation with the VMP and vestibular Sway tests.

Whole-brain DTI parameters, with the exception of AD, showed clear discrimination between patients and controls groups.

In particular, Fractional Anisotropy (FA) is expected to increase during the first days after the brain trauma (Mac Donald et al., 2007) and consequently decrease with time, mainly because of neuroinflammatory processes (Sharp et al., 2014). In this acute cohort of TBI patients, I note that the FA in patients was already lower than in controls, and there was a significant difference between patients-controls data, following previously published literature (Soares et al., 2013), (Kinnunen et al., 2011). On the other hand, Mean Diffusivity (MD) and Radial Diffusivity (RD) are expected to initially decrease and then increase after TBI (Soares et al., 2013), (Kinnunen et al., 2011). Here, I observed such a trend towards increase with a statistically notable difference between patient/control groups.

Whole-brain Axial Diffusivity (AD) has shown to be more challenging to interpret in the acute setting of TBI due to its dynamically changing profile. On average, the literature suggests that very close to the event, the AD values of TBI patients are lower compared to controls (Mac Donald et al., 2007), (Sidasos et al., 2008). However, increasing time after the traumatic incident correlates positively with an increase in AD, suggesting an ongoing axonal recovery (Kinnunen et al., 2011). Patients in this study were scanned on average 24 days (median = 21 days, range [9-77days]) after their TBI, and although individual regions of interest, as discussed further in this thesis, showed a varying increase/decrease of AD, there was a slight overall trend towards increase for mean whole-brain AD analysis, as observed here. Considering that there were many examples of the dynamic nature of AD during the acute TBI in this thesis, I remained cautious not to overinterpret these results.

Further, when looking into the VMP or vestibular Sway division methods, there was some evidence of the main effect of subgroups, which, however, was not confirmed by statistical analysis - only vestibular Sway achieved a significant effect of sub-group (i.e. between controls and patients with poor vestibular balance) for FA, MD and RD. The significance shown by the vestibular-Sway division remained even if taking AGE and GENDER as covariates.

Interestingly, no correlation was observed for ‘patients only’ DTI parameters and the vestibular motion perception (VMP) task and/or the vestibular-driven Sway task, possibly due to the primarily moderate TBI. Importantly, even if most of the patients in this TBI cohort were classified as *moderate-severe* based on Mayo classification criteria (Malec et al., 2007), this group incorporated in itself a quite broad spectrum of traumatic brain insult.

Lastly, in concordance with previously published data (Pfefferbaum et al., 2000), FA was shown to decrease with AGE, with the association being more evident for controls than for “all patients”. However, patients with abnormal VMP and vestibular Sway also showed a clear trend towards a decrease of FA with AGE.

B. Whole-Brain Voxelwise analysis

In this section of my study, I investigated the neural correlates of vestibular-guided spatial orientation and vestibular-guided postural control in acute TBI via whole-brain voxelwise DTI analysis. Importantly, I observed the effect that acute TBI damage has on these two crucial modalities. In Table. 12, I summarised the significant and *tendency* contrasts (correlations and t-tests) from the DTI voxelwise analysis reported as of now. As seen throughout this section “A”, the table presents multiple examples of comparisons and “abnormal VMP to Sway” or “abnormal Sway to VMP” correlations in support of the suggested vestibular link between spatial and postural processing.

<i>FA (VMP division)</i> correl abnormal VMP to Sway, $p = 0.0854$ t-test abnormal VMP < controls, $p = 0.016^*$ normal VMP < controls, $p = 0.0192^*$	<i>MD (VMP division)</i> correl abnormal VMP to Sway, $p = 0.0634$ t-test abnormal VMP > controls, $p = 0.0351^*$	<i>AD (VMP division)</i> correl abnormal VMP to VMP, $p = 0.0649$ normal VMP to Sway, $p = 0.0909$ t-test abnormal VMP > controls, $p = 0.0776$	<i>RD (VMP division)</i> correl abnormal VMP to Sway, $p = 0.0677$ t-test abnormal VMP > controls, $p = 0.0154^*$ normal VMP > controls, $p = 0.0473^*$
<i>FA (Sway division)</i> correl abnormal Sway to VMP, $p = 0.0719$ abnormal Sway to EOG, $p = 0.0214^*$ t-test abnormal Sway < normal Sway, $p = 0.0359^*$ abnormal Sway < controls, $p = 0.0011^{**}$ normal Sway < controls, $p = 0.066$	<i>MD (Sway division)</i> correl abnormal Sway to VMP, $p = 0.0486^*$ abnormal Sway to EOG, $p = 0.0067^{**}$ t-test abnormal Sway > normal Sway, $p = 0.0321^*$ abnormal Sway > controls, $p = 0.0076^{**}$	<i>AD (Sway division)</i> correl abnormal Sway to VMP, $p = 0.0771$ abnormal Sway to EOG, $p = 0.0123^*$ t-test abnormal Sway > controls, $p = 0.0368^*$	<i>RD (Sway division)</i> correl abnormal Sway to VMP, $p = 0.0456^*$ abnormal Sway to EOG, $p = 0.005^{**}$ t-test abnormal Sway > normal Sway, $p = 0.0309^*$ abnormal Sway > controls, $p = 0.0021^{**}$
FA correl patients to Sway, $p = 0.0386^*$ t-test patients < controls, $p = 0.0035^{**}$	MD correl patients to VMP, $p = 0.0973$ patients to Sway, $p = 0.0411^*$ t-test patients > controls, $p = 0.0443^*$	AD correl patients to Sway, $p = 0.063$ t-test -	RD correl patients to Sway, $p = 0.0407^*$ t-test patients > controls, $p = 0.0093^{**}$

Table .12. Summary of DTI whole-brain voxelwise analysis for VMP (first row), Sway (second row) and patient-control (third row) division methods. The first row discusses the vestibular motion perception (VMP) division for FA, MD, AD and RD. In addition, I look separately at correlations and comparison contrasts, as I did during the more detailed overview presented in this Chapter. I summarise the vestibular Sway performance in the same manner as the VMP division. Lastly, I have the patient-control division, similarly separated into correlation and comparison contrasts.

4.1. Fractional anisotropy (FA)

Patients' FA significantly correlated to their vestibular-guided Sway performance (Table.12, first column, 3rd row). For the comparison (t-test) analysis, patients and controls achieved a significantly different result with patients FA < controls FA, being consistent with previously published research (Soares et al., 2013), (Kinnunen et al., 2011).

VMP division

Abnormally performing patients for the VMP task (Table.12, first column, 1st row) showed only a tendency towards a notable correlation with vestibular Sway, which would have strongly contributed to the idea of a link between vestibular spatial and vestibular postural processing.

Further, irrespective of whether showing a normal or abnormal VMP performance, patients showed a lower and significantly different FA value than controls.

Sway division

For Sway division (Table.12, first column, 2nd row), I observe an opposite tendency to the one previously discussed, i.e. abnormally performing patients for the vestibular Sway task were close to a significant correlation with VMP. Again, this would have contributed to the suggested vestibular link, especially considering that it was a result based on fractional anisotropy analysis, i.e. the proxy measure of white matter integrity in DTI analysis.

While patients with poor balance showed a lower FA than controls, here I further note that vestibular Sway-based division turned out to be more sensitive to discriminate also among patients, indicating that abnormal Sway FA < normal Sway FA.

4.2. Mean diffusivity (MD)

For mean diffusivity, there was a trend towards a notable correlation between ongoing white matter changes in the patients (irrespective of division) and VMP. Further, similar to FA analysis, also for MD, I note an important correlation of the patient's MD to vestibular Sway (Table.12, second column, 3rd row). Lastly, patients and controls displayed statistically different mean diffusivity, with patients MD > controls MD, in concordance with previous research (Soares et al., 2013), (Kinnunen et al., 2011).

VMP division

The tendency towards a significant correlation between abnormally VMP patients and vestibular Sway became stronger for MD than for FA, potentially also contributing to the suggested vestibular link between them.

Patients with poor vestibular-guided spatial orientation also showed a higher MD than controls, i.e. abnormal VMP MD > controls MD (Table.12, second column, 1st row).

Sway division

I note a highly important correlation for my research questions, i.e. “abnormally performing Sway patients to VMP”, which was a strong example of the link between vestibular-guided spatial and postural processing sharing common/partial neural correlates ($R^2 = 0.52$) (Fig.66).

Further, patients with poor balance continued to demonstrate higher MD than controls. In addition, vestibular-driven Sway division again managed to distinguish between patients with poor (i.e. abnormal) and good (i.e. normal) balance performance by achieving a significant difference for “abnormal Sway MD > normal Sway MD” (Table.12, second column, 2nd row).

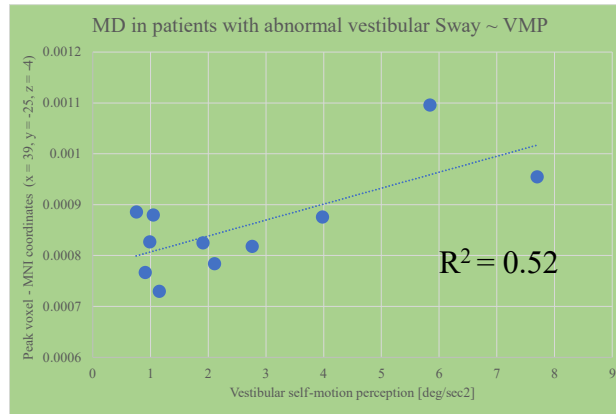


Figure.66. Correlation between abnormal Sway patients and VMP (MD parameter).

4.3. Axial diffusivity (AD)

Considering the highly dynamic nature of axial diffusivity (AD) during acute TBI, the AD analysis is not presented with the same weighting as the rest of the DTI parameters discussed. There were no notable contrasts for patient/control division (Table.12, third column, 3rd row).

VMP division

There were two tendencies worth mentioning – a trend towards significance for “abnormal VMP AD > controls AD” and a tendency for a correlation of “abnormal VMP to VMP” (Table.12, third column, 1st row).

Sway division

Still, for the Sway division, AD achieved notable discrimination between abnormally performing patients and controls (Table.12, third column, 2nd row).

4.4. Radial diffusivity (RD)

Patients' RD analysis showed a significant link to their own performance on the vestibular-guided Sway task (Table.12, fourth column, 3rd row). In addition, patients' RD was significantly different from the controls' RD, similar to what was presented for FA and MD (lower for FA and higher for MD).

VMP division

The previously discussed trend towards a notable correlation between abnormal VMP patients and Sway remained a trend also for RD.

However, radial diffusivity of patients with abnormal and normal VMP were statistically different from controls, with patients showing a higher RD value (Table.12, fourth column, 1st row).

Sway division

Correlation-wise, I note an important contrast, for the second time after MD analysis, i.e. “abnormally performing Sway patients to VMP”. The latter was yet another strong addition to the link between vestibular spatial and postural control.

Here again, Sway division turned out to be a more sensitive way to discriminate between patients’ groups by registering a notable difference between patients with poor and good balance. In addition, poor balance patients showed higher RD than controls (Table.12, fourth column, 2nd row).

4.5. EOG (all parameters/all divisions)

Interestingly, for all four parameters (FA, MD, AD and RD), only patients with poor balance (i.e. abnormally performing patients for the vestibular Sway task) showed a significant link to EOG (Table.12, all columns, 2nd row). Potentially, the wide spread of the vestibular Sway across the brain was unable to miss the correlation to the vestibular-ocular reflex as another vestibular-related process. On the other hand, the vestibular spatial task, representing a much narrow region, concentrating mainly but not exclusively to the right of the brain, was not able to establish this link to the VOR.

5. Discussion/Conclusion

In this sub-Chapter, I investigated the neural correlates of vestibular-guided spatial orientation and vestibular-guided postural control in acute TBI via voxelwise DTI analysis. My main finding was that patients exhibiting abnormal vestibular postural performance showed a notable correlation between their DTI-derived parameters (MD and RD) in the Right Inferior longitudinal fasciculus and the degree to which their vestibular self-motion perception was impaired as a result of the traumatic brain injury event (Calzolari and Chepishcheva et al., 2021). In addition, multiple examples of comparisons and “abnormal VMP to Sway” or “abnormal Sway to VMP” correlations implied of the suggested vestibular link between spatial and postural processing.

Whole-brain DTI analysis showed that FA, MD and RD were sensitive DTI parameters (Sidaros et al., 2008), (Kinnunen et al., 2011) towards vestibular-driven spatial and postural deficits in this cohort of acute traumatic brain injury patients. Indeed, the mentioned FA and RD behaviour coincided also with a previous report in concussed athletes screened 2 days, 2 weeks and 2 months after the event (Murugavel et al., 2014). They showed that the significantly increased RD and decreased FA measures in right hemispheric clusters were the most sensitive DTI parameters for concussive brain injury reported within the first 72h post-event (Murugavel et al., 2014).

Further, the decrease in FA and increase in RD in my study might suggest that a vestibular “mechanism for rehabilitation” (Hummel et al., 2014) was in place during the acute state of traumatic brain damage, similar to the changes occurring in patients with bilateral vestibular failure (BVF) (Hummel et al.,

2014). Interestingly, a DTI study investigating white matter changes in patients with BVF and highly trained balance professionals such as ballet dancers, figure skaters and slackliners showed a similar decrease in FA and an increase in RD in all groups (Hummel et al., 2014). All of them, i.e. vestibular patients and professionals who underwent extensive vestibular training, need to make an extra effort to retain postural stability, or they would otherwise fall. Consequently, they need to “suppress or reinterpret vestibular input to maintain balance” (Hummel et al., 2014). In such a case, and also during the acute state of TBI, vestibular input might be reduced and thus play a minimal role. This would work as a shield mechanism that the brain uses to protect itself from the complex incoming vestibular signals that it cannot otherwise cope with as they would cause falls. This reminds of the III hypothesis of this study. It suggests that in a situation when the brain is already overloaded enough from the ongoing traumatic brain injury, the vestibular signals that might be incongruent with other incoming sensory signals (e.g. visual or proprioceptive) would be seen as a burden rather than as an additional source of information on how to retain proper balance. Consequently, if these vestibular signals are suppressed, more “computational power” would be left for visual input. Indeed, the latter often dominates over the vestibular input (e.g. when in the light) and can serve as a partial compensation in cases of vestibular dysfunction. However, important to note is that the pathological loss of vestibular function can never be fully compensated by other systems, even after training (Carriot et al., 2015), (Cullen, 2019).

Further, my whole-brain DTI analysis suggested that vestibular-driven postural damage was spread widely across the white matter of both brain hemispheres, possibly more reliable on interhemispheric communication. On the other hand, vestibulo-spatial deficits seem more concentrated to the right of the brain, keeping in agreement with the spatial and vestibular research for right hemispheric dominance (Dieterich et al., 2003). Still, it is important to note that vestibular-spatial deficits implicated also some left-hemispheric brain areas for axial diffusivity analysis suggesting further research is needed.

The Right Inferior longitudinal fasciculus (rILF) appeared as a significant white matter tract across my vestibular-based whole-brain voxelwise DTI analysis, especially for FA, MD and RD parameters. The Inferior longitudinal fasciculus (ILF) is an association tract in the inferior region of the brain (Jolly et al., 2021), connecting the occipital and temporo-occipital area with the antero-temporal area (Herbet et al., 2018). Thus, it was implicated in memory and facial recognition (Hodgetts et al., 2015). The Inferior longitudinal fasciculus was also previously reported in several TBI (Niogi et al., 2008), (Hulkower et al., 2013), (Narayana et al., 2015) and concussion studies (Murugavel et al., 2014) and showed a relationship to cognitive and functional changes after TBI (Edlow et al., 2016), (Jolly et al., 2021). Its decreased FA values were also suggested to contribute to the more unfavourable outcome for patients after severe TBI (Perlberg et al., 2009).

Based on the frequency with which the right ILF appeared in my statistically significant and *tendency* correlations and comparisons FA analysis, it suggested a potential strong link to vestibulo-spatial/vestibulo-postural abnormalities during the acute state of TBI. Such a statistically significant link could not be demonstrated for this study based on FA data, but a larger sample and/or patients with

a more severe TBI might be able to confirm this notion. However, even in this TBI cohort, MD and RD analyses showed that the Right Inferior longitudinal fasciculus managed to establish a notable link between vestibular spatial and vestibular postural modalities.

Interestingly, for DTI whole-brain analysis neither of the vestibular-based processes (i.e. spatial or postural) was able to establish a notable correlation on their own to WM abnormalities after acute TBI. It was the combination between the two, i.e. “abnormal Sway to VMP” and “abnormal VMP to Sway” that drove the results closer to significance. Thus, based on my findings in this DTI voxelwise analysis, the vestibular-spatial and vestibular-postural processing in acute TBI might share some “common brain areas”. Possibly, but not definitely, also “common mechanisms”, expressed through the overlapping brain regions of FA-, MD- and RD-based results. However, I cannot exclude that these were separate but vestibular-overlapping effects, as the spatial and postural modalities are two highly complex processes that are also distinct in their functioning and can implicate WM tracts specific only for one or the other modality (i.e. spatial or postural).

Importantly, the significant correlation between vestibular-based postural stability and VMP performance for MD (Fig. 66) was driven by patients with abnormal vestibular Sway balance (i.e. on a soft surface, eyes-closed condition), but no such correlation was present for normally performing vestibular Sway patients or controls (Calzolari and Chepishcheva et al., 2021). A similar correlation, again only for abnormally performing vestibular Sway patients, even if not statistically notable, was present in the same brain region but for FA analysis (Calzolari and Chepishcheva et al., 2021). Thus, these findings supported the idea that the Right Inferior longitudinal fasciculus represented a circuit whose damage was linked to both loss of vestibular perception of self-motion and vestibular imbalance (Calzolari and Chepishcheva et al., 2021). Lastly, the MD and RD analyses did not establish any statistically notable correlations between abnormally performing patients for the vestibular Sway task and vestibular motion perception in the Left Inferior longitudinal fasciculus, stressing the right-hemispheric lateralisation of the vestibular signal for the above finding (Dieterich et al., 2003).

A further important finding was that the correlation between abnormally performing VMP patients to vestibular Sway (i.e. the opposite of what we discussed so far) showed the strongest *tendency* towards significance for FA, MD and RD analyses, with contrast values above 0.9. Whereas the brain regions implicated in these *tendency* correlations were several, the Inferior longitudinal fasciculus R appeared common for MD and RD. Again, these tendency correlations were only for the abnormally performing VMP patients but not for normally performing VMP patients and controls. These, even if not statistically notable contrasts, suggested potential further support to the hypothesised link between vestibular-driven spatial and postural processing.

B. DTI WHITE MATTER TRACTS with VESTIBULAR INPUT

1. Introduction

The previous section of this Chapter V discussed some WM tracts as being most often involved in the significant contrasts of the spatial (vestibular self-motion perception) and postural (vestibular Sway) tasks. In this sub-Chapter, I continued this WM tracts exploration based on their mean values derived from the DTI TBSS (Jolly et al., 2021). I also added tracts that did not reach statistical significance during the whole-brain DTI analysis but showed to be frequent throughout this analysis in their tendency towards statistical relevance. In addition, as based on previous research (Lopez & Blanke, 2011), (Hummel et al., 2014), (Wijesinghe et al., 2015), the selected tracts (Fig. 67) have already been mentioned as implicated with the vestibular system. Thus, I present a selection of thirty vestibular-involved WM tracts to statistically investigate how they linked to the vestibular-guided spatial and postural performance of the moderate-severe acute TBI patients (i.e. Hypothesis I). My objective for this section B was:

- 1) Were there any specific white matter tracts linked to vestibular spatial and/or vestibular postural impairment during acute TBI?

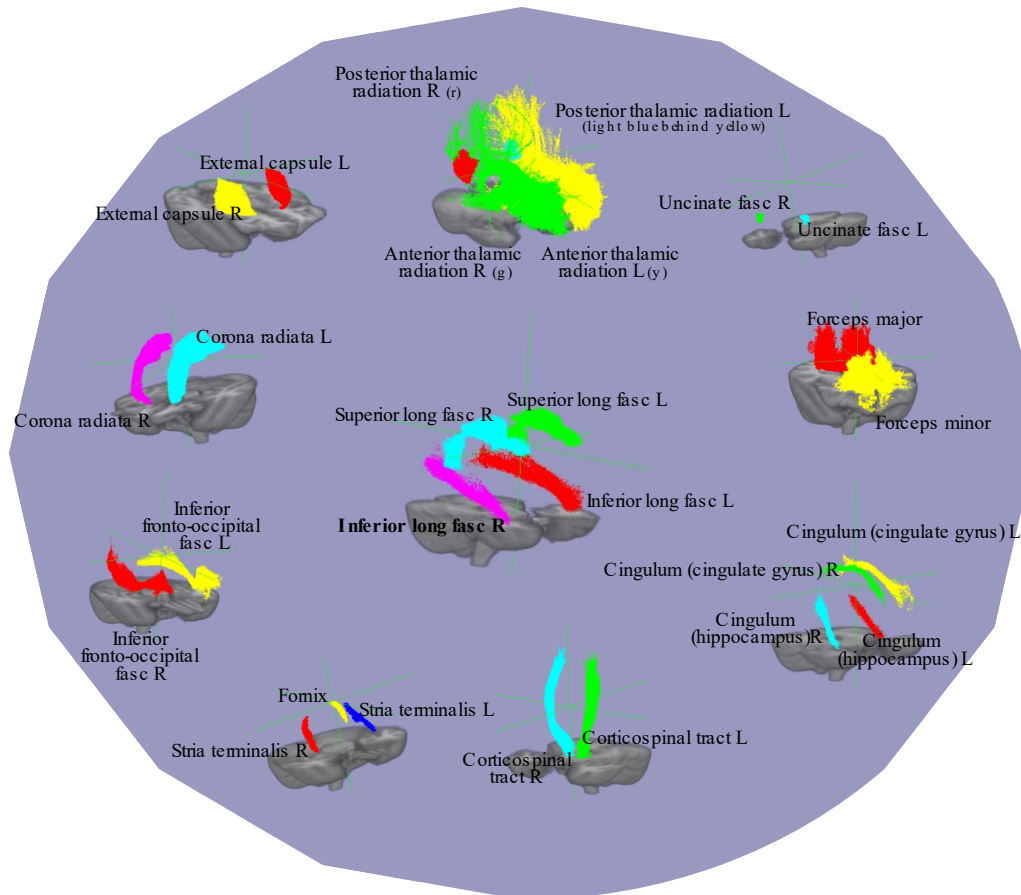


Figure 67. Most common White Matter Tracts present in the DTI Whole-Brain voxelwise analysis. Masks used are from ICBM-DTI-81 WM labels atlas (Mori et al., 2008) and the JHU white matter tractography atlas (Hua et al., 2008) (non-radiological orientation).

2. Materials and Methods

2.1. Recruitment of patients

Please refer to Chapter II for the inclusion/exclusion criteria of this study and to Chapter III for more detailed information about acute TBI patients and their demographics. Importantly, only 30 acute TBI patients and 36 healthy controls completed the imaging part of the study.

2.2. Methodology

Even if during my whole-brain DTI analysis I managed to stress the important role of the Right Inferior longitudinal fasciculus, in this section “B”, I went further by extending this knowledge. I looked at a selection of 30 white matter tracts (Fig.67), some of which were a potential candidate for yet another white matter tract that could be central for vestibular-guided spatial and/or postural processing.

Please refer to Chapter II. for a detailed explanation of the tasks used in this Chapter, the general scheme of the whole DTI analysis and importantly the DTI WM tract analysis.

Neuroimaging:

If taking FA as an example, to extract mean FA values for each of the selected WM tracts on an individual participant level, the concatenated skeletonised images derived from DTI TBSS were separated using `fslsplit` into their individual FA skeleton maps (Jolly et al., 2021). Then, the derived masks from the FSL JHU ICBM-DTI-81 atlas (Mori et al., 2008) and JHU WM tractography atlas (Hua et al., 2008) were intersected with each individual skeletonised FA map to extract the value of the mean FA for each participant using `fslstats` (Jolly et al., 2021).

General information:

- 1) The Corpus Callosum was analysed in detail (i.e. mean value and voxelwise analyses) in Chapter VII. Still, it was also displayed in this section to allow for comparison with the rest of the WM tracts.
- 2) Corona radiata is a crucial WM tract and presented with its several subdivisions throughout the detailed whole-brain analysis – anterior R/L, posterior R/L and superior R/L. Considering that the number of WM tracts I selected for this additional exploration was already high, in the main plots, I included only a summary mask of the Corona tract (R/L), with the idea to explore its subdivisions in a separate plot (please check Appendix).
- 3) Fornix has its own plot (please check Appendix), as its values were incompatible with the rest of the WM tracts and would have caused scale/dimension issues.
- 4) No WM tracts passing through the brainstem and cerebellum were analysed (e.g. the inferior/superior/middle cerebellar peduncle), even if these two structures possess important vestibular fibres and these tracts could have delivered scientifically interesting insights for the

vestibular-driven link between acute TBI and postural control. The reason for this decision was based on the fact that the DTI protocol that researchers used for the main study for which this imaging received funding and was collected (i.e. my doctoral study was not the primary study for this data collection effort) was not optimal for DTI imaging of the cerebellum and brainstem.

- 5) I have concentrated mainly, but not exclusively, on WM tracts that are bigger (with several exceptions, e.g. Fornix, Stria terminalis, Uncinate fasciculi) to minimise the error that could accompany the extraction of mean values from smaller masks and thus account for possible limitations in the quality of the diffusion-weighted images (Jolly et al., 2021).

2.3. Statistical analysis

For my analysis, I use three types of division: (1) patient/control, (2) based on their vestibular motion perception performance (VMP) (i.e. into normal/abnormal performance), and (3) based on their Sway 95% confidence ellipse/posturography performance in the eyes-closed condition on a foamy surface, i.e. vestibular-driven posturography condition (similarly, into normal/abnormal performance).

The Shapiro-Wilk test informed the use of parametric statistics. For all analyses, the alpha-level was set at 0.05.

DTI WM tracts analysis:

A group-level comparison between acute TBI patients and controls was performed for mean value FA, MD, AD and RD using the independent sample t-test. To quantify the effects reported, t-statistics data were included. Further, one-way ANOVA was performed for the four DTI measures to assess the difference between abnormal VMP/normal VMP/control or abnormal Sway/normal Sway/control groups. To quantify the effects reported, eta squared values for F-tests were included. All significant results were further investigated with a Post Hoc with Bonferroni corrections.

Lastly, a ‘patient only’ correlation analysis using the Pearson’s test informed about the potential link between VMP/Sway tests and the WM tracts from the four DTI parameters.

3. Results

To improve the readability of the Results, I summarised all the statistical information from this section “B” directly on the plots presented. The plots display VMP and vestibular Sway divisions (Fig. 68 and Fig. 69). Tables about the analysis of variance and correlations, alongside the patient/control WM tracts plot are available in Appendix. In addition, there I attached a detailed report about the WM tracts analysis. Only WM tracts whose significant ANOVA showed a difference based on vestibular aetiology were mentioned in the report and later, in the Discussion/Conclusion.

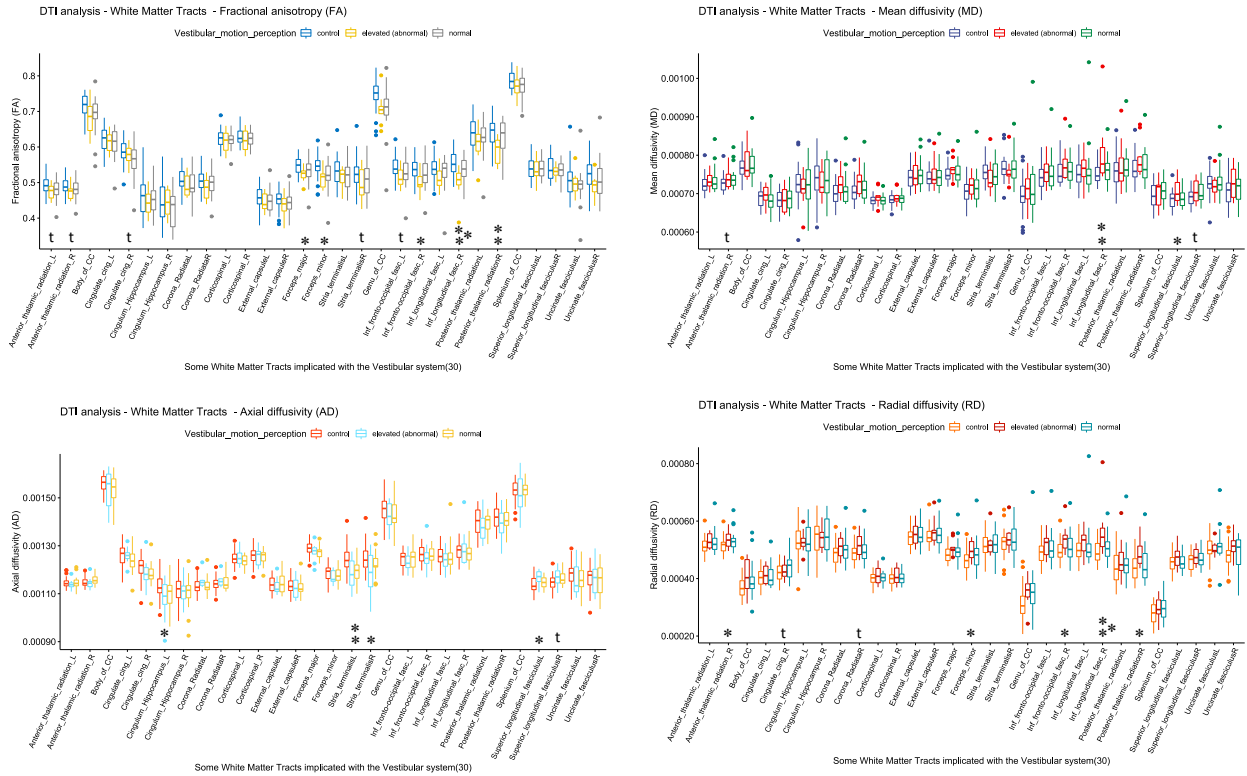


Figure. 68. DTI WM Tracts – VMP division. Legend – an asterisk “*” indicates a statistically significant result, whereas “t”- a tendency towards significance (I consider tendency any p -value between [0.1 - 0.051]).

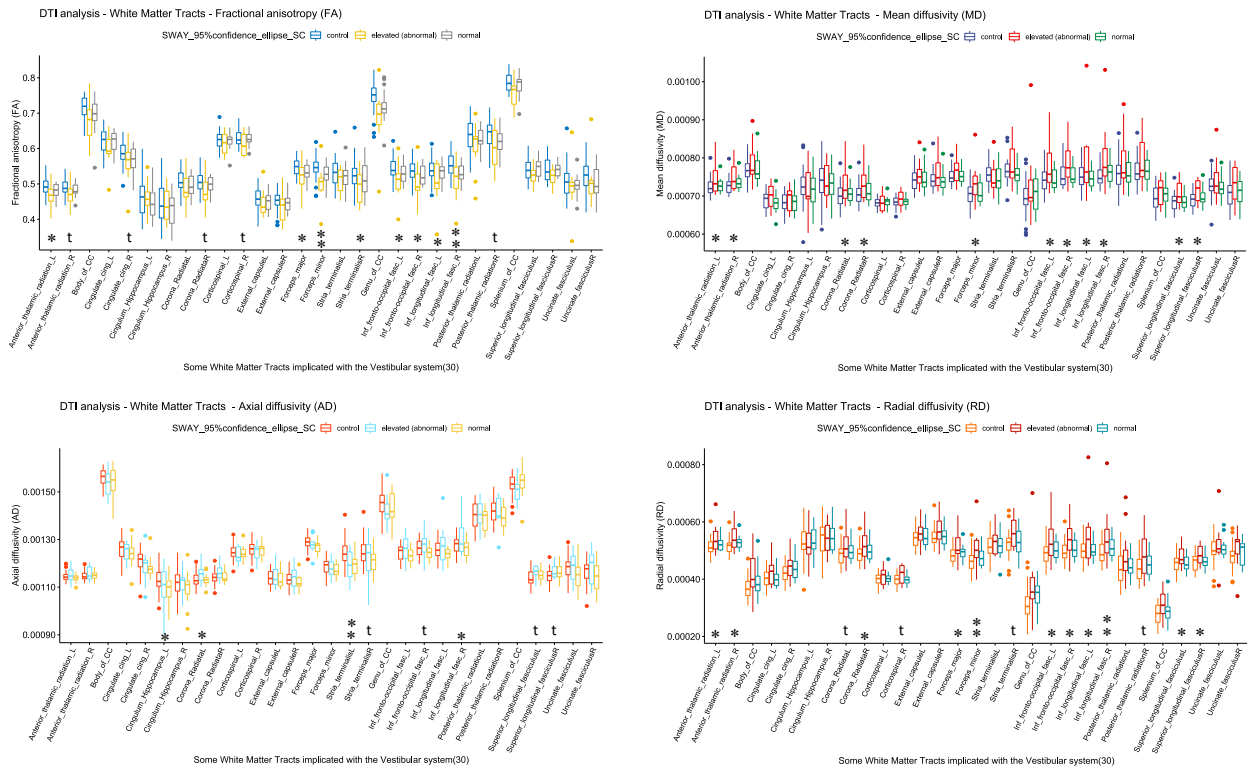


Figure. 69. DTI WM Tracts – Sway division. Legend – an asterisk “*” indicates a statistically significant result, whereas “t”- a tendency towards significance (I consider tendency any p -value between [0.1 - 0.051]).

4. Discussion/Conclusion

In this sub-study, I performed an exploratory analysis of the white matter tracts that were significantly associated with the vestibular spatial and vestibular postural processing during the whole-brain DTI analysis of this acute TBI cohort. Whereas my analysis showed several tracts that might be implicated as important for these two modalities of central vestibular processing, four white matter tracts deserved more special attention: (1) the *Right Inferior longitudinal fasciculus (rILF)*, as already witnessed by the whole-brain voxelwise DTI analysis in section “A” (Calzolari and Chepishcheva et al., 2021) and also in this section “B”, (2) the *Right Inferior Fronto-occipital fasciculus*, (3) the *Anterior Corona Radiata R* and (4) the *Fornix*.

The selection of white matter tracts with vestibular input proved to be a rational method to look at acute brain trauma and its effect on vestibular-driven spatial and postural processing. The detailed statistical exploration showed that some WM tracts were more sensitive towards *vestibular-based* traumatic brain injury damage. This was supported by a statistically notable analysis of variance and a consequent multiple comparison investigation mainly revealing a significant difference between “*abnormal VMP/Sway patients – controls*”. Thus, a possible disadvantage might exist for acute TBI patients in two ecological and highly vestibular involved processes, such as spatial orientation and balance.

Notably, this WM tracts investigation was performed not only to look for statistically notable results but also for trends that could be confirmed or refuted in a bigger cohort with more severe TBI cases or in a longitudinal design. Thus, while some of the WM tracts achieved significant results, others remained frequent but insignificant throughout the whole-brain analysis and also here – during this exploratory ROI analysis. Still, my literature review (Lopez & Blanke, 2011), (Hummel et al., 2014), (Wijesinghe et al., 2015) confirmed that all of these WM tracts had been previously implicated with the vestibular system, thus becoming a logical target that was potentially capable of providing more insight about the spatial and postural aspects from a vestibular system point of view. Interestingly, all the tracts mentioned in this section play a crucial role in the intercommunication among brain structures, and some of them are spread over a wider brain area, not only cortical but also subcortical. This once more stresses the multiple connections that the vestibular system establishes throughout the brain (Hummel et al., 2014).

My analysis showed a clear patient/control distinction for FA and RD parameters, with FA in patients being lower than in controls (“due to loss of coherence in the main preferred diffusion direction” (Soares et al., 2013)), whereas RD was higher in patients as compared to controls (Hummel et al., 2014), (Murugavel et al., 2014). Still, mean diffusivity (MD) did not show the anticipated trend. As previously noted, MD after TBI is expected to initially decrease and then increase in TBI patients (Kinnunen et al., 2011) as compared to controls “as a result of increased free diffusion” (Soares et al., 2013). However, there was not a clear tendency towards this increase in my WM tracts analysis. This was most probably due to the highly changing profile of the white matter, especially in the acute state of TBI and the overall lower axial diffusivity (AD) with which MD has a direct link. This might suggest that even if there was

some ongoing axonal recovery (as assumed in the AD section of this Chapter VI), the re-myelination process might have not been as widely present as it would be expected to become at a later point. Another implication was the varied timing of the brain scan among patients after their TBI (median = 21 days, range [9-77days]) which made it more difficult to group the changes in WM stabilisation. Still, it is of note that only four patients had their scans after one month (i.e. 33days, 41days, 46days and 77days, respectively) post-injury, with one reason being their longer PTA. Even if the optimal time when the acute diffusion tensor imaging should be performed is not yet known, it was suggested that the subacute period after day 7 can already be considered “appropriate” (Edlow et al., 2016). This was the case also in this acute TBI cohort. Importantly, even if resolving oedema might lead to difficulties interpreting acute TBI data, acquiring information during the acute state after TBI and not only longitudinally is equally instrumental in guiding timely medical decisions, prospective problem-solving and better outcomes for the patients.

Following the patients/control results, also VMP and Sway division methods displayed clearer discrimination for FA and RD than for MD and AD. In particular, they showed a pattern in concordance with previous research (Hummel et al., 2014), (Murugavel et al., 2014) with FA in abnormally performing VMP/Sway patients being lower and RD being higher as compared to controls. Vestibular motion perception division for FA implicated several WM tracts that seemed to play a more critical role in the transfer of spatial orientation information under vestibular guidance and signified the difference after TBI damage as compared to controls. Further, the vestibular Sway-based division for FA also pointed to a number of WM tracts that might link TBI damage and vestibular-driven postural instability. Some of them were mutual with the VMP division such as (1) *Forceps minor*, (2) *Inferior fronto-occipital fasciculus R*, (3) *Inferior longitudinal fasciculus R*, (4) *Fornix* and (5) *Anterior corona radiata R*. Others were only Sway-based specific (1) *Anterior thalamic radiation L*, (2) *Inferior fronto-occipital fasciculus L*, (3) *Inferior longitudinal fasciculus L*, (4) *Anterior corona radiata L*, (5) *Stria terminalis R* and (6) *Forceps major* or VMP specific - *Posterior thalamic radiation R*.

As a result of the different division methods, the *Inferior longitudinal fasciculus R (rILF)* stood out as a tract implicated both by the vestibular-guided spatial navigation and vestibular-guided posturography, both in the whole-brain analysis (Calzolari and Chepishcheva et al., 2021) and also here. The second tract that my analysis pointed to is the *Inferior Fronto-occipital fasciculus R (rIFOF)*. This was the second most important WM tract in my vestibular-based whole-brain DTI analysis and naturally it stood out also during this exploration of WM tracts. The *rIFOF* is yet another crucial tract, implicated in goal-oriented behaviour and often damaged after traumatic brain injury (Kraus et al., 2007), (Narayana et al., 2015), (Edlow et al., 2016), (Jolly et al., 2021). The third tract that attracted more attention is part of the crucial Corona Radiata WM tract – this was the *Anterior Corona Radiata R*. The fibres of the Corona Radiata link the cerebral cortex, the thalamus and the brainstem while also playing a crucial role in one of the four vestibular pathways, as described in Chapter I. In fact, it is part of the central vestibular pathway reaching the cerebral cortex and contributing to the conscious

awareness of the vestibular signal. This tract has also been reported in several TBI studies (Kraus et al., 2007), (Narayana et al., 2015), (Edlow et al., 2016).

Lastly, the ***Fornix*** was another WM tract that my analysis highlighted. It emerges from a highly spatial structure such as the hippocampus, arches above the thalamus, and plays a crucial role in the intercommunication of the brain, including spatial orientation and memory. This made its reported link to VMP especially important. The ***Fornix*** has also been presented as a tract often damaged after TBI and showing a reduction in its post-trauma volume (Gale et al., 1993), (Tomaiuolo et al., 2004), (Nakayama et al., 2006). In addition, ***Fornix*** showed a strong link also to vestibular Sway performance as a consequence of the widespread areas vestibular Sway involved (as already seen in this Chapter VI and further in Chapter VII). Importantly, however, ***Fornix*** indicated statistically significant results with both VMP and Sway, which were not entirely vestibular-based, as was the case with the other three tracts – the ***rILF***, ***rIFOF*** and the ***Anterior Corona radiata R***.

Interestingly, previous research implicated the ***rILF*** and the ***Fornix*** with semantic (i.e. ILF) and episodic (i.e. Fornix) memory (Hodgetts et al., 2017), in addition to facial (i.e. ILF) and spatial (i.e. Fornix) perception (Hodgetts et al., 2015). Thus, my findings seemed to add valuable information about how these two highly visually involved WM tracts were possibly linked to spatial navigation and postural control, even under a central vestibular level processing.

An important consideration in this WM tract analysis was that Fornix is a small-sized tract, and caution must be taken with the overinterpretation of its results as it renders further and more detailed investigation. Importantly, as mentioned in the Material and Methods section of this sub-study, even if I mostly tried to consider bigger tracts for this mask-based WM tract analysis (Jolly et al., 2021), I also included several smaller WM tracts, important from the perspective of the central vestibular system. Among them was also Fornix. Due to its small size, Fornix might have required a bigger, more severe cohort of TBI patients to establish a voxelwise-based significance, but its emerging role in this WM exploratory analysis might suggest it would be a strong candidate.

To conclude, while this was not the first study to point to the ***ILF***, ***IFOF***, the ***Anterior Corona radiata*** and ***Fornix*** as implicated in white matter damage after TBI (Kraus et al., 2007), (Kinnunen et al., 2011), (Hulkower et al., 2013), (Narayana et al., 2015), (Edlow et al., 2016), (Jolly, 2020), (Jolly et al., 2021), this was the first study that was attempting to link vestibular-driven spatial and postural processing with acute white matter damage due to TBI (Calzolari and Chepicheva et al., 2021). In doing so, this study implicated the ***rILF*** and three more WM tracts as presenting their possible circuits whose lesion might be linked to loss of vestibular motion perception and vestibular imbalance.

Chapter VII

Vestibular regions and CC - TBI study

In this Chapter VII, I continued to investigate the same general issues as outlined in Chapter III and Chapter VI while extending the more rigid approach of a whole-brain analysis (presented in Chapter VI, section A) and applying a region of interest analysis (ROI).

My ROI analysis concentrated on exploring (1) the biggest commissural fibre, i.e. the Corpus Callosum (CC) by using DTI mean value and voxelwise analyses, followed by VBM WM analysis (please check Appendix for further details about VBM analysis). Once my investigation of CC was completed, in one final section of this acute TBI study, I explored (2) a selection of eleven brain regions that the literature has shown to be essential integrators of central vestibular input (Kahane et al., 2003), (Lopez & Blanke, 2011), (Kaski et al., 2016), (A. Jacob et al., 2020). In particular, these were the Amygdala, Entorhinal Cortex (ETC), Caudate, Putamen, Left Thalamus, Right Thalamus, Insula and Hippocampus (A. Jacob et al., 2020), along with the right TPJ (anterior portion), right TPJ (posterior portion) (Lopez & Blanke, 2011), (Kaski et al., 2016) and OP2 region (Kahane et al., 2003). These eleven “vestibular regions”, as I refer to them from now on, are expected to play a crucial role in vestibular-guided spatial and postural processing. I investigated their behaviour via mean value and voxelwise DTI and VBM analyses (please check Appendix for further details about VBM analysis).

For my analysis in this Chapter VII, I used (1) JHU ICBM-DTI-81 white-matter labels atlas (Mori et al., 2008), (2) JHU white matter tractography atlas (Hua et al., 2008), (3) Harvard-Oxford cortical structural atlas (Desikan et al., 2006), (4) Harvard-Oxford subcortical structural atlas (Desikan et al., 2006), (5) Mars TPJ connectivity-based parcellation atlas (Mars et al., 2012) and (6) Juelich Histological Atlas (Eickhoff et al., 2005).

I. CORPUS CALLOSUM (CC)

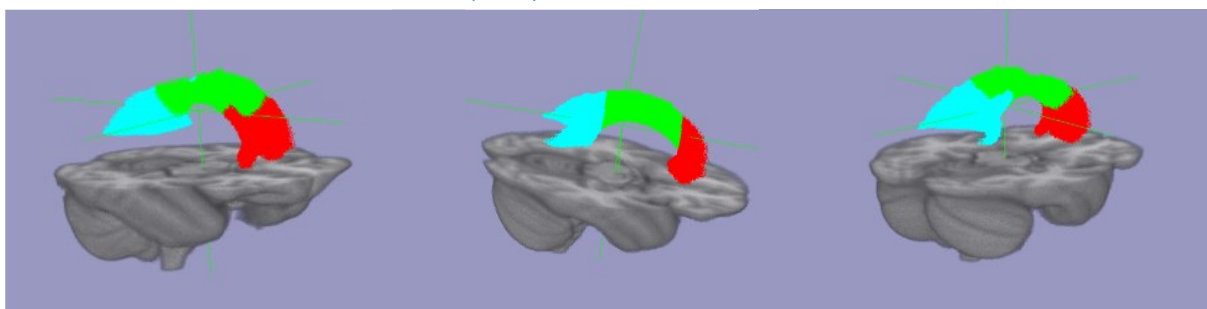


Figure. 70. **Corpus Callosum in 3D view** – structure - Splenium (light blue), Body (green), Genu (red).

1. Introduction

As the biggest collection of white matter in the brain and an indispensable path for interhemispheric communication, the Corpus Callosum (CC) plays a central role in the brain and drew special attention to my investigation of the vestibular-guided spatial and postural control in this cohort of acute traumatic brain injury patients (Fig. 70).

Corpus callosum (CC) is the largest commissural fibre in the brain and is often damaged after TBI (Nakayama et al., 2006), (Kraus et al., 2007), (Hulkower et al., 2013), (Sharp et al., 2014), (Jolly, 2020), (Bourke et al., 2021), (Jolly et al., 2021). This is mainly because of high-tension/forces that are predominantly affecting sulcal brain regions (Ghajari et al., 2017). One consequence of TBI on the Corpus Callosum, especially in callosal regions connecting parietal and temporal cortices, is the long-term disability that it can cause (Treble et al., 2013), also in the cognitive domain (Niogi et al., 2008), (Kinnunen et al., 2011), (Arenth et al., 2014), (Edlow et al., 2016). This, in turn, can have a negative effect on two highly cognitive and vestibular-implicated modalities, such as spatial navigation and postural control (Camicioli et al., 1997), (Smith, 1997), (Brandt et al., 2005).

Importantly, as a bi-hemispheric vestibular link passes via the antero-caudal region of the Splenium of the Corpus Callosum (Kirsch et al., 2016), the CC becomes a potential driver of bi-hemispheric loss of vestibular signal exchange in the cases of a TBI lesion. However, several complications arise from this suggestion – there are no acute TBI data discussing the integrity of the CC from a vestibular system point of view that could facilitate our better understanding of the amount of vestibular callosal damage after TBI and subsequently, its potential effect upon the spatial and postural dysfunction after TBI (i.e. Hypothesis I). Consequently, my objectives for this sub-Chapter were:

1. To investigate if vestibular-guided spatial and postural modalities shared a common neuronal network, potentially within the Corpus Callosum?
2. To investigate if the integrity of the Corpus Callosum was linked to loss of vestibular motion perception or vestibular imbalance during acute TBI?

2. Materials and Methods

2.1. Recruitment of patients

Please refer to Chapter II for the inclusion/exclusion criteria of this study and to Chapter III for a more detailed information about acute TBI patients and their demographics. Importantly, only 30 acute TBI patients and 36 healthy controls completed the imaging part of the study.

2.2. Methodology

The previously conducted whole-brain DTI and VBM analyses did not directly inform the specific regions that I explored in my ROI analysis, but they stressed the importance and the need to perform such a more detailed regional analysis. In this section, I concentrated on the biggest commissural WM tract whose SPLENIUM has been specifically implicated with the vestibular system.

I divided the Corpus Callosum in three regions, i.e. GENU, BODY and SPLENIUM and performed mean value and voxelwise analysis to address my hypotheses and their objectives.

Please refer to Chapter II. for a detailed explanation of the tasks used in this Chapter and the general scheme of the DTI analysis.

2.3. Statistical analysis

For my analysis, I use three types of division: (1) patient/control, (2) based on their vestibular motion perception performance (VMP) (i.e. into normal/abnormal performance), and (3) based on their Sway 95% confidence ellipse/posturography performance in the eyes-closed condition on a foamy surface, i.e. vestibular-driven posturography condition (similarly, into normal/abnormal performance).

The Shapiro-Wilk test informed the use of parametric statistics. For all analyses, the alpha-level was set at 0.05.

DTI – mean value analysis:

First, I investigated for a statistical difference between patient/control performance based on the DTI-derived parameters in the Corpus Callosum – FA, MD, AD, RD. A group-level comparison was performed using the independent sample t-test. To quantify the effects reported, t-statistics data were included.

One-way ANOVA was performed for the four DTI measures to assess the difference between abnormal VMP/normal VMP/control or abnormal Sway/normal Sway/control groups. To quantify the effects reported, eta squared values for F-tests were included. All significant results were further investigated with a Post Hoc with Bonferroni corrections.

Lastly, a ‘patient only’ correlation analysis using the Pearson’s test informed about the potential link between VMP/Sway tests and the four DTI parameters within the CC.

For ease of interpretation, all statistical results for t-tests and ANOVA are displayed directly on the accompanying plots, while detailed tables for patient/control, VMP and Sway divisions, alongside the patient/control plot are available in Appendix.

DTI – voxelwise analysis:

Similar to the whole-brain voxelwise analysis (Chapter VI), here I performed a GLM-based voxelwise correlation and comparison analysis for the three regions of the CC (i.e. SPLENIUM, BODY and GENU). With respect to the plots presented, I only concentrated on two division methods: the vestibular spatial (via the VMP task) and vestibular postural aspect (via the vestibular Sway task) of acute TBI. I summarised the results for each region of the CC on a single plot and kept the same organisation throughout this Chapter VII.

In the results section, I presented the DTI voxelwise analysis in a summarised form only via these plots. However, the complete information, i.e. MNI coordinates of all maximum intensity voxels and details about clusters and their size/location is available in Appendix.

This DTI analysis presented only contrasts corrected for multiple hypothesis testing at a threshold of 0.05 via fsl randomise (Winkler et al., 2014) with 10,000 permutations for each contrast. The contrasts were the primary findings of this analysis and, as such, were displayed in the following images. It is of note that the output of the voxelwise contrast was a value that, when subtracted from “1.0” provided the p -value of this contrast.

Importantly, I report not only statistically significant contrasts (i.e. contrast value ≥ 0.95), but also something I called “tendencies”. They had contrast values between [0.9 – 0.949], and their corresponding p -values were between [0.1 and 0.051].

3. Results

A. DTI MEAN VALUE ANALYSIS

In this exploratory analysis, I looked at mean values derived post DTI TBSS after applying atlas-based masks for the specific callosal regions of interest (i.e. SPLENIUM, BODY and GENU).

For fractional anisotropy, the patient/control division showed a clear difference for all three subcomponents of the CC, and controls persistently displayed higher FA than patients. Still, the significance in GENU ($p = 0.003^{**}$) was higher than it was for SPLENIUM ($p = 0.04^{*}$) and BODY ($p = 0.01^{*}$).

For mean diffusivity, there was no statistically meaningful difference for either of the three callosal subregions, with SPLENIUM and GENU showing visibly higher values for patients MD and BODY having close values for both patients and controls. Further, axial diffusivity (AD) showed its dynamic profile with patients’ atrophy in the CC displaying a trend towards lower AD values as compared to controls. No statistical difference was reached for the patient/control division.

Lastly, radial diffusivity (RD) showed a clear pattern for patients to display higher RD values as compared to controls, reaching a statistical difference for BODY ($p = 0.02^{*}$) and GENU ($p = 0.01^{*}$), but only a tendency for SPLENIUM ($p = 0.06$).

3.1. Vestibular Motion Perception (VMP) division

Vestibular motion perception division (Fig. 71) showed that controls displayed higher FA values than the abnormally performing VMP patients.

Analysis of variance for FA showed a main effect of group for GENU ($p = 0.01^{*}$, with a tendency for “control - abnormal patients”) and BODY ($p = 0.04^{*}$, with no comparison remaining significant).

Mean diffusivity and axial diffusivity did not show any significant effect of group for VMP, but an overall tendency for controls to display the lowest MD values and highest AD values as compared to the patients’ groups. Lastly, radial diffusivity (RD) controls’ performance was lower in value compared

to the abnormally and normally performing VMP patients for all three CC sub-regions. While there was no main effect of sub-group for SPLENIUM and BODY, it was the GENU that showed a statistically significant result ($p = 0.04^*$), which, however, did not survive multiple comparisons.

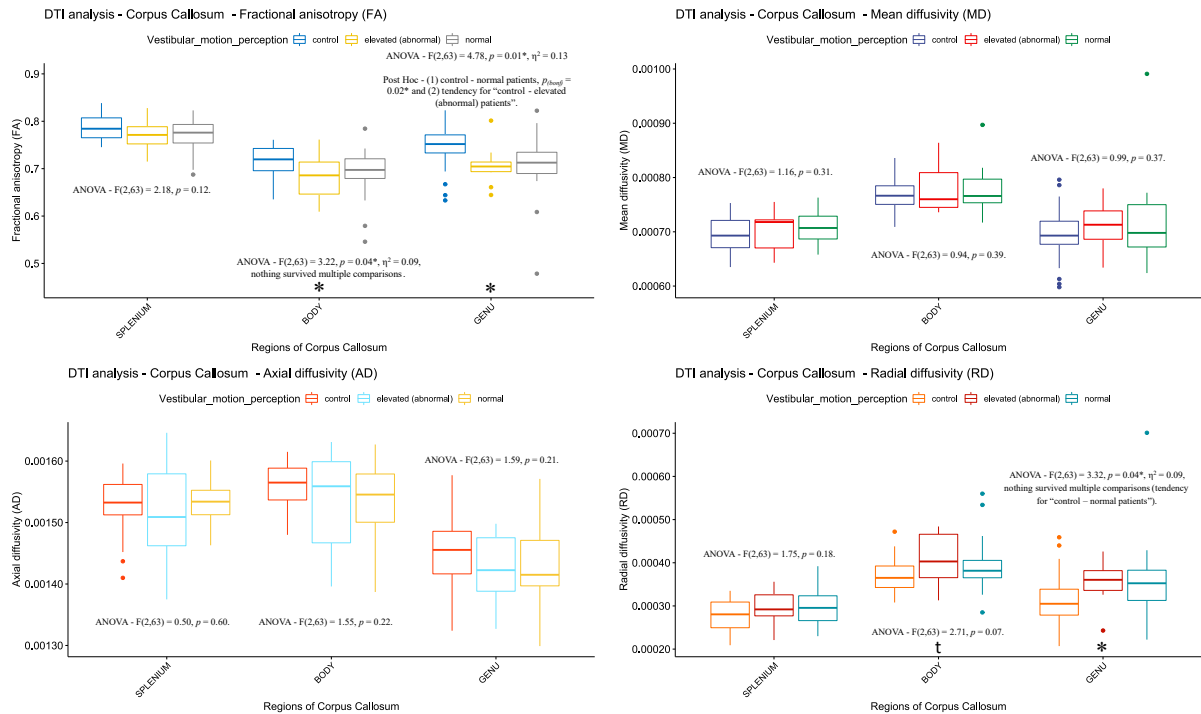


Figure. 71. DTI analysis – Corpus Callosum (CC) with its three regions SPLENIUM, BODY and GENU – Vestibular motion perception (VMP) division (medians + IQR). Legend – an asterisk “*” indicates a statistically significant result, whereas “t” - a tendency towards significance (I consider tendency any p -value between [0.1 - 0.051]).

A correlation analysis between “patients only” data and the VMP test showed no statistically notable results for BODY and GENU. Still, for SPLENIUM, I note a *tendency* towards significance for “VMP data – Axial Diffusivity (AD)” (Pearson’s $r = -0.35, p = 0.05$).

3.2. Vestibular Sway division

Vestibular Sway division (Fig. 72) showed more statistically significant results than VMP division. There was a clear tendency for controls FA to show higher values than patients FA, and “normal Sway patients FA > abnormal Sway patients FA”.

The FA for all three callosal regions showed a significant main effect of group (SPLENIUM $p = 0.01^*$, BODY $p = 0.02^*$ and GENU, $p = 0.003^{**}$), and a following Post Hoc analysis revealed that it was the “control – elevated (abnormal) Sway patients” that drove the significance for all these statistically notable results. In addition, a tendency towards significance was also noted for SPLENIUM – “normal Sway patients ~ elevated (abnormal) Sway patients”.

Mean diffusivity and Axial diffusivity showed no statistical importance of sub-group, but similar to VMP division – a tendency for controls’ data to be lower than patients’ MD and higher than patients’

AD data, respectively. Lastly, radial diffusivity displayed again a clear discrimination between groups. In particular, ANOVA for all three regions was significant - SPLENIUM ($p = 0.03^*$), BODY ($p = 0.03^*$) and GENU ($p = 0.01^*$) and multiple hypothesis testing showed that these results were driven by the “*control – elevated (abnormal) Sway patients*” comparison.

A correlation analysis between “*patients only*” data and the FA, MD, AD and RD parameters showed two significant correlations only for SPLENIUM – (1) “*Sway data – FA*” ($r = -0.38, p = 0.03^*$) and (2) “*Sway data – RD*” ($r = 0.36, p = 0.04^*$).

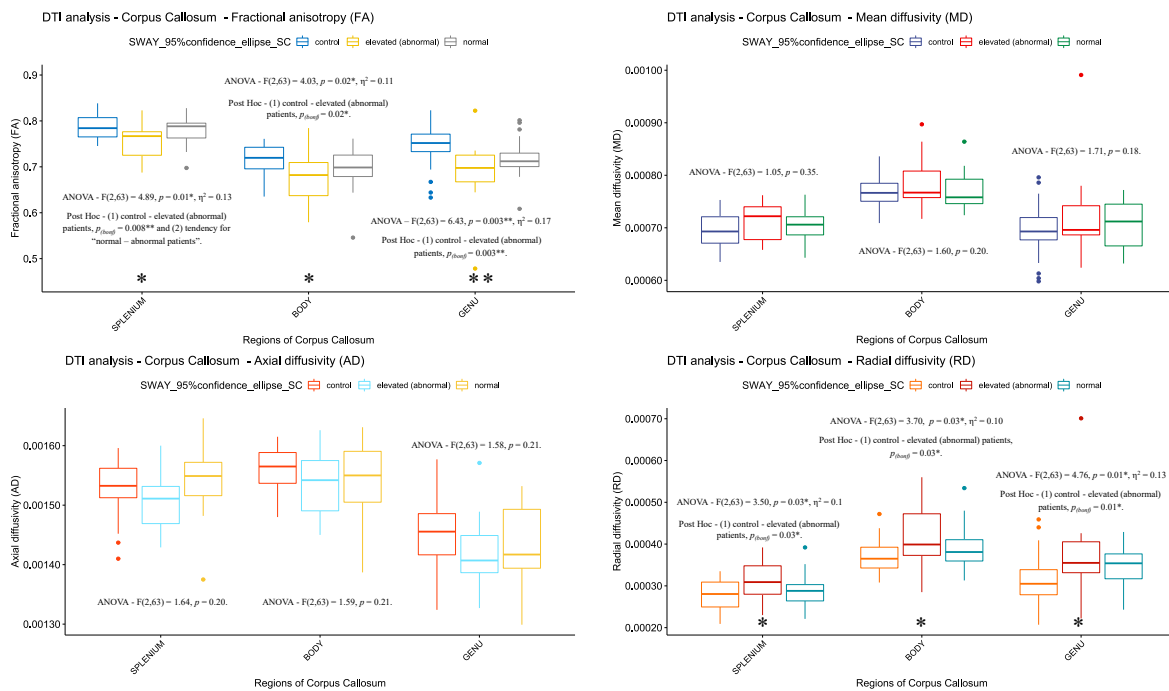


Figure. 72. DTI analysis – Corpus Callosum (CC) with its three regions SPLENIUM, BODY and GENU – Sway 95% confidence ellipse, SC condition division (medians + IQR). Legend – an asterisk “*” indicates a statistically significant result, whereas “t” - a tendency towards significance (I consider tendency any p -value between [0.1 - 0.051]).

B. VOXELWISE ANALYSIS – DTI

Similar to the whole-brain voxelwise analysis (Chapter VI, section “A”), here I performed a GLM-based voxelwise correlation and comparison analysis for the three regions of the CC (i.e. SPLENIUM, BODY and GENU). For this voxelwise analysis, I concentrated on the vestibular spatial (via the VMP task) and vestibular postural aspect (via the vestibular Sway task) of acute TBI. I summarised the results for each region of the CC on a single plot (Fig.73, Fig. 74 and Fig. 75) and kept the same organisation throughout this Chapter VII.

Here, I presented the voxelwise analysis only via these plots. However, the detailed report about the MNI coordinates of all maximum intensity voxels/cluster specifications is available in Appendix.

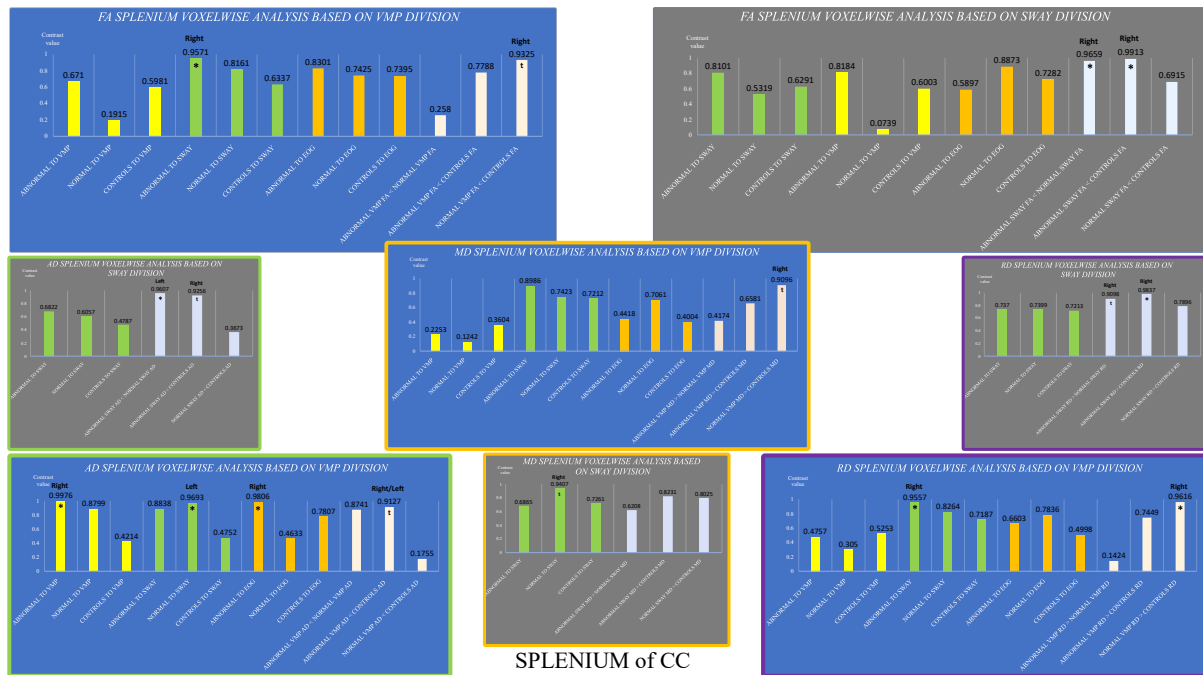


Figure. 73. DTI voxelwise analysis – SPLENIUM of Corpus Callosum. The plot displays FA, MD, AD and RD summarised data based on the VMP division (blue background colour) or Vestibular Sway division (grey background colour). For easier interpretation, I have coloured the border of Mean Diffusivity maps (ORANGE colour, in the centre), Axial Diffusivity maps (GREEN colour, on the left) and Radial Diffusivity maps (LILAC colour, on the right). Further, an asterisk ** denotes any significant contrast (i.e. contrast value ≥ 0.95 , and corresponding p -value ≤ 0.05) and 't' represents a tendency towards significance (i.e. any contrast value in the range = $[0.9 - 0.949]$ and corresponding p -value = $[0.1-0.051]$). On the plots, I have incorporated correlation and comparison contrasts together. Correlation is a different colour depending on the type of input data – VMP (YELLOW colour), SWAY (GREEN colour) followed by differently coloured bar charts for t-tests bars. Lastly, above each contrast of note, I have indicated if this was a notable contrast in the Left or the Right hemisphere of the ROI.

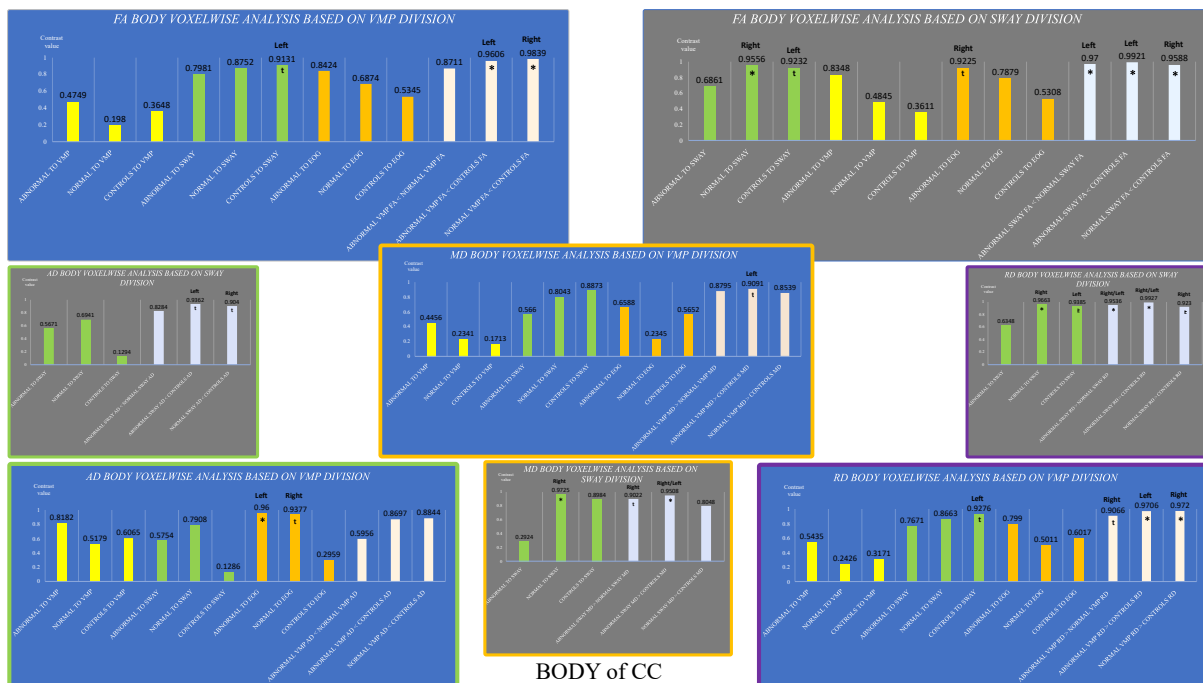


Figure. 74. DTI voxelwise analysis – BODY of Corpus Callosum. The plot displays FA, MD, AD and RD summarised data based on the VMP division (blue background colour) or Vestibular Sway division (grey background colour). For easier interpretation, I have coloured the border of Mean Diffusivity maps (ORANGE colour, in the centre), Axial Diffusivity maps (GREEN colour, on the left) and Radial Diffusivity maps (LILAC colour, on the right). Further, an asterisk ** denotes any significant contrast (i.e. contrast value ≥ 0.95 , and corresponding p -value ≤ 0.05) and 't' represents a tendency towards significance (i.e. any contrast value in the range = $[0.9 - 0.949]$ and corresponding p -value = $[0.1-0.051]$). On the plots, I have incorporated correlation and comparison contrasts together. Correlation is a different colour depending on the type of input data – VMP (YELLOW colour), SWAY (GREEN colour) followed by differently coloured bar charts for t-tests bars. Lastly, above each contrast of note, I have indicated if this was a notable contrast in the Left or the Right hemisphere of the ROI.

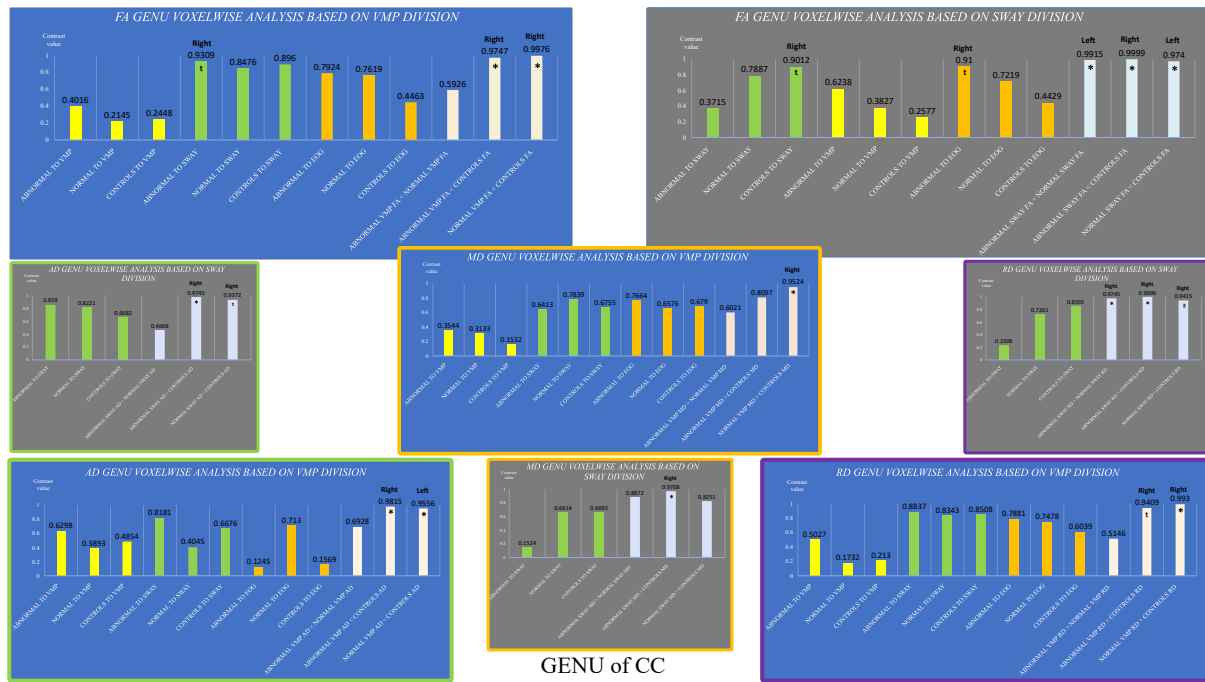


Figure. 75. DTI voxelwise analysis – GENU of Corpus Callosum. The plot displays FA, MD, AD and RD summarised data based on the VMP division (blue background colour) or Vestibular Sway division (grey background colour). For easier interpretation, I have coloured the border of Mean Diffusivity maps (ORANGE colour, in the centre), Axial Diffusivity maps (GREEN colour, on the left) and Radial Diffusivity maps (LILAC colour, on the right). Further, an asterisk “*” denotes any significant contrast (i.e. contrast value ≥ 0.95 , and corresponding p-value ≤ 0.05) and ‘t’ represents a tendency towards significance (i.e. any contrast value in the range = [0.9 – 0.949] and corresponding p-value = [0.1-0.051]). On the plots, I have incorporated correlation and comparison contrasts together. Correlation is a different colour depending on the type of input data – VMP (YELLOW colour), SWAY (GREEN colour) and EOG (ORANGE colour) followed by differently coloured bar charts for t-tests bars. Lastly, above each contrast of note, I have indicated if this was a notable contrast in the Left or the Right hemisphere of the ROI.

4. Summary/Discussion

A. Mean value analysis

In this exploratory analysis, I investigated whether the integrity of the Corpus Callosum reflected on the loss of vestibular motion perception or vestibular imbalance during acute TBI. Based on my findings from the mean value DTI analysis, acute traumatic brain injury (aTBI) showed a distinctive effect on the three regions of the Corpus Callosum, and I summarised the patient/control, VMP and Sway results from this section in Table.13.

When dividing into “patient/control” subgroups, patients FA < controls FA for all three regions of the CC, in agreement with previous literature (Kinnunen et al., 2011), (Jolly, 2020). In fact, the decrease in FA reflects a less organised diffusion in all directions (Soares et al., 2013), consistent with a TBI impairment.

While FA is a ratio measure, MD, AD and RD may provide more nuanced information that FA might not be sensitive enough to pick up (Jolly, 2020). A higher mean diffusivity (MD) is expected in patients after TBI and was also seen in the CC of the acute TBI patients from this study. Still, no statistical significance was reached for MD patient/control division, and I observed only a trend in the SPLENIUM and GENU (not even passing the threshold for “*tendency*” I set in this study). Further, axial diffusivity (AD) showed to be lower in patients, which was indicative of an ongoing WM injury

and a process of axonal reparation/re-myelination that had not yet widely started in the Corpus Callosum (as discussed in the AD section, Chapter VI). Lastly, radial diffusivity (RD) presented the effects of TBI in an expected way based on literature, showing a distinctive patients RD > controls RD.

Region of the Corpus Callosum	patient-control	VMP division	Sway division
SPLENIUM	FA (*), RD (t)	-	FA (*), RD (*)
BODY	FA (*), AD (t), RD (*)	FA (*n/a), RD (t)	FA (*), RD (*)
GENU	FA (*), AD (t), RD (*)	RD (*n/a)	FA (*), RD (*)

Table. 13. Corpus Callosum DTI mean value analysis – summary of significant(‘**’) and tendency-based (‘t’) results for patient/control and VMP/Sway division methods. (*n/a) – means a statistically notable result that did not survive Post Hoc.

Next, both the VMP and vestibular Sway division methods for FA showed mostly a clear tendency to logically discriminate between patients and controls in a way that was in agreement with previously published TBI research (Kinnunen et al., 2011), (Jolly, 2020). In particular, *by observation* abnormally performing patients FA < normally performing patients FA < controls FA (for both divisions). Thus, they presented as two appropriate methods (i.e. still with vestibular Sway being better than VMP) to reflect the acute callosal spatial/postural impairment from a vestibular system point of view. Indeed, fractional anisotropy (FA) showed the best discrimination for data across the divisions irrespective of whether patients were taken as one group and compared to controls or divided based on their VMP/Sway performance. The second-best parameter to discriminate among groups was RD, followed by MD and lastly, AD.

With respect to the division methods, I more often note a significant main effect of sub-group for vestibular Sway as compared to VMP, stressing the potentially more substantial effect that vestibular Sway had in the CC after TBI. Thus, the Sway division was capable to reflect the functional changes in balance regarding central vestibular processing during the acute state of TBI and might imply a link between vestibular-driven Sway and white matter atrophy in the Corpus Callosum for acute TBI. Importantly, vestibular Sway indicated the importance of all three Corpus Callosum sub-components through the balance task in “the soft surface, eyes-closed” posturography condition.

Another interesting finding was that, even if the three CC regions showed statistically significant results across the division methods (i.e. patient/control, VMP, Sway), an effect of group was *slightly* more significant in the anterior part of the Corpus Callosum, i.e. in the GENU than in the BODY and/or the SPLENIUM as based on this mean value analysis. Importantly, a study with a blast-induced TBI on rats also showed that based on DTI analysis, structures such as the GENU were more affected than BODY or SPLENIUM (Venkatasubramanian et al., 2020). In addition, another study also showed that in a mild TBI cohort, less than 3 months post-trauma, a more frontal region such as the GENU was linked to DTI abnormalities, possibly due to vasogenic oedema being present there (Rutgers et al., 2008). Indeed,

some brain regions are more susceptible to TBI than others, “independent of the biomechanical load dynamic of the injury” (Murugavel et al., 2014). However, finding a formula that fits all TBI cases is difficult, and even if researchers (both for animal-based and human-based TBI studies) try to specify brain regions commonly affected after TBI, these findings should be interpreted with caution.

Lastly, a clear pattern between “*abnormal Sway patients - control*” was established for vestibular Sway with statistically significant results after Post Hoc for FA and RD (for all three CC regions), whereas mostly a tendency was noted for the VMP division (Fig. 71. and Fig.72). Still, while callosal damage was definitely present in this acute TBI cohort, no distinct pattern between “*normally - abnormally performing*” patients for the VMP/Sway tasks could be established for this mean value analysis, although a single tendency existed for Sway division – “FA normal Sway – FA abnormal Sway” for SPLENIUM (Fig. 72). This changed for the voxelwise vestibular Sway-based analysis, where I managed to achieve a notable discrimination between “normally and abnormally” performing patients for the vestibular-guided Sway task for all three regions of the CC (i.e. SPLENIUM, BODY and GENU), but not for the VMP task.

B. DTI Voxelwise analysis – Corpus Callosum

The data from the CC voxelwise DTI analysis are summarised in Table. 14. (part 1 and part 2).

Region of the Corpus Callosum	FA (VMP division)	FA (Sway division)	MD (VMP division)	MD (Sway division)
SPLENIUM	correl abnormal VMP to Sway, p = 0.0429* t-test normal VMP < controls, p = 0.0675	correl - t-test abnormal Sway < normal Sway, p = 0.0341* abnormal Sway < controls, p = 0.0087**	correl - t-test normal VMP > controls, p = 0.0904	correl normal Sway to Sway, p = 0.0593 t-test -
BODY	correl - t-test abnormal VMP < controls, p = 0.0394* normal VMP < controls, p = 0.0161*	correl normal Sway to Sway, p = 0.0444* abnormal Sway to EOG, p = 0.0775 t-test abnormal Sway < normal Sway, p = 0.03* abnormal Sway < controls, p = 0.0079** normal Sway < controls, p = 0.0412*	correl - t-test abnormal VMP > controls, p = 0.0909	correl normal Sway to Sway, p = 0.0275* t-test abnormal Sway > normal Sway, p = 0.0978 abnormal Sway > controls, p = 0.0492*
GENU	correl abnormal VMP to Sway, p = 0.0691 t-test abnormal VMP < controls, p = 0.0253* normal VMP < controls, p = 0.0024**	correl abnormal Sway to EOG, p = 0.09 t-test abnormal Sway < normal Sway, p = 0.0085** abnormal Sway < controls, p = 0.0001*** normal Sway < controls, p = 0.026*	correl - t-test normal VMP > controls, p = 0.0476*	correl - t-test abnormal Sway > controls, p = 0.0292*

Table. 14. Summary for CC voxelwise DTI analysis – FA and MD (1/2).

SPLENIUM

For the VMP division, I note a single significant comparison discriminating between normal VMP patients RD > controls RD. Correlation-wise, axial diffusivity (AD) showed a notable result for “*abnormal VMP to VMP*”, which should be interpreted with caution due to the highly changing profile of AD in the acute setting of TBI.

Importantly, FA and RD showed a notable correlation for “*abnormal VMP to Sway*”, which, even if subtle, was of interest. This might support the suggested link between vestibular spatial and vestibular

postural processing, especially considering that the SPLENIUM is implicated as a region through which there is a bi-hemispheric vestibular passage (Kirsch et al., 2016).

For the Sway division, SPLENIUM reached an important statistical significance showing that “*abnormal Sway patients < normal Sway patients*” for FA and AD. The former discrimination between patients on a FA level was an important finding providing the possibility to discern a pattern of callosal damage between patients with and without vestibular postural dysfunction. Further, “*abnormal Sway patients and controls*” were also statistically different for FA (<) and RD (>).

Correlation-wise, there were no significant correlations.

BODY

For the VMP division – there was a notable difference for “*abnormal VMP patients and controls*” and “normal VMP patients and controls” for FA (<) and RD (>), but no notable correlations.

For the vestibular Sway division, there was a significant statistical difference between “*abnormally and normally performing Sway patients*” for FA (<) and RD (>) and also for “*abnormal Sway patients and controls*” for FA (<), MD (>) and RD (>). This was the second example of the important finding providing the possibility to discriminate between patients with good/bad vestibular balance. Still, caution must be taken, as FA, MD and RD also showed a notable correlation with non-vestibular nature - “normal Sway patients to Sway”.

Region of the Corpus Callosum	AD (VMP division)	AD (Sway division)	RD (VMP division)	RD (Sway division)
SPLENIUM	correl abnormal VMP to VMP, p = 0.0024** normal VMP to Sway, p = 0.0307* abnormal VMP to EOG, p = 0.0194* t-test abnormal VMP < controls, p = 0.0873	correl - t-test abnormal Sway < normal Sway, p = 0.0393* abnormal Sway < controls, p = 0.0744	correl abnormal VMP to Sway, p = 0.0443* t-test normal VMP > controls, p = 0.0384*	correl - t-test abnormal Sway > normal Sway, p = 0.0902 abnormal Sway > controls, p = 0.0163*
BODY	correl abnormal VMP to EOG, p = 0.04* normal VMP to EOG, p = 0.0623 t-test -	correl - t-test abnormal Sway < controls, p = 0.0638 normal Sway < controls, p = 0.096	correl - t-test abnormal VMP > normal VMP, p = 0.0934 abnormal VMP > controls, p = 0.0294* normal VMP > controls, p = 0.028*	correl normal Sway to Sway, p = 0.0337* t-test abnormal Sway > normal Sway, p = 0.0464* abnormal Sway > controls, p = 0.0073** normal Sway > controls, p = 0.077
GENU	correl - t-test abnormal VMP < controls, p = 0.0185* normal VMP < controls, p = 0.0444*	correl - t-test abnormal Sway < controls, p = 0.0255* normal Sway < controls, p = 0.0628	correl - t-test abnormal VMP > controls, p = 0.0591 normal VMP > controls, p = 0.007**	correl - t-test abnormal Sway > normal Sway, p = 0.0255* abnormal Sway > controls, p = 0.0004*** normal Sway > controls, p = 0.0585

Table. 14. Summary for CC voxelwise DTI analysis – AD and RD (2/2).

GENU

The Genu of the CC has been previously implicated as an essential region damaged after TBI (Niogi et al., 2008), (Edlow et al., 2016). In my study, both division methods (i.e. VMP and vestibular Sway) achieved statistical significance only for comparison contrasts but not for correlations contrasts.

For the VMP division, “normal VMP patients and controls” was notable for all four DTI parameters (FA (<), MD (>), AD (<) and RD (>)), whereas “*abnormal VMP patients and controls*” was statistically meaningful for FA and AD only.

Sway division showed a main effect between “*abnormal Sway patients and controls*” for all four DTI parameters (FA (<), MD (>), AD (<) and RD (>)). Importantly, for FA and RD, I also note an important discrimination between “*abnormal Sway and normal Sway patients*”. Thus, the GENU potentially gave the third example of the finding providing the possibility to differentiate white matter atrophy in the CC between patients based on their vestibular postural performance. Still, similar to BODY, a notable correlation of non-vestibular nature - “normal Sway patients to Sway” for FA and a tendency for RD were present.

5. Conclusion

In this sub-study, I investigated whether VMP and vestibular Sway shared a common neuronal network within the Corpus Callosum and whether the callosal integrity reflected on the loss of VMP or vestibular imbalance during acute TBI. My main findings suggested that there was a link between vestibular-guided Sway performance and WM atrophy in all three callosal regions during the acute state of TBI, but this link was not present for vestibular motion perception.

Damage to the Corpus Callosum is an often reported abnormality after TBI (Tomaiuolo et al., 2004), (Nakayama et al., 2006), (Niogi et al., 2008), (Ham & Sharp, 2012), (Hulkower et al., 2013), (Edlow et al., 2016), leading to both cognitive and functional impairment. In my study, both for DTI and VBM analyses (please check Appendix for further details about VBM analysis), there were some examples of the suggested link between vestibular self-motion perception and vestibular Sway processing. However, these notable findings were more often based on the link between “neuronal correlates of imbalance to VMP” rather than the “neuronal correlate of impaired vestibular motion perception to Sway”.

Correlation-wise, DTI voxelwise analysis showed that on a patient/control level, patients FA correlated significantly only to vestibular Sway in the SPLENIUM and GENU. However, when **comparing** the difference between patient/control groups, there was always a significant difference in the FA analysis with patients FA < controls FA for all three regions – GENU, BODY and SPLENIUM.

The DTI voxelwise analysis showed that white matter integrity in abnormal VMP patients differs from controls, specifically via FA (BODY and GENU) and RD (BODY) analyses.

Further, my mean value DTI analysis suggested that concerning the division methods, vestibular Sway was more sensitive compared to VMP division, thus implying a link between vestibular-driven Sway and WM atrophy in the CC for acute TBI. This notion was also confirmed by the DTI voxelwise analysis.

Vestibular Sway, both the mean value analysis and voxelwise DTI analyses indicated a widespread link with the three regions explored, i.e. GENU, BODY and SPLENIUM, via FA and RD parameters. Specifically, the voxelwise Sway-based FA and RD analyses for all three areas were consistently significant for the discrimination between “*abnormal Sway patients and controls*”. What was even

more interesting was that for vestibular Sway, but not for VMP, there was a clear discrimination among patients via statistically significant results. In particular, the “*abnormal Sway - normal Sway*” difference suggested a distinct pattern of callosal damage between patients with vestibular imbalance and those who did not have any detectable central vestibular damage affecting their balance performance. This suggestion was strongest for SPLENIUM, followed by BODY and GENU, where some non-vestibular links for FA might have interfered.

However, the DTI analysis presented the GENU with slightly more statistically significant results (patient-control, VMP and vestibular Sway division methods) and lower p -values compared to BODY and SPLENIUM. Even if an interesting result, I interpreted it with caution as more robust results are needed to imply a real difference between the CC regions. Still if I take this idea a step further, a study about blast-induced traumatic brain injury in rats found that the severity of the blast injury was “spatially dependent along the medial-lateral and rostrocaudal directions” (Venkatasubramanian et al., 2020). In particular, blast injury was “more severe closer to the midline” and severity changed in the rostrocaudal direction (i.e. GENU to SPLENIUM direction) (Venkatasubramanian et al., 2020). This suggestion in the animal model was similar to human studies reporting that mild TBI led to reduced FA in the GENU (Rutgers et al., 2008), whereas more severe TBI - showed a decreased FA also in the posterior CC, i.e. the SPLENIUM (Rutgers et al., 2008), (Perlbarg et al., 2009). Thus, even if it is difficult to find a formula linking the severity/type of injury to an exact brain location, the slightly more significant results about GENU in my cohort of mostly moderate TBI patients (“moderate–severe” based on Mayo criteria (Malec et al., 2007)) seemed to be potentially adequate based on these findings. However, the vestibular involvement of GENU during acute TBI renders a separate and further investigation, as already stated. In addition, the lack of more severe TBI cases in my acute cohort might also explain the lower number of significant contrasts for the SPLENIUM and the lack of a clear link to the vestibular self-motion perception, even if the SPLENIUM is a highly vestibular-implicated region (Kirsch et al., 2016). Most importantly, significant correlations of non-vestibular nature were hardly registered for the SPLENIUM analysis (both for DTI and not at all for VBM analyses). These contrasts of non-vestibular aetiology appeared mostly for BODY and GENU, implying (1) the diverse nature of the pathways passing through them and the lower sensitivity towards the vestibular signal they have. In addition, the overall lack of these non-vestibular contrasts in the SPLENIUM when attempting to link to two highly vestibular tasks, such as the VMP and the vestibular posturography, (2) served as a proof of the established vestibular role of the SPLENIUM (Kirsch et al., 2016).

In summary, the vestibular Sway performance showed a wider distribution across the three CC regions and a statistically significant and robust discrimination for FA for all three regions – GENU, BODY and SPLENIUM. Thus, my voxelwise analysis suggested a link between vestibular-guided Sway performance and callosal damage during acute TBI.

II. VESTIBULAR REGIONS

1. Introduction

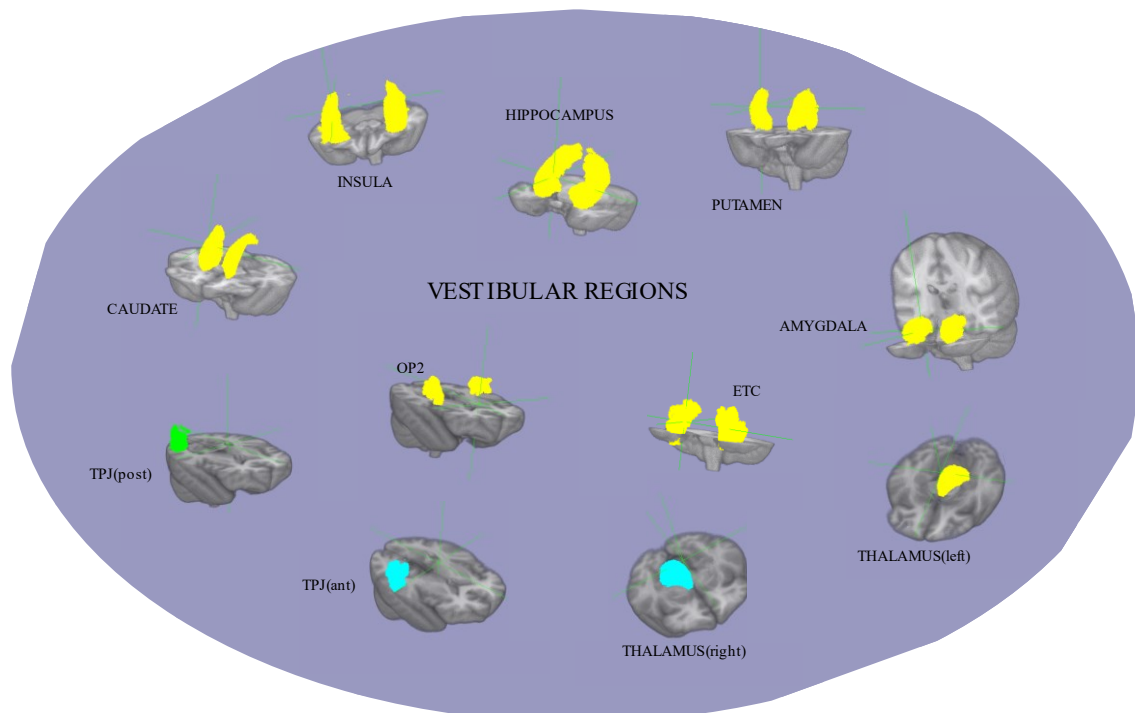


Figure. 76. Eleven brain regions known for their link to the Vestibular system (non-radiological orientation). (Masks based on Harvard-Oxford cortical and subcortical structural atlas (Desikan et al., 2006), Mars TPJ connectivity-based parcellation atlas (Mars et al., 2012) and Juelich Histological atlas (Eickhoff et al., 2005)).

Caloric reflex and transcranial magnetic stimulation, alongside brain imaging (e.g. functional MRI) studies, have shown that vestibular stimulation can activate a number of cortical and subcortical regions, among which are the hippocampus, insula, OP2 and the TPJ (Kahane et al., 2003), (Brandt et al., 2005), (Lopez & Blanke, 2011), (Kaski et al., 2016), (Padova et al., 2020). Some of these brain structures are especially interesting for my vestibular-driven study not only because of their implication with the vestibular system but also because they are already prominent regions in the spatial orientation and/or balance processing. However, it is unknown how brain damage in the acute setting of TBI affects a broader network of such cortical and subcortical structures known to receive vestibular input. Thus, my objectives for this sub-Chapter were as follows:

1. To investigate if vestibular-guided spatial and postural modalities shared a common neuronal network in a selection of eleven brain regions known to receive vestibular input?
2. To investigate if the integrity of these vestibular cortical and subcortical regions was linked to loss of vestibular motion perception or postural disturbance during acute TBI?

2. Materials and Methods

2.1. Recruitment of patients

Please refer to Chapter II for the inclusion/exclusion criteria of this study and to Chapter III for a more detailed information about acute TBI patients and their demographics. Importantly, only 30 acute TBI patients and 36 healthy controls completed the imaging part of the study.

2.2. Methodology

The previously conducted whole-brain analysis did not directly inform the specific regions that I explored in my ROI analysis, but it stressed the importance and the need to perform such a more detailed region of interest analysis. In this section, I looked at a selection of eleven brain structures that are thought to play a central role as vestibular signal mediators either through a direct link to the putative vestibular cortex or via their actual role as a building block of this putative structure (Fig.76). In particular, these were the Amygdala, Entorhinal cortex (ETC), Caudate, Putamen, Left Thalamus, Right Thalamus, Insula and the Hippocampus (Hitier et al., 2014), (Kamil et al., 2018), (A. Jacob et al., 2020), along with the right TPJ (anterior portion), right TPJ (posterior portion) (Lopez & Blanke, 2011), (Kaski et al., 2016) and the OP2 region (Kahane et al., 2003). While this was not an exhaustive list of vestibular implicated brain areas, I selected these specific regions as they proved to be more approachable for segmentation based on the resolution limitations of my MRI scans and the specific scanning protocols used. Thus, my selection represented a good number of vestibular regions that helped me address the hypotheses and objectives mentioned above.

Please refer to Chapter II. for a detailed explanation of the tasks used in this Chapter and the general scheme of the DTI analysis.

2.3. Statistical analysis

For my analysis, I use three types of division: (1) patient/control, (2) based on their vestibular motion perception performance (VMP) (i.e. into normal/abnormal performance), and (3) based on their Sway 95% confidence ellipse/posturography performance in the eyes-closed condition on a foamy surface, i.e. vestibular-driven posturography condition (similarly, into normal/abnormal performance).

The Shapiro-Wilk test informed the use of parametric statistics. For all analyses, the alpha-level was set at 0.05.

DTI – mean value analysis:

A group-level comparison between acute TBI patients and controls was performed for mean value FA, MD, AD and RD in the eleven vestibular regions using the independent sample t-test. To quantify the effects reported, t-statistics data were included.

One-way ANOVA was performed for the four DTI measures to assess the difference between abnormal VMP/normal VMP/control or abnormal Sway/normal Sway/control groups. To quantify the effects

reported, eta squared values for F-tests were included. All significant results were further investigated with a Post Hoc with Bonferroni corrections.

Lastly, a ‘patient only’ correlation analysis using the Pearson’s test informed about the potential link between VMP/Sway tests and the four DTI parameters within the eleven vestibular regions.

For ease of interpretation, all statistical results for t-tests and ANOVA are displayed directly on the accompanying plots, while detailed tables for patient/control, VMP and Sway divisions, alongside the patient/control plot are available in Appendix.

DTI – voxelwise analysis:

Similar to the whole-brain DTI voxelwise analysis (Chapter VI), here I performed a GLM-based voxelwise correlation and comparison analysis for the eleven vestibular regions. With respect to the plots presented, I only concentrated on two division methods: the vestibular spatial (via the VMP task) and vestibular postural aspect (via the vestibular Sway task) of acute TBI. I summarised the results for each region on a single plot and kept the same organisation throughout this Chapter VII.

In this section, I presented the voxelwise analysis in a summarised form only via these plots. However, the complete information, i.e. MNI coordinates of all maximum intensity voxels and details about clusters and their size/location is available in Appendix.

This DTI analysis presented only contrasts corrected for multiple hypothesis testing at a threshold of 0.05 via fsl randomise (Winkler et al., 2014) with 10,000 permutations for each contrast. The contrasts were the primary findings of this analysis and, as such, were displayed in the following images. It is of note that the output of the voxelwise contrast was a value that, when subtracted from “1.0” provided the *p*-value of this contrast.

Importantly, I report not only statistically significant contrasts (i.e. contrast value ≥ 0.95), but also something I called “tendencies”. They had contrast values between [0.9 – 0.949], and their corresponding *p*-values were between [0.1 and 0.051].

3. Results

A. MEAN VALUE ANALYSIS

First, I extracted mean ROI values for FA, MD, AD and RD for all of the selected eleven vestibular regions based on the whole-brain mean results from DTI TBSS. For the patient/control division, an independent sample t-test between patients and controls was performed.

For Fractional anisotropy (FA), I note a significant difference for HIPPOCAMPUS ($p = 0.03^*$) and right TPJ (ant) ($p = 0.04^*$), and a tendency towards significance for AMYGDALA and THALAMUS (Right). There was a general trend for this cohort of acute TBI patients to show lower FA results than controls FA for almost all vestibular regions I investigated, except for OP2.

Mean diffusivity (MD) achieved a higher number of significant results, i.e. for THALAMUS (Left) ($p = 0.04^*$), THALAMUS (Right) ($p = 0.003^{**}$) and right TPJ (post) ($p = 0.03^*$), while no tendencies were observed. Still, an apparent increase of MD, even if not reaching statistical difference with controls, was also noted in the AMYGDALA, ETC, INSULA and right TPJ (ant).

Further, axial diffusivity had only one significant difference for patient/control, i.e. for THALAMUS (Right) ($p = 0.02^*$) and a tendency in the CAUDATE and HIPPOCAMPUS. Generally, as axial diffusivity (AD) has a more varying profile as it changes dynamically during the acute TBI, its values presented a “current state”. Importantly, increased values, indicative of an ongoing reparation process, were seen in the ETC, THALAMUS (Right and Left), OP2 and right TPJ (post). On the other hand, in the AMYGDALA, CAUDATE, PUTAMEN and right TPJ (ant) the values were still decreased as compared to controls, suggesting no commenced process of remyelination/repair.

Lastly, radial diffusivity showed a statistically meaningful difference for THALAMUS (Left) ($p = 0.02^*$), THALAMUS (Right) ($p = 0.002^{**}$) and right TPJ (ant) ($p = 0.04^*$) and a tendency towards significance for HIPPOCAMPUS and right TPJ (post).

Finally, a correlation analysis between the DTI parameters and the VMP and Vestibular Sway tasks was performed for all eleven vestibular regions (table available in Appendix). With respect to the correlations with the VMP task (*patients-only* data), there was a tendency towards significance in the HIPPOCAMPUS and the THALAMUS (Right), while a statistical result was reached for OP2 (for FA) and right TPJ (ant) (for AD). Notably, the vestibular Sway correlated to more of the selected structures – INSULA (for MD and AD), OP2 (for MD and RD) and right TPJ (post) (for FA, MD and RD), while showing a tendency towards significance in the ETC and right TPJ (ant).

3.1. Vestibular Motion Perception (VMP) division

All results from the detailed statistical analysis of the VMP division are summarised in Fig. 77. FA analysis showed that *by observation controls FA > abnormal VMP patients FA* in all selected regions. However, the VMP division showed a statistically significant main effect of group only for the AMYGDALA ($p = 0.05^*$).

Further, I note a more varying picture for the three diffusivity parameters (i.e. MD, AD and RD). Generally, for MD and RD, *abnormal VMP patients > controls*. In particular, there were significant results for MD, AD and RD for THALAMUS (Right), but ANOVA showed they were not vestibular-based. Further, there were two tendencies observed – right TPJ (post) (for MD) and THALAMUS (Left) (for MD and RD).

For AD, half of the regions showed a decreased and the rest – increased values for abnormally VMP patients as compared to controls and no group pattern could be established. There is one statistically meaningful vestibular-based result in the CAUDATE ($p = 0.01^*$).

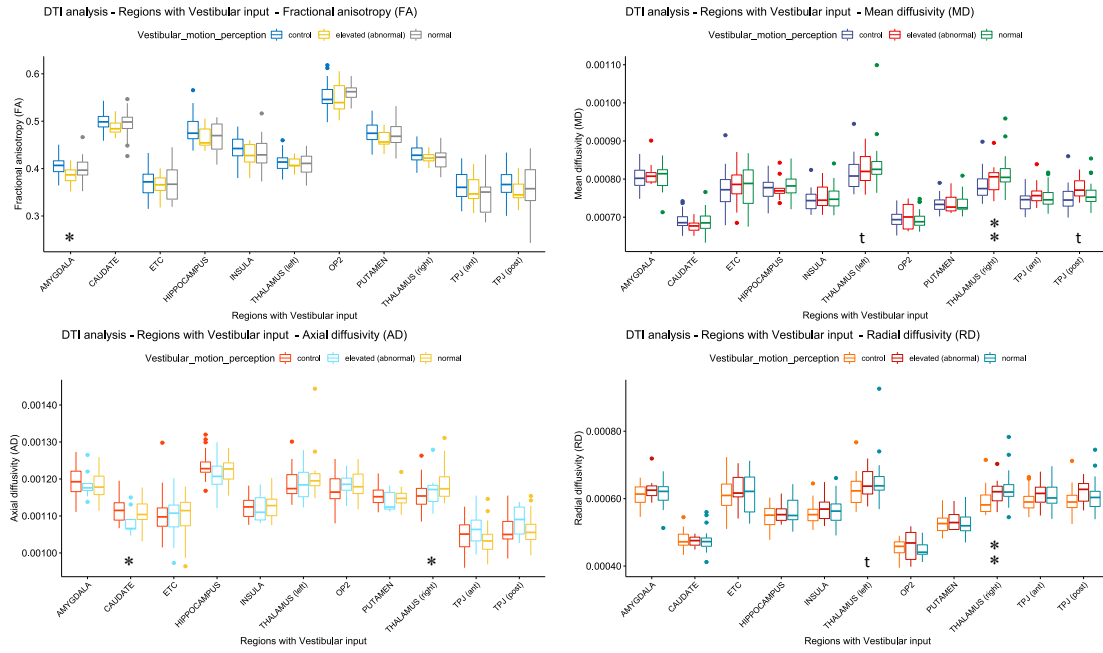


Figure. 77. DTI analysis – Mean values for Vestibular regions – Vestibular Motion Perception (VMP) division. Legend – an asterisk “*” indicates a statistically significant effect of group, whereas “t” displays a tendency towards a statistically significant result (I consider tendency any p -value between [0.1 and 0.051]).

3.2. Vestibular Sway division

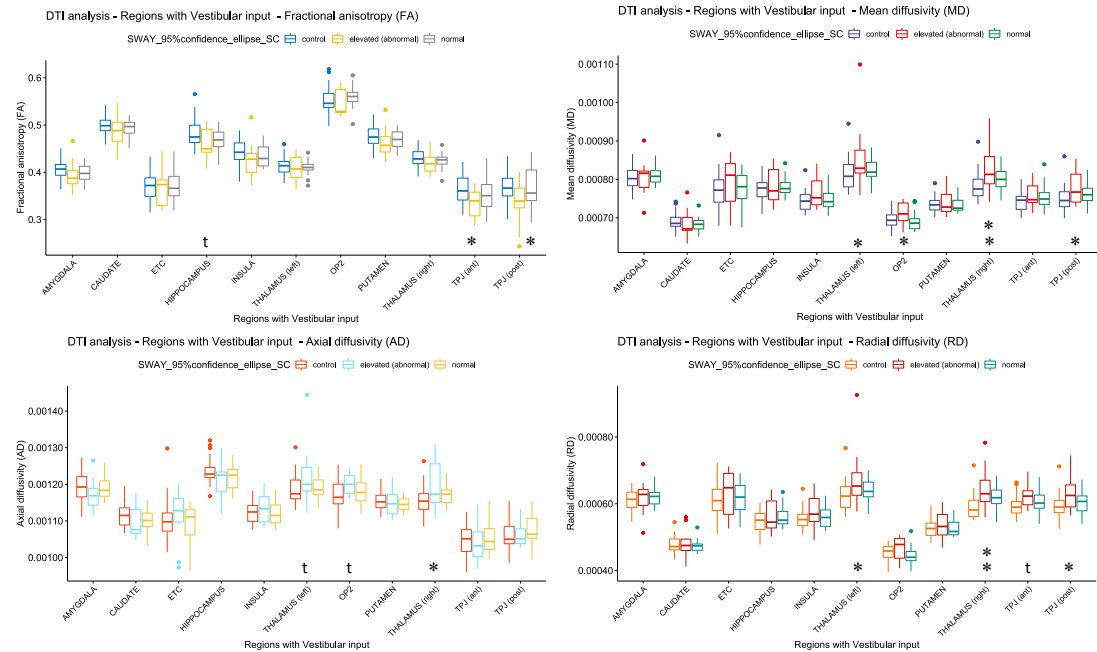


Figure. 78. DTI analysis Mean-values for Vestibular regions – Vestibular Sway 95% confidence ellipse division. Legend – an asterisk “*” indicates a statistically significant effect of group, whereas “t” displays a tendency towards a statistically significant result (I consider tendency any p -value between [0.1 and 0.051]).

All results from the detailed statistical analysis for Sway division are summarised in Fig. 78.

The Sway division for FA showed a significant main effect of group in the right TPJ (ant + post) ($p = 0.04^*$ and $p = 0.04^*$, respectively) and one tendency towards significance for the HIPPOCAMPUS. The discrimination between groups followed an expected trend (*i.e. controls FA > patients with good*

balance FA > patients with poor balance FA) in all regions, except for the ETC.

Mean diffusivity (MD) showed four notable regions – (1) the two THALAMI (Right + Left) ($p = 0.003^{**}$ and $p = 0.02^{*}$, respectively), (2) OP2 ($p = 0.03^{*}$) and (3) right TPJ (post) ($p = 0.04^{*}$). Other regions for MD displayed a similar trend, even if not reaching statistical significance. Further, axial diffusivity (AD) had two areas with tendencies towards significance - (1) THALAMUS (Left) and (2) OP2. It also presented one statistically significant result showing a main effect of vestibular balance in the THALAMUS (Right) ($p = 0.02^{*}$).

Lastly, Sway-based radial diffusivity (RD) showed a notable effect of Sway sub-groups in (1) the two THALAMI (Right + Left) ($p = 0.002^{**}$ and $p = 0.01^{*}$, respectively) and (2) right TPJ (post) ($p = 0.02^{*}$) and a tendency in the right TPJ (ant).

B. VOXELWISE ANALYSIS – DTI

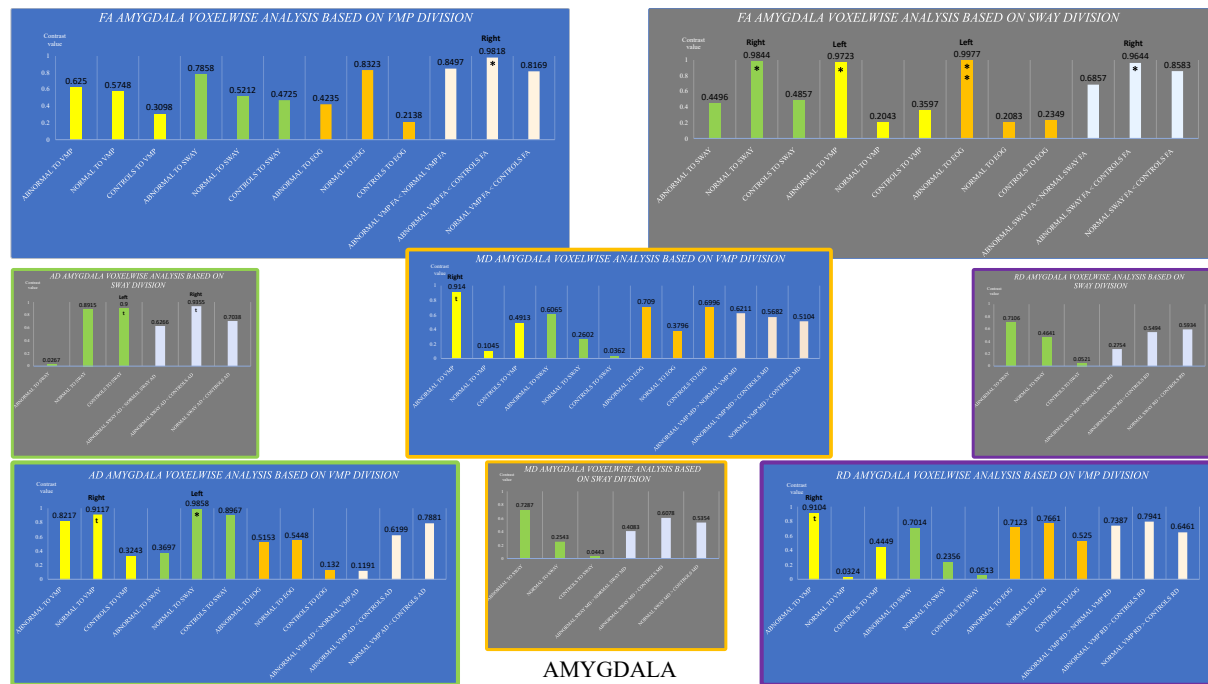


Figure. 79. DTI voxelwise analysis – AMYGDALA. The plot displays FA, MD, AD and RD summarised data based on the VMP division (blue background colour) or Vestibular Sway division (grey background colour). For easier interpretation, I have coloured the border of Mean Diffusivity maps (ORANGE colour, in the centre), Axial Diffusivity maps (GREEN colour, on the left) and Radial Diffusivity maps (LILAC colour, on the right). Further, an asterisk ** denotes any significant contrast (i.e. contrast value ≥ 0.95 , and corresponding p -value ≤ 0.05) and * represents a tendency towards significance (i.e. any contrast value in the range = $[0.9 - 0.949]$ and corresponding p -value = $[0.1 - 0.051]$). On the plots, I have incorporated correlation and comparison contrasts together. Correlation is a different colour depending on the type of input data – VMP (YELLOW colour), SWAY (GREEN colour) and EOG (ORANGE colour) followed by differently coloured bar charts for t-tests bars. Lastly, above each contrast of note, I have indicated if this was a notable contrast in the Left or the Right hemisphere of the ROI.

After completing a mean value TBSS exploration of the eleven regions with vestibular input, my next step was to perform voxelwise DTI analysis. All results in this sub-Chapter were organised specifically in the form of the already-known summary plots, with each of the eleven brain regions presented on a single plot dedicated to that region (Fig. 79 through Fig. 89). Similar to the CC-section, a detailed report discussing the results of the eleven vestibular regions is available in Appendix. It contains information about the patient/control, VMP/ Sway divisions while providing critical details about MNI coordinates

of the maximum intensity voxels/cluster specifications for significant and tendency results.

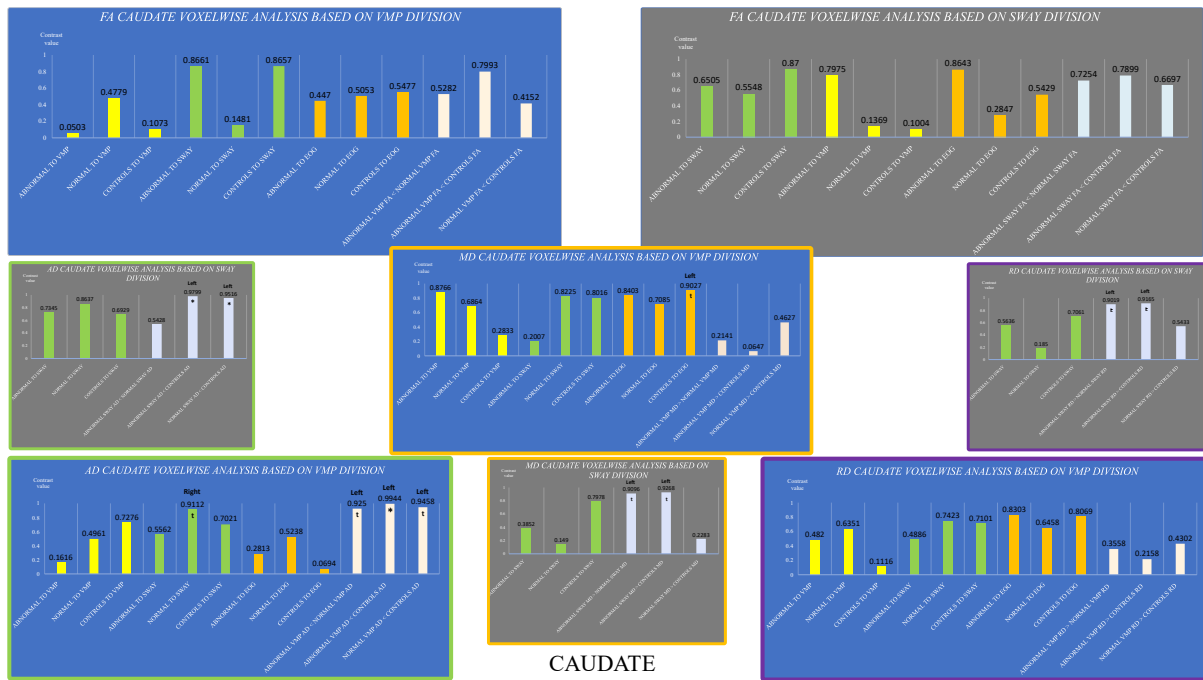


Figure. 80. DTI voxelwise analysis – CAUDATE. The plot displays FA, MD, AD and RD summarised data based on the VMP division (blue background colour) or Vestibular Sway division (grey background colour). For easier interpretation, I have coloured the border of Mean Diffusivity maps (ORANGE colour, in the centre), Axial Diffusivity maps (GREEN colour, on the left) and Radial Diffusivity maps (LILAC colour, on the right). Further, an asterisk ‘*’ denotes any significant contrast (i.e. contrast value ≥ 0.95 , and corresponding p -value ≤ 0.05) and ‘t’ represents a tendency towards significance (i.e. any contrast value in the range = $[0.9 - 0.949]$ and corresponding p -value = $[0.1-0.051]$). On the plots, I have incorporated correlation and comparison contrasts together. Correlation is a different colour depending on the type of input data – VMP (YELLOW colour), SWAY (GREEN colour) and EOG (ORANGE colour) followed by differently coloured bar charts for t-tests bars. Lastly, above each contrast of note, I have indicated if this was a notable contrast in the Left or the Right hemisphere of the ROI.

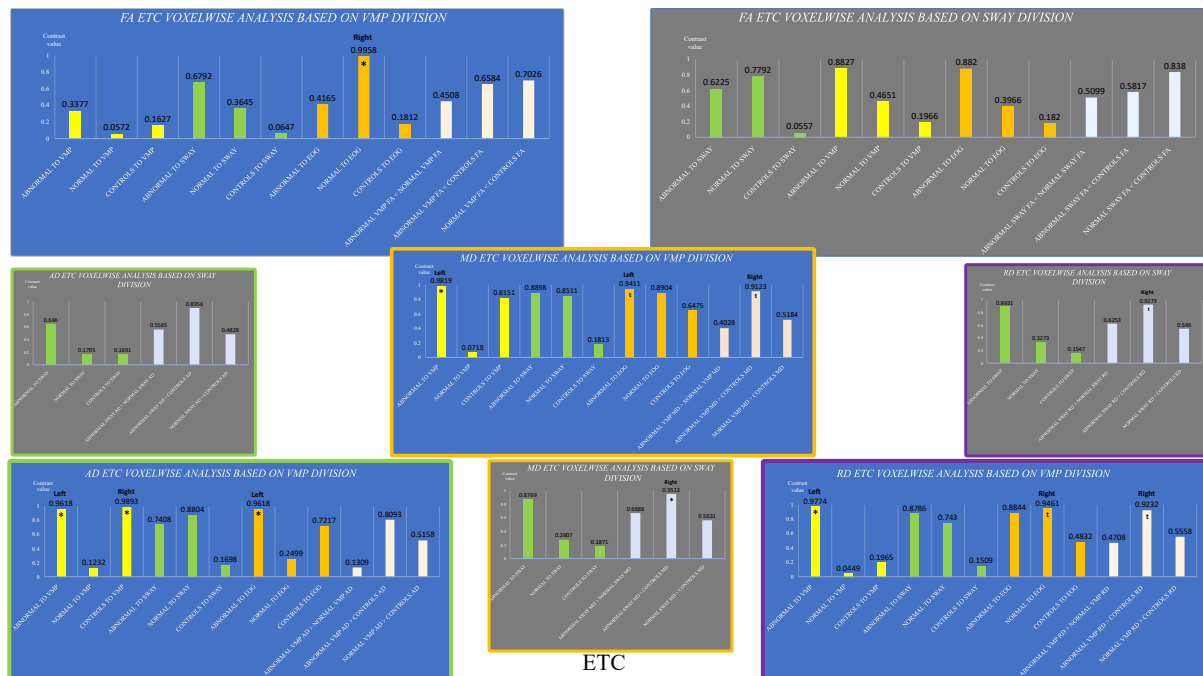
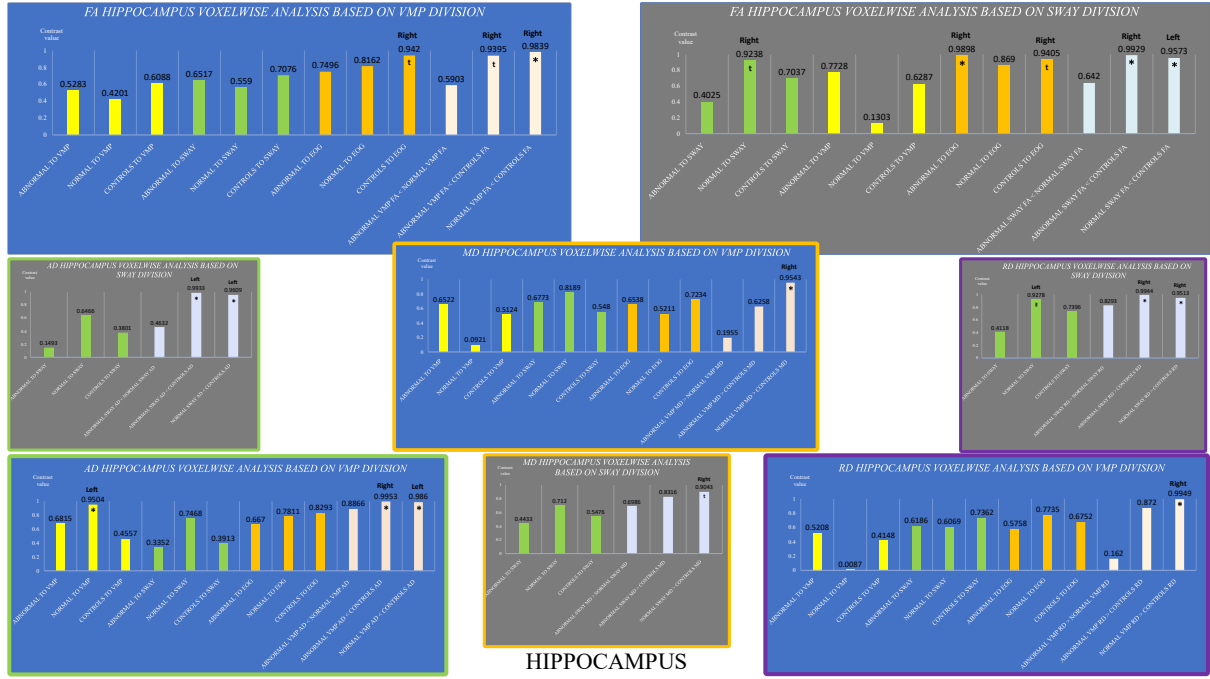
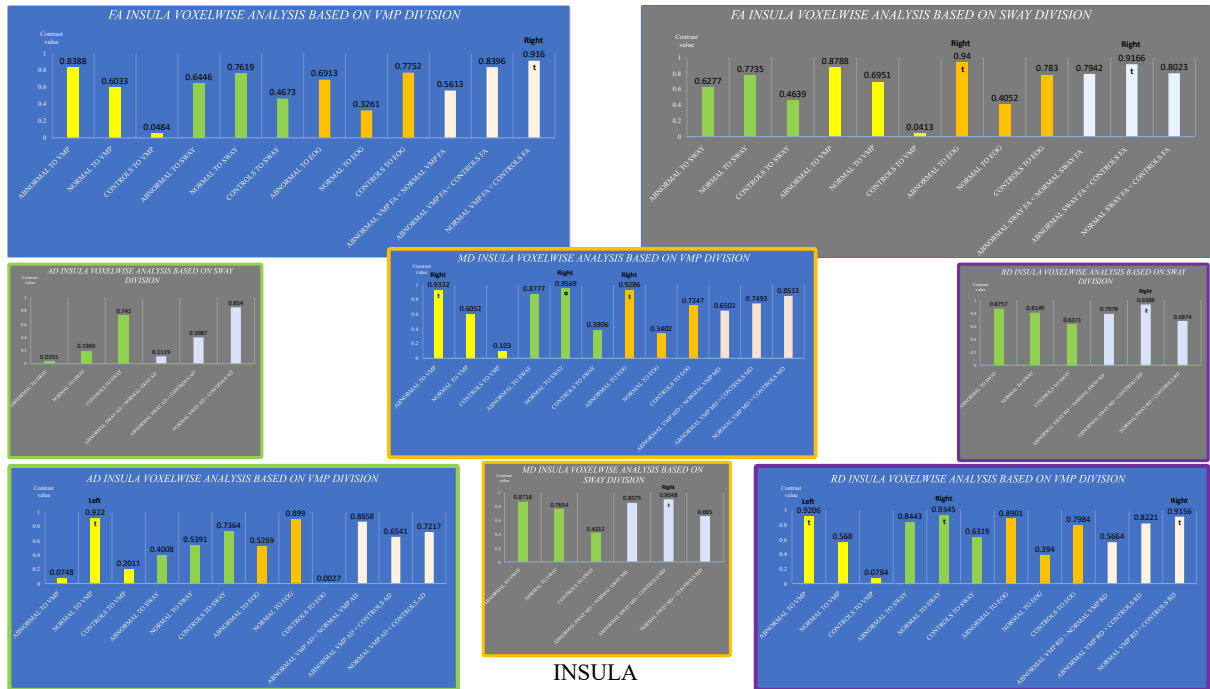


Figure. 81. DTI voxelwise analysis – ETC. The plot displays FA, MD, AD and RD summarised data based on the VMP division (blue background colour) or Vestibular Sway division (grey background colour). For easier interpretation, I have coloured the border of Mean Diffusivity maps (ORANGE colour, in the centre), Axial Diffusivity maps (GREEN colour, on the left) and Radial Diffusivity maps (LILAC colour, on the right). Further, an asterisk ‘*’ denotes any significant contrast (i.e. contrast value ≥ 0.95 , and corresponding p -value ≤ 0.05) and ‘t’ represents a tendency towards significance (i.e. any contrast value in the range = $[0.9 - 0.949]$ and corresponding p -value = $[0.1-0.051]$). On the plots, I have incorporated correlation and comparison contrasts together. Correlation is a different colour depending on the type of input data – VMP (YELLOW colour), SWAY (GREEN colour) and EOG (ORANGE colour) followed by differently coloured bar charts for t-tests bars. Lastly, above each contrast of note, I have indicated if this was a notable contrast in the Left or the Right hemisphere of the ROI.



HIPPOCAMPUS

Figure 82. DTI voxelwise analysis – HIPPOCAMPUS. The plot displays FA, MD, AD and RD summarised data based on the VMP division (blue background colour) or Vestibular Sway division (grey background colour). For easier interpretation, I have coloured the border of Mean Diffusivity maps (ORANGE colour, in the centre), Axial Diffusivity maps (GREEN colour, on the left) and Radial Diffusivity maps (LILAC colour, on the right). Further, an asterisk ‘*’ denotes any significant contrast (i.e. contrast value ≥ 0.95 , and corresponding p -value ≤ 0.05) and ‘t’ represents a tendency towards significance (i.e. any contrast value in the range = $[0.9 - 0.949]$ and corresponding p -value = $[0.1 - 0.051]$). On the plots, I have incorporated correlation and comparison contrasts together. Correlation is a different colour depending on the type of input data – VMP (YELLOW colour), SWAY (GREEN colour) and EOG (ORANGE colour) followed by differently coloured bar charts for t-tests bars. Lastly, above each contrast of note, I have indicated if this was a notable contrast in the Left or the Right hemisphere of the ROI.



INSULA

Figure 83. DTI voxelwise analysis – INSULA. The plot displays FA, MD, AD and RD summarised data based on the VMP division (blue background colour) or Vestibular Sway division (grey background colour). For easier interpretation, I have coloured the border of Mean Diffusivity maps (ORANGE colour, in the centre), Axial Diffusivity maps (GREEN colour, on the left) and Radial Diffusivity maps (LILAC colour, on the right). Further, an asterisk ‘*’ denotes any significant contrast (i.e. contrast value ≥ 0.95 , and corresponding p -value ≤ 0.05) and ‘t’ represents a tendency towards significance (i.e. any contrast value in the range = $[0.9 - 0.949]$ and corresponding p -value = $[0.1 - 0.051]$). On the plots, I have incorporated correlation and comparison contrasts together. Correlation is a different colour depending on the type of input data – VMP (YELLOW colour), SWAY (GREEN colour) and EOG (ORANGE colour) followed by differently coloured bar charts for t-tests bars. Lastly, above each contrast of note, I have indicated if this was a notable contrast in the Left or the Right hemisphere of the ROI.

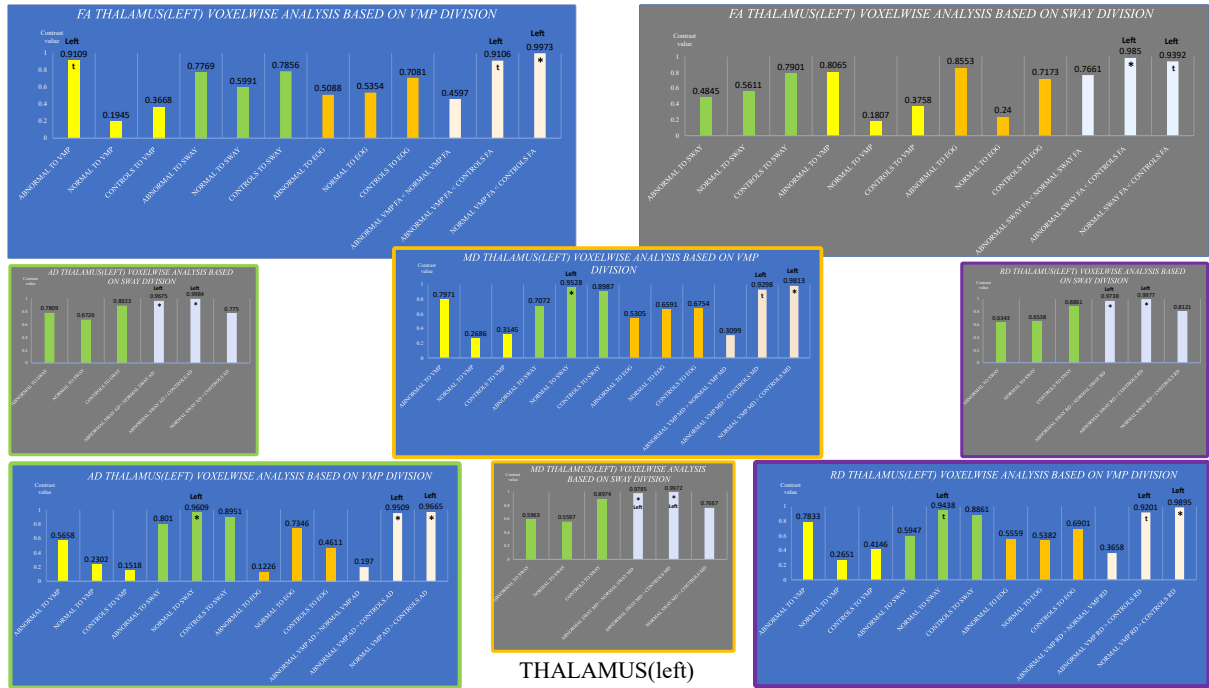


Figure. 84. DTI voxelwise analysis – THALAMUS (left). The plot displays FA, MD, AD and RD summarised data based on the VMP division (blue background colour) or Vestibular Sway division (grey background colour). For easier interpretation, I have coloured the border of Mean Diffusivity maps (ORANGE colour, in the centre), Axial Diffusivity maps (GREEN colour, on the left) and Radial Diffusivity maps (LILAC colour, on the right). Further, an asterisk ‘*’ denotes any significant contrast (i.e. contrast value ≥ 0.95 , and corresponding p -value ≤ 0.05) and ‘t’ represents a tendency towards significance (i.e. any contrast value in the range = [0.9 – 0.949] and corresponding p -value = [0.1-0.051]). On the plots, I have incorporated correlation and comparison contrasts together. Correlation is a different colour depending on the type of input data – VMP (YELLOW colour), SWAY (GREEN colour) and EOG (ORANGE colour) followed by differently coloured bar charts for t-tests bars. Lastly, above each contrast of note, I have indicated if this was a notable contrast in the Left or the Right hemisphere of the ROI.

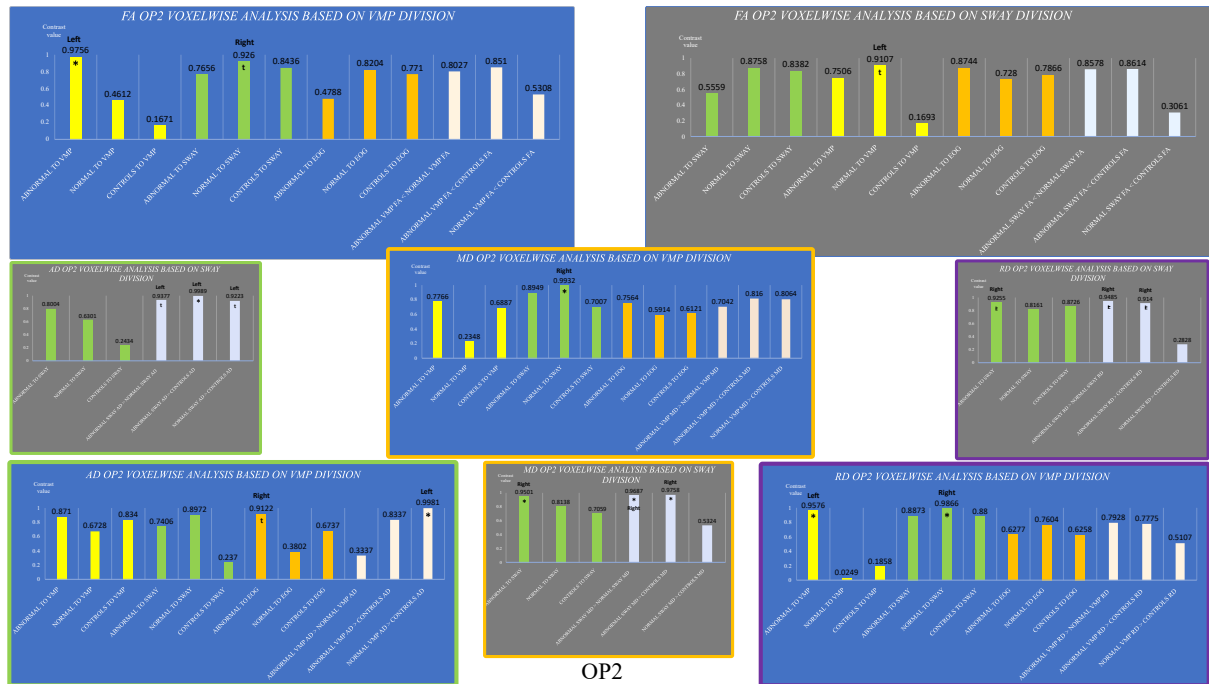


Figure. 85. DTI voxelwise analysis – OP2. The plot displays FA, MD, AD and RD summarised data based on the VMP division (blue background colour) or Vestibular Sway division (grey background colour). For easier interpretation, I have coloured the border of Mean Diffusivity maps (ORANGE colour, in the centre), Axial Diffusivity maps (GREEN colour, on the left) and Radial Diffusivity maps (LILAC colour, on the right). Further, an asterisk ‘*’ denotes any significant contrast (i.e. contrast value ≥ 0.95 , and corresponding p -value ≤ 0.05) and ‘t’ represents a tendency towards significance (i.e. any contrast value in the range = [0.9 – 0.949] and corresponding p -value = [0.1-0.051]). On the plots, I have incorporated correlation and comparison contrasts together. Correlation is a different colour depending on the type of input data – VMP (YELLOW colour), SWAY (GREEN colour) and EOG (ORANGE colour) followed by differently coloured bar charts for t-tests bars. Lastly, above each contrast of note, I have indicated if this was a notable contrast in the Left or the Right hemisphere of the ROI.

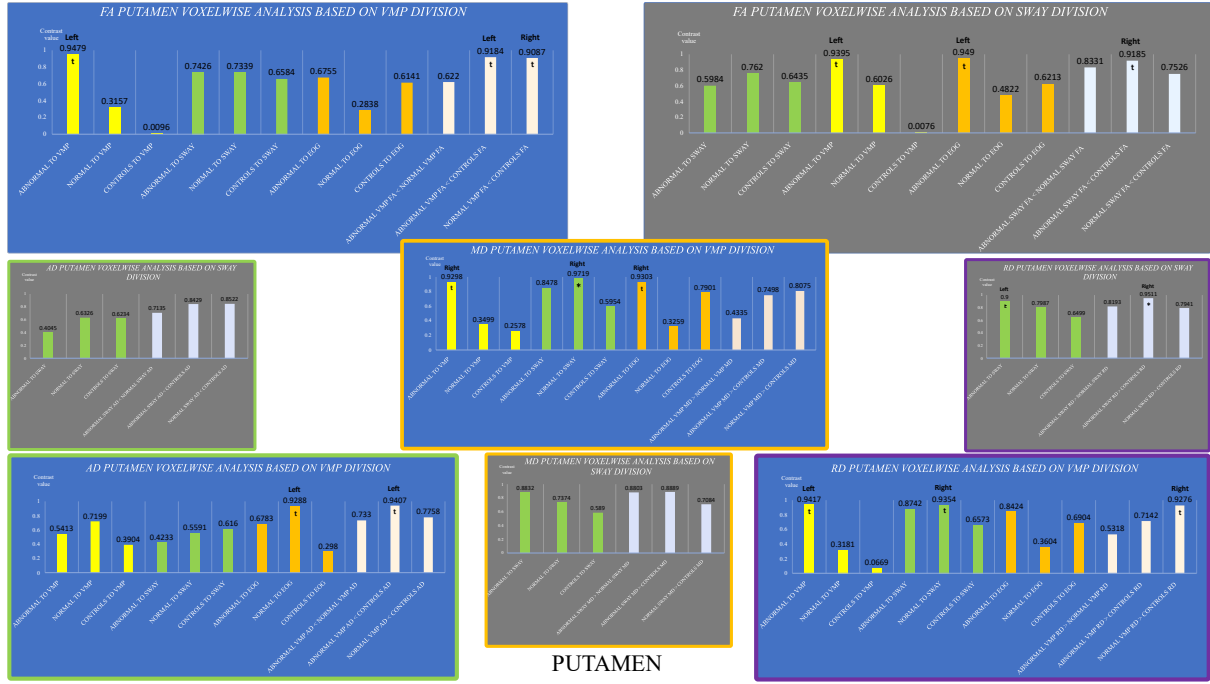


Figure. 86. DTI voxelwise analysis – PUTAMEN. The plot displays FA, MD, AD and RD summarised data based on the VMP division (blue background colour) or Vestibular Sway division (grey background colour). For easier interpretation, I have coloured the border of Mean Diffusivity maps (ORANGE colour, in the centre), Axial Diffusivity maps (GREEN colour, on the left) and Radial Diffusivity maps (LILAC colour, on the right). Further, an asterisk '*' denotes any significant contrast (i.e. contrast value ≥ 0.95 , and corresponding p -value ≤ 0.05) and 't' represents a tendency towards significance (i.e. any contrast value in the range = $[0.9 - 0.949]$ and corresponding p -value = $[0.1-0.051]$). On the plots, I have incorporated correlation and comparison contrasts together. Correlation is a different colour depending on the type of input data – VMP (YELLOW colour), SWAY (GREEN colour) and EOG (ORANGE colour) followed by differently coloured bar charts for t-tests bars. Lastly, above each contrast of note, I have indicated if this was a notable contrast in the Left or the Right hemisphere of the ROI.

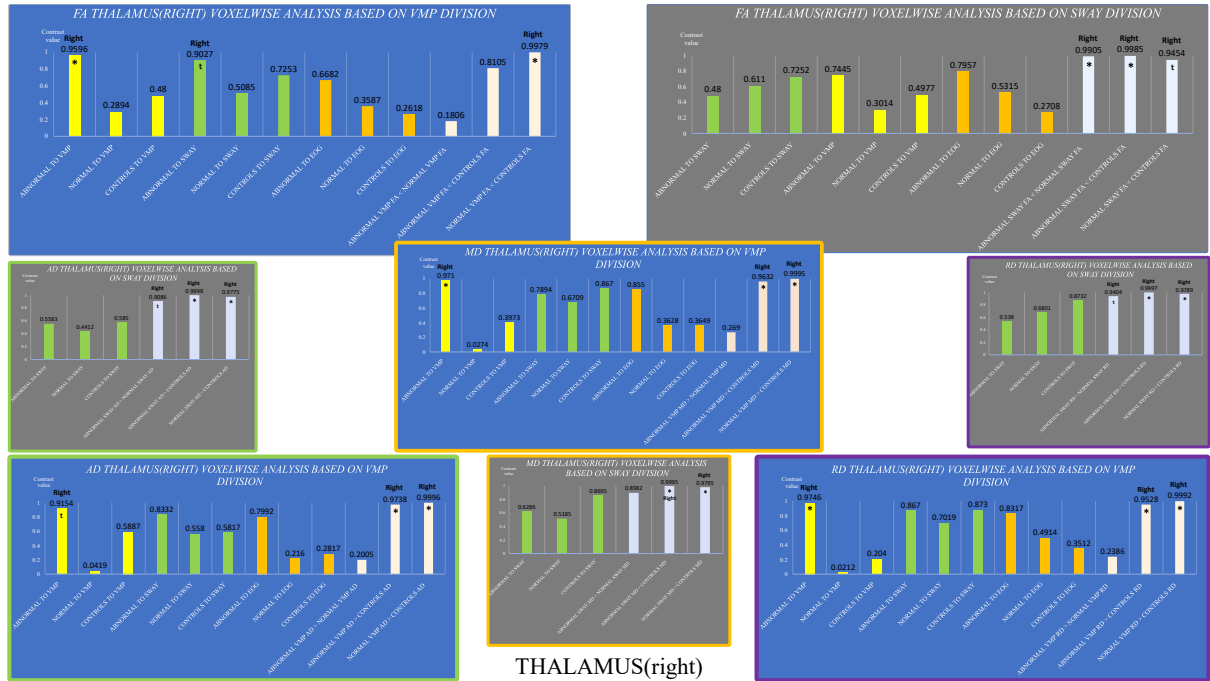


Figure. 87. DTI voxelwise analysis – THALAMUS (right). The plot displays FA, MD, AD and RD summarised data based on the VMP division (blue background colour) or Vestibular Sway division (grey background colour). For easier interpretation, I have coloured the border of Mean Diffusivity maps (ORANGE colour, in the centre), Axial Diffusivity maps (GREEN colour, on the left) and Radial Diffusivity maps (LILAC colour, on the right). Further, an asterisk '*' denotes any significant contrast (i.e. contrast value ≥ 0.95 , and corresponding p -value ≤ 0.05) and 't' represents a tendency towards significance (i.e. any contrast value in the range = $[0.9 - 0.949]$ and corresponding p -value = $[0.1-0.051]$). On the plots, I have incorporated correlation and comparison contrasts together. Correlation is a different colour depending on the type of input data – VMP (YELLOW colour), SWAY (GREEN colour) and EOG (ORANGE colour) followed by differently coloured bar charts for t-tests bars. Lastly, above each contrast of note, I have indicated if this was a notable contrast in the Left or the Right hemisphere of the ROI.

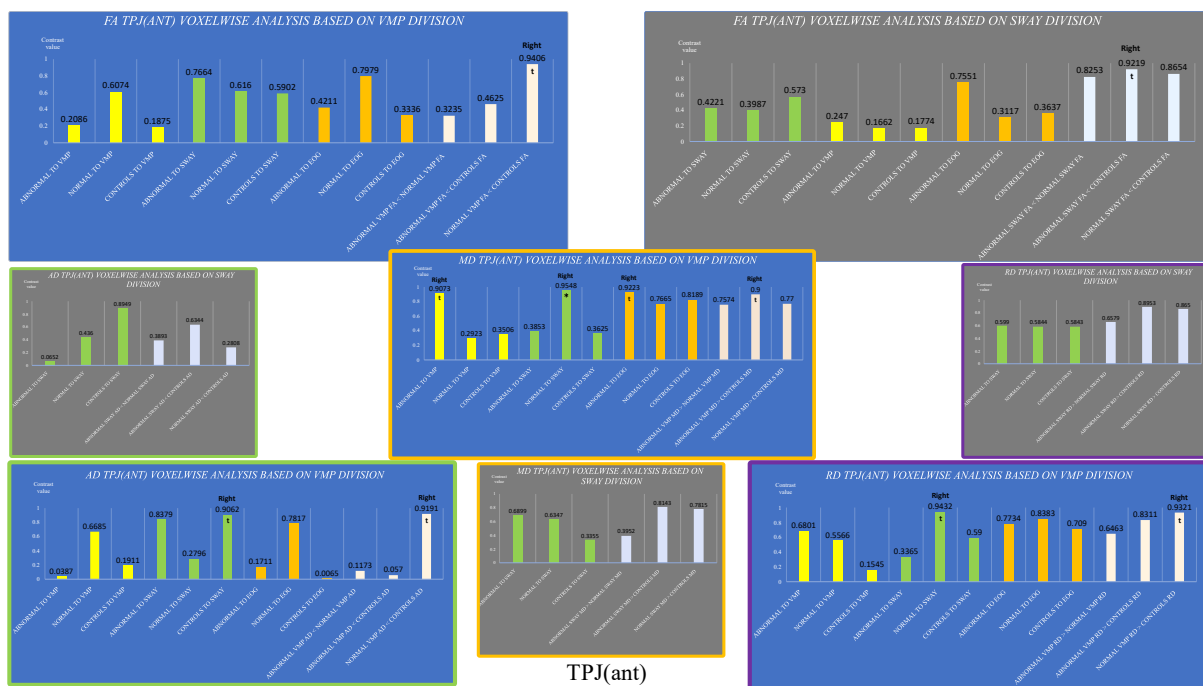


Figure 88. DTI voxelwise analysis – TPJ (ant). The plot displays FA, MD, AD and RD summarised data based on the VMP division (blue background colour) or Vestibular Sway division (grey background colour). For easier interpretation, I have coloured the border of Mean Diffusivity maps (ORANGE colour, in the centre), Axial Diffusivity maps (GREEN colour, on the left) and Radial Diffusivity maps (LILAC colour, on the right). Further, an asterisk ‘*’ denotes any significant contrast (i.e. contrast value ≥ 0.95 , and corresponding p -value ≤ 0.05) and ‘t’ represents a tendency towards significance (i.e. any contrast value in the range = $[0.9 - 0.949]$ and corresponding p -value = $[0.1-0.051]$). On the plots, I have incorporated correlation and comparison contrasts together. Correlation is a different colour depending on the type of input data – VMP (YELLOW colour), SWAY (GREEN colour) and EOG (ORANGE colour) followed by differently coloured bar charts for t-tests bars. Lastly, above each contrast of note, I have indicated if this was a notable contrast in the Left or the Right hemisphere of the ROI.

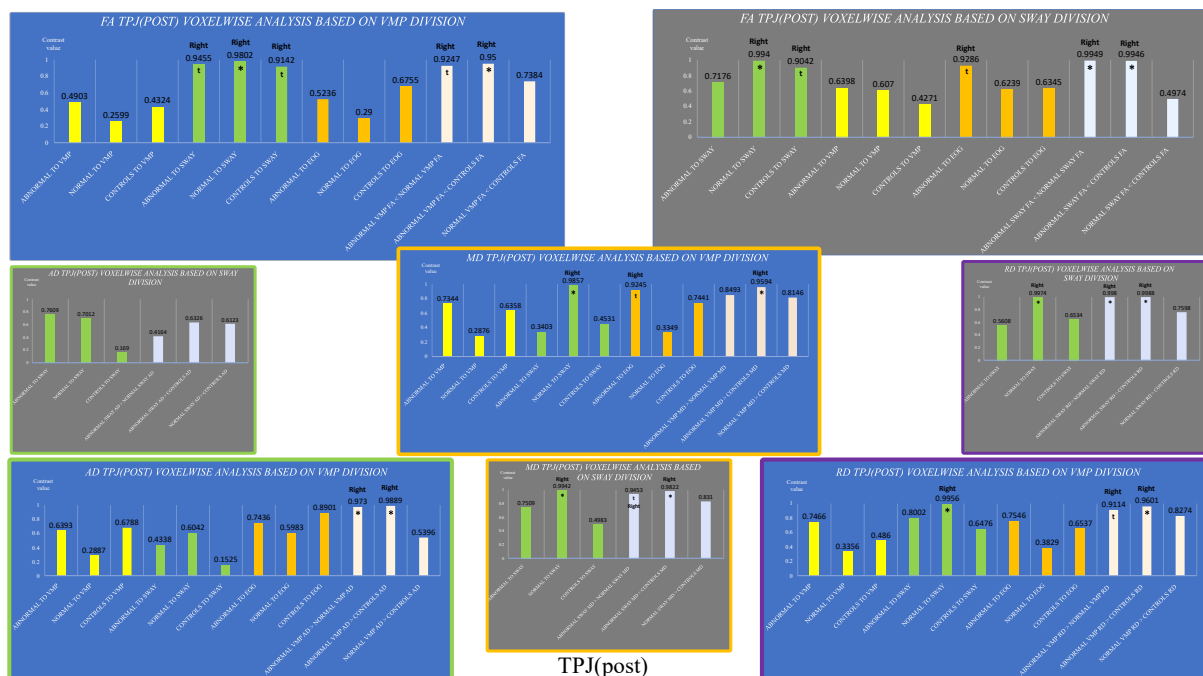


Figure 89. DTI voxelwise analysis – TPJ (post). The plot displays FA, MD, AD and RD summarised data based on the VMP division (blue background colour) or Vestibular Sway division (grey background colour). For easier interpretation, I have coloured the border of Mean Diffusivity maps (ORANGE colour, in the centre), Axial Diffusivity maps (GREEN colour, on the left) and Radial Diffusivity maps (LILAC colour, on the right). Further, an asterisk ‘*’ denotes any significant contrast (i.e. contrast value ≥ 0.95 , and corresponding p -value ≤ 0.05) and ‘t’ represents a tendency towards significance (i.e. any contrast value in the range = $[0.9 - 0.949]$ and corresponding p -value = $[0.1-0.051]$). On the plots, I have incorporated correlation and comparison contrasts together. Correlation is a different colour depending on the type of input data – VMP (YELLOW colour), SWAY (GREEN colour) and EOG (ORANGE colour) followed by differently coloured bar charts for t-tests bars. Lastly, above each contrast of note, I have indicated if this was a notable contrast in the Left or the Right hemisphere of the ROI.

4. Summary/Discussion

A. Mean value analysis – DTI analysis

In this sub-section, I investigated the TBSS-derived DTI parameters in a selected set of eleven vestibular regions. In Table. 15, I present a summary plot of the results discussed during this exploratory mean value analysis.

The mean value analysis (Table. 15) shows that there was a general trend in the “*patient-control*” data for FA (patients FA < controls FA), MD (patients MD > controls MD) and RD (patients RD > controls RD), which agrees with previous TBI research (Soares et al., 2013), (Kinnunen et al., 2011). Still, some differences were present, possibly due to the dynamic nature of the white matter during acute TBI. One such example for FA was seen for OP2, where patients FA > controls FA. As research suggests that right after brain trauma, FA can increase (Mac Donald et al., 2007) and is expected to stabilise within days, the finding for OP2 was not seen as “abnormal”. Instead, it suggested that the white matter in this specific region had not yet stabilised and decreased in value, which led to this result.

Further, the analysis indicated that acute TBI affected a highly ‘spatial orientation’ region such as the HIPPOCAMPUS, whose damage led patients’ FA to statistically differentiate from healthy controls. This agreed with the current scientific evidence that the HIPPOCAMPUS, as a highly vulnerable to damage region, was also affected by TBI (Kotapka et al., 1992), leading to a possible decreased sense of spatial orientation after TBI. Importantly, however, no statistically significant results for central vestibular-based processing (VMP/Sway) were established for this structure.

Brain region with Vestibular Input	patient-control	VMP division	Sway division
AMYGDALA	FA (t)	FA (*)	-
CAUDATE	AD (t)	AD (*)	-
ETC	-	-	-
HIPPOCAMPUS	FA (*), AD (t), RD (t)	-	FA (t)
INSULA	-	-	-
THALAMUS (left)	MD (*), RD (*)	MD (t), RD (t)	MD (*), AD (t), RD (*)
OP2	-	-	MD (*), AD (t)
PUTAMEN	-	-	-
THALAMUS (right)	FA (t), MD(*), AD(*), RD(*)	-	MD(*), AD(*), RD(*)
TPJ (ant)	FA (*), RD(*)	-	FA (*), RD(t)
TPJ (post)	MD (*), RD(t)	MD(t)	FA(*), MD(*), RD(*)

Table. 15. ROI DTI mean values statistical analysis – summary of t-tests and ANOVA results for patient/control and VMP/Sway division methods.

Another interesting finding was that there was a FA tendency towards significance in the brain’s relay station – the THALAMUS, and more specifically in the Right THALAMUS, which is in agreement with the established right hemispheric spatial and vestibular dominance (Dieterich et al., 2003), (Philbeck et al., 2006), (Zu Eulenburg et al., 2012), (Dieterich & Brandt, 2018). This right-sided brain

damage is expected to mainly affect behaviour on the contralateral, i.e. the left side of the brain, and consequently lead to dysfunction such as “an increased Left-sided VMP threshold” as compared to Right-sided VMP threshold. This, as seen in Chapter III, was not observed in this TBI cohort, possibly due to the smaller sample size or lack of more severe cases. Therefore, not surprisingly, at this point, the general mean value analysis showed that both THALAMI (Right + Left) achieved an equally significant effect of Sway-based group for MD and RD (Table. 15) and no notable results for VMP.

Next, the right TPJ is another region implicated with motion duration and vestibular spatial perception (Kaski et al., 2016). In my mean value analysis, patient/control analysis showed some statistically notable results, which further investigation revealed to be Sway-based rather than VMP-based. In addition, the TPJ (post) showed more significant results for vestibular Sway than the TPJ (ant).

As observed for the VMP division of FA (Fig. 77), all of the vestibular regions managed to visually, if not statistically, reflect the decrease in vestibular-guided spatial orientation via white matter atrophy. In particular, elevated motion perception patients had the lowest values as compared to the rest of the participants. However, the three diffusivity parameters (i.e. MD, AD and RD) did not establish such a concise hierarchy among groups. Still, in general, the VMP division suggested a more critical role for the AMYGDALA (FA) in the spatial orientation under vestibular guidance during acute TBI.

Further, the vestibular Sway division (Fig. 78) showed a link to acute TBI damage in almost all selected vestibular regions via its FA and RD analyses, with some exceptions present. Thus, it had a better potential than the VMP division to reflect the WM changes with respect to central vestibular processing after acute TBI. Notably, the Sway-based division established an important role for both THALAMI (Right + Left) and the TPJ area (post) in the posturography under vestibular guidance.

Overall, a correlation analysis between the selected eleven vestibular regions and the VMP/Sway tests showed more notable results for vestibular-driven Sway than the VMP task. In addition, Sway division offered more significant results after multiple comparison corrections than VMP, which agreed with the observed widespread effect of the vestibular Sway damage during acute TBI.

In summary, mean value exploratory analysis for the eleven vestibular regions gave a general overview of their relationship to VMP and vestibular Sway during acute TBI. However, it showed its inferiority in detecting the subtle link to the vestibular signal.

B. DTI – voxelwise analysis

For this DTI voxelwise analysis, I investigated if vestibular-guided spatial and postural processing shared common neuronal correlates in a set of eleven vestibular regions. I also explored if the available white matter in these highly grey matter structures was linked to loss of VMP or vestibular imbalance during acute TBI. I summarised my findings in two tables – Table. 16 and Table. 17. Additional information about the results of the VBM analysis of the 11 vestibular regions is available in Appendix.

Brain region with Vestibular Input	FA (VMP division)	FA (Sway division)	MD (VMP division)	MD (Sway division)
AMYGDALA	correl - t-test abnormal VMP < controls, p = 0.0182*	correl normal Sway to Sway, p = 0.0156* abnormal Sway to VMP, p = 0.0277* abnormal Sway to EOG, p = 0.0023** t-test abnormal Sway < controls, p = 0.0356*	correl abnormal VMP to VMP, p = 0.086 t-test -	correl - t-test -
CAUDATE	correl - t-test -	correl - t-test -	correl - t-test -	correl - t-test abnormal Sway > normal Sway, p = 0.0904 abnormal Sway > controls, p = 0.0732
ETC	correl normal VMP to EOG, p = 0.0042** t-test -	correl - t-test -	correl abnormal VMP to VMP, p = 0.0181* abnormal VMP to EOG, p = 0.0589 t-test abnormal VMP > controls, p = 0.0877	correl - t-test abnormal Sway > controls, p = 0.0487*
HIPPOCAMPUS	correl - t-test abnormal VMP < controls, p = 0.0605 normal VMP < controls, p = 0.0161*	correl normal Sway to Sway, p = 0.0762 abnormal Sway to EOG, p = 0.0102* t-test abnormal Sway < controls, p = 0.0071** normal Sway < controls, p = 0.0427*	correl - t-test normal VMP > controls, p = 0.0457*	correl - t-test normal Sway > controls, p = 0.0957
INSULA	correl - t-test normal VMP < controls, p = 0.084	correl abnormal Sway to EOG, p = 0.06 t-test abnormal Sway < controls, p = 0.0834	correl abnormal VMP to VMP, p = 0.0668 normal VMP to Sway, p = 0.0431* abnormal VMP to EOG, p = 0.0714 t-test -	correl - t-test abnormal Sway > controls, p = 0.0952

Table. 16. Summary for ROI voxelwise analysis – FA and MD (1/2).

AMYGDALA

Even if the AMYGDALA is involved in the vestibular pathways, one of its main functions is linked to emotional processing as part of the limbic system. This way, a possible impairment of the AMYGDALA is suggested to lead to stress or depressive disorders after TBI (Han et al., 2015), (McCorkle et al., 2021), which in turn might affect spatial and postural performance.

Based on the mean value analysis, the AMYGDALA showed its potential to be a sensitive brain structure to vestibular-driven spatial impairment by showing a main effect of sub-group for FA. Further, for voxelwise analysis, there was a significant difference in FA values with *patients FA < controls FA*. In addition, AMYGDALA confirmed its ability to distinguish between abnormally performing VMP patients and controls, with *abnormal VMP patients FA < controls FA*.

Mean and radial diffusivity managed to show only a *tendency* in an important for my study correlation of “abnormal VMP patients to VMP”, thus implying that the AMYGDALA could be implicated as a possibly important region for the interaction of the vestibular and spatial pathways.

The AMYGDALA’s link to vestibular Sway was also present with the ability to distinguish between abnormal Sway patients and controls and also to establish the crucial correlation between “*abnormal Sway patients to VMP*” (for FA only).

HIPPOCAMPUS

The HIPPOCAMPUS is often damaged after TBI (Tomaiuolo et al., 2004). Memory impairment is yet another consequence of the traumatic brain event, and hippocampal atrophy, present in around 84% of the cases (Kotapka et al., 1992), has been linked to it (Bigler et al., 1996). One aspect that needs further

attention and is strongly HIPPOCAMPUS dependent is spatial navigation which may relate to difficulties orientating, learning new routes or recognising known ones (Skelton et al., 2005). In addition, the HIPPOCAMPUS has shown its strong link to the vestibular signal and its central processing (Smith, 1997), (Stackman et al., 2002), (Previc et al., 2014), (Aitken et al., 2018).

The mean value analysis in my study showed a significant main effect for the “*patient-control*” division for FA, which was confirmed by the voxelwise investigation (patients FA < controls FA).

Voxelwise investigation for the VMP division showed a significant difference between “normal VMP patients ~ controls” for FA, MD, AD and RD. This indicated that the hippocampal damage might have been of a non-vestibular spatial aetiology. Importantly, this is not the first case when the structure-function relationship was suggested to require more time after TBI to become significant. Bigler et al. suggested that the hippocampal atrophy established statistically notable correlations with memory and visuospatial skills only after day 90 post-injury (Bigler et al., 1996).

Interestingly, voxelwise investigation for Sway division indicated significant differences for both “abnormal/normal Sway patients ~ control” comparisons for FA, AD and RD, which, similarly to VMP division, suggested that the difference might be only partially vestibular-related. Thus, no “central vestibular processing – hippocampal damage” link was established in this cohort of acute TBI patients.

Brain region with Vestibular Input	FA (VMP division)	FA (Sway division)	MD (VMP division)	MD (Sway division)
THALAMUS (left)	correl abnormal VMP to VMP, $p = 0.0891$ t-test abnormal VMP < controls, $p = 0.0894$ normal VMP < controls, $p = 0.0027^{**}$	correl - t-test abnormal Sway < controls, $p = 0.015^{*}$ normal Sway < controls, $p = 0.0608$	correl normal VMP to Sway, $p = 0.0472^{*}$ t-test abnormal VMP > controls, $p = 0.0702$ normal VMP > controls, $p = 0.0187^{*}$	correl - t-test abnormal Sway > normal Sway, $p = 0.0215^{*}$ abnormal Sway > controls, $p = 0.0028^{**}$
OP2	correl abnormal VMP to VMP, $p = 0.0244^{*}$ normal VMP to Sway, $p = 0.074$ t-test -	correl normal Sway to VMP, $p = 0.0893$ t-test -	correl normal VMP to Sway, $p = 0.0068^{**}$ t-test -	correl abnormal Sway to Sway, $p = 0.0499^{*}$ t-test abnormal Sway > normal Sway, $p = 0.0313^{*}$ abnormal Sway > controls, $p = 0.0242^{*}$
PUTAMEN	correl abnormal VMP to VMP, $p = 0.0521$ t-test abnormal VMP < controls, $p = 0.0816$ normal VMP < controls, $p = 0.0913$	correl abnormal Sway to VMP, $p = 0.0605$ abnormal Sway to EOG, $p = 0.051$ t-test abnormal Sway < controls, $p = 0.0815$	correl abnormal VMP to VMP, $p = 0.0702$ normal VMP to Sway, $p = 0.0281^{*}$ abnormal VMP to EOG, $p = 0.0697$ t-test -	correl - t-test -
THALAMUS (right)	correl abnormal VMP to VMP, $p = 0.0404^{*}$ abnormal VMP to Sway, $p = 0.0973$ t-test normal VMP < controls, $p = 0.0021^{**}$	correl - t-test abnormal Sway < normal Sway, $p = 0.0095^{**}$ abnormal Sway < controls, $p = 0.0015^{**}$ normal Sway < controls, $p = 0.0546$	correl abnormal VMP to VMP, $p = 0.029^{*}$ t-test abnormal VMP > controls, $p = 0.0368^{*}$ normal VMP > controls, $p = 0.0005^{***}$	correl - t-test abnormal Sway > controls, $p = 0.0005^{***}$ normal Sway > controls, $p = 0.0205^{*}$
TPJ (ant)	correl - t-test normal VMP < controls, $p = 0.0594$	correl - t-test abnormal Sway < controls, $p = 0.0781$	correl abnormal VMP to VMP, $p = 0.0927$ normal VMP to Sway, $p = 0.0452^{*}$ abnormal VMP to EOG, $p = 0.0777$ t-test abnormal VMP > controls, $p = 0.1$	correl - t-test -
TPJ (post)	correl abnormal VMP to VMP, $p = 0.0545$ normal VMP to Sway, $p = 0.0198^{*}$ t-test abnormal VMP < normal VMP, $p = 0.0753$ abnormal VMP < controls, $p = 0.05^{*}$	correl normal Sway to Sway, $p = 0.006^{**}$ abnormal Sway to EOG, $p = 0.0714$ t-test abnormal Sway < normal Sway, $p = 0.0051^{**}$ abnormal Sway < controls, $p = 0.0054^{**}$	correl normal VMP to Sway, $p = 0.0143^{*}$ abnormal VMP to EOG, $p = 0.0755$ t-test abnormal VMP > controls, $p = 0.0406^{*}$	correl normal Sway to Sway, $p = 0.0058^{**}$ t-test abnormal Sway > normal Sway, $p = 0.0547$ abnormal Sway > controls, $p = 0.0178^{*}$

Table. 16. Summary for ROI voxelwise analysis – FA and MD (2/2).

CAUDATE

The CAUDATE and PUTAMEN are part of the nuclei comprising the dorsal striatum of the basal ganglia (Smith, 2018), which, among others, plays a crucial role in voluntary movements. As discussed in (Smith, 2018), galvanic vestibular stimulation (GVS) and cold caloric reflex (i.e. calorics) vestibular

stimulation managed to trigger an increase in the activity of both the CAUDATE and the PUTAMEN, thus implying a link between these basal ganglia nuclei and the vestibular system.

Interestingly, in earlier animal studies, the CAUDATE nucleus has been implicated with egocentric navigational skills because isolated impairment in the CAUDATE led to a selective decrease only for egocentric-based tasks (Potegal, 1972).

In my study, CAUDATE mean value analysis showed a main effect of VMP division only for AD. Similarly, voxelwise analysis achieved significant results also only for AD – “abnormal < controls” (VMP division) and “abnormal/normal < controls” (Sway division). Thus, no central vestibular processing link was able to be established.

PUTAMEN

In the previous paragraph regarding the CAUDATE, I also mentioned that PUTAMEN, as part of the basal ganglia, is involved in voluntary movements and shows a link to the vestibular system. In addition to the HIPPOCAMPUS, ETC and the THALAMUS, the basal ganglia is suggested to “subserve spatial cognition” (Padova et al., 2020).

Mean value TBSS analysis did not show any significant results for PUTAMEN. On the other side, for voxelwise analysis, I note only a close *tendency* towards significance for “***abnormally performing patients to VMP***” (FA, for VMP and Sway division), (MD, for VMP division), (RD, for VMP division). By showing such a consistent tendency towards significance for these highly vestibular-based correlations, the PUTAMEN drew additional attention as a possible candidate for a region crucial for vestibular-based central processing during acute TBI.

Lastly, I note a single statistically notable result for RD - “***abnormal Sway patients > controls***”.

ETC

Located in the medial temporal lobe, the entorhinal cortex (ETC) not only processes vestibular information (A. Jacob et al., 2020) but plays a central role in memory, spatial navigation, path integration (more precisely, the medial ETC (McNaughton et al., 2006), (P. Jacob et al., 2014)) and the perception of time, i.e. temporal memory in the scale of seconds and even minutes (more precisely the lateral ETC (Montchal et al., 2019)). Interestingly, “damage to the ETC is common in patients who experience TBI, stroke and Alzheimer's disease”(Davis et al., 2001), which might consequently lead to difficulties in spatial learning.

Still, the mean value TBSS analysis did not show any significant results for ETC, irrespective of the division method. Conversely, voxelwise DTI analysis for ETC achieved an important result by its significant correlations for “***abnormal VMP patients to VMP***” for MD, AD and RD. In addition, while “***abnormally performing patients > controls***” was close to significance for (MD, VMP division) and

(RD, VMP and Sway division), it was statistically significant for (MD, Sway division). Still, because of the significant correlation it achieved (i.e. “*abnormal VMP patients to VMP*”), the ETC seemed to be more of a VMP rather than a Sway region, even if vestibular Sway is also represented.

Brain region with Vestibular Input	AD (VMP division)	AD (Sway division)	RD (VMP division)	RD (Sway division)
AMYGDALA	correl normal VMP to VMP, $p = 0.0883$ normal VMP to Sway, $p = 0.0142^*$ t-test -	correl - t-test abnormal Sway < controls, $p = 0.0645$	correl abnormal VMP to VMP, $p = 0.0896$ t-test -	correl - t-test -
CAUDATE	correl normal VMP to Sway, $p = 0.0888$ t-test abnormal VMP < normal VMP, $p = 0.075$ abnormal VMP < controls, $p = 0.0056^{**}$ normal VMP < controls, $p = 0.0542$	correl - t-test abnormal Sway < controls, $p = 0.0201^*$ normal Sway < controls, $p = 0.0484^*$	correl - t-test -	correl - t-test abnormal Sway > normal Sway, $p = 0.0981$ abnormal Sway > controls, $p = 0.0835$
ETC	correl abnormal VMP to VMP, $p = 0.0382^*$ abnormal VMP to EOG, $p = 0.0382^*$ t-test -	correl - t-test -	correl abnormal VMP to VMP, $p = 0.0226^*$ normal VMP to EOG, $p = 0.0539$ t-test abnormal VMP > controls, $p = 0.0768$	correl - t-test abnormal Sway > controls, $p = 0.0721$
HIPPOCAMPUS	correl normal VMP to VMP, $p = 0.0496^*$ t-test abnormal VMP < controls, $p = 0.0047^{**}$ normal VMP < controls, $p = 0.014^*$	correl - t-test abnormal Sway < controls, $p = 0.0067^{**}$ normal Sway < controls, $p = 0.0391^*$	correl - t-test normal VMP > controls, $p = 0.0051^{**}$	correl normal Sway to Sway, $p = 0.0722$ t-test abnormal Sway > controls, $p = 0.0056^{**}$ normal Sway > controls, $p = 0.0487^*$
INSULA	correl normal VMP to VMP, $p = 0.078$ t-test -	correl - t-test -	correl abnormal VMP to VMP, $p = 0.0794$ normal VMP to Sway, $p = 0.0655$ t-test normal VMP > controls, $p = 0.0844$	correl - t-test abnormal Sway > controls, $p = 0.0612$

Table. 17. Summary for ROI voxelwise analysis – AD and RD (1/2).

INSULA

As part of the putative vestibular cortex, the INSULA plays a crucial role in the processing of central vestibular signals. While the anterior INSULA might be more, but not exclusively, involved in emotions and emotional awareness as part of the limbic system, the posterior INSULAR cortex suggests being more implicated in proprioception and balance (Gu et al., 2013). Close to the posterior insula (Kahane et al., 2003), (Frank & Greenlee, 2018) and “extending into the posterior parts of the insular lobe” (Eickhoff et al., 2006) is the region of the putative parieto-insular vestibular cortex PIVC. The latter is located in the posterior parietal operculum area OP2 (Eickhoff et al., 2006) and is distinct from the visual-vestibular parieto-insular cortex (PIC) located in the retroinsular cortex (Frank & Greenlee, 2018)

Research suggests an altered functional connectivity of the INSULA with the frontal and midline structures can lead to cognitive self-appraisal mismatch for patients after concussion (Churchill et al., 2021).

For this spatial and postural study under vestibular guidance, I note that the TBSS mean value analysis did not show any main effect of group, both between patient/control division and when divided as per VMP/Sway performance criteria. Surprisingly, also voxelwise analysis confirmed the lack of statistical significance among groups. Still, even if “*abnormal VMP patients to VMP*” achieved only a tendency towards significance for MD and RD, it was a close to significance result, implying the possible link between INSULA and vestibular spatial processing.

OP2

Anatomical segmentation of the cerebral cortex indicated that the human PIVC is located in the OP2 area of the posterior parietal operculum (Kahane et al., 2003), (Eickhoff et al., 2006), (Frank & Greenlee, 2018) implying the crucial role this region plays in central vestibular processing.

In this study, mean value analysis showed a significant main effect of vestibular Sway sub-group only for mean diffusivity (MD) and a tendency for axial diffusivity (AD), also confirmed by voxelwise analysis.

However, voxelwise analysis showed two principal correlations for patients, i.e. patients FA to VMP and patients FA to vestibular Sway were statistically notable, implying the strong link between patients' damage in the OP2 and central vestibular processing. Further, the OP2 achieved important significant discrimination between patients themselves, "*abnormal Sway MD > normal Sway MD*", followed by a borderline meaningful correlation between "*abnormal Sway patients MD to Sway*".

However, most notably in this OP2 analysis was the notable correlation "*abnormal VMP patients to VMP*", which was present for FA and also for RD. This correlation made it the second region (with ETC being the first) to stress the link between damage in the OP2 and vestibular-guided spatial impairment.

THALAMUS (Left + Right)

The brain relay station, the THALAMUS, is penetrated by a path through which the central vestibular signal reaches conscious awareness by entering the cerebral cortex. Being not only vestibular- involved but also crucial for navigation and postural control (Taube, 2007), (Hitier et al., 2014), (Cullen, 2019), the THALAMUS presents a central structure to investigate in this acute TBI study. Here, I divided the THALAMUS into two parts – Left and Right and discussed them separately.

The mean value analysis for THALAMUS (Left) showed a significant difference for the patient/control division and the Sway-based division for MD and RD. On the other side, the same analysis for THALAMUS (Right) displayed a significant main effect for MD, AD and RD for patient/control and Sway divisions.

Further, voxelwise DTI analysis for THALAMUS (Left) showed a notable comparison for patients FA < controls FA and confirmed that abnormal Sway patients differed from controls for FA, MD, AD and RD. Even more interesting was that "*abnormal Sway > normal Sway*" for MD, AD and RD. With respect to VMP division, "*normal VMP patients ~ controls*" comparisons were significantly different for all four DTI parameters, i.e. FA, MD, AD and RD, indicating that the damage in the Left THALAMUS was not of a vestibular-spatial aetiology. In summary, the bi-hemispheric spread of the vestibular Sway coincided with the role that the damage to the THALAMUS Left might have played in acute TBI patients with vestibular imbalance.

Voxelwise analysis for THALAMUS (Right) showed that *patients FA < controls FA* and *patients FA to Sway* were statistically significant. Concerning the VMP division, I note that “*abnormal VMP patients > controls*” (for MD, AD and RD), in addition to being strongly supported by an important and a significant result for “*abnormal VMP patients to VMP*” for FA, MD and RD. Still, even if these results might have suggested some critical role for THALAMUS (right) in vestibular-guided spatial orientation, caution must be taken as this voxelwise analysis pointed also to a non-vestibular, but significant discrimination for “normal VMP patients ~ controls” (FA, MD, AD and RD). Therefore, this result renders further investigation from a vestibular system point of view as to establish the involvement of the Right THALAMUS in the vestibular self-motion perception.

Lastly, I looked at the Sway-based division for Right THALAMUS and note that correlation-wise, there was nothing to report. However, for the comparison between subgroups, there were three comparisons of note – (1) “*abnormal ~ controls*” was significantly different for all four parameters – FA, MD, AD and RD, (2) “*abnormal < normal*” for FA, which was important discrimination achieved within the patients’ group. Lastly, similar to the VMP division, there was this non-vestibular significance present, i.e. “normal > controls” for MD, AD and RD, but importantly these correlations were less robust and did not include the FA analysis.

Brain region with Vestibular Input	AD (VMP division)	AD (Sway division)	RD (VMP division)	RD (Sway division)
THALAMUS (left)	correl normal VMP to Sway, $p = 0.0391^*$ t-test abnormal VMP > controls, $p = 0.0491^*$ normal VMP > controls, $p = 0.0335^*$	correl - t-test abnormal Sway > normal Sway, $p = 0.0325^*$ abnormal Sway > controls, $p = 0.0016^{**}$	correl normal VMP to Sway, $p = 0.0562^*$ t-test abnormal VMP > controls, $p = 0.0799$ normal VMP > controls, $p = 0.0105^*$	correl - t-test abnormal Sway > normal Sway, $p = 0.0262^*$ abnormal Sway > controls, $p = 0.0023^{**}$
OP2	correl abnormal VMP to EOG, $p = 0.0878$ t-test normal VMP > controls, $p = 0.0019^{**}$	correl - t-test abnormal Sway > normal Sway, $p = 0.0623$ abnormal Sway > controls, $p = 0.0011^{**}$ normal Sway > controls, $p = 0.0777$	correl abnormal VMP to VMP, $p = 0.0424^*$ normal VMP to Sway, $p = 0.0134^*$ t-test -	correl abnormal Sway to Sway, $p = 0.0745$ t-test abnormal Sway > normal Sway, $p = 0.0515$ abnormal Sway > controls, $p = 0.086$
PUTAMEN	correl normal VMP to EOG, $p = 0.0712$ t-test abnormal VMP < controls, $p = 0.0593$	correl - t-test -	correl abnormal VMP to VMP, $p = 0.0583$ normal VMP to Sway, $p = 0.0646$ t-test normal VMP > controls, $p = 0.0724$	correl abnormal Sway to Sway, $p = 0.1$ t-test abnormal Sway > controls, $p = 0.0489^*$
THALAMUS (right)	correl abnormal VMP to VMP, $p = 0.0846$ t-test abnormal VMP > controls, $p = 0.0262^*$ normal VMP > controls, $p = 0.0004^{***}$	correl - t-test abnormal Sway > normal Sway, $p = 0.0914$ abnormal Sway > controls, $p = 0.0002^{***}$ normal Sway > controls, $p = 0.0225^*$	correl abnormal VMP to VMP, $p = 0.0254^*$ t-test abnormal VMP > controls, $p = 0.0472^*$ normal VMP > controls, $p = 0.0008^{***}$	correl - t-test abnormal Sway > normal Sway, $p = 0.0596$ abnormal Sway > controls, $p = 0.0003^{***}$ normal Sway > controls, $p = 0.0211^*$
TPJ (ant)	correl - t-test normal VMP < controls, $p = 0.0809$	correl - t-test -	correl normal VMP to Sway, $p = 0.0568$ t-test normal VMP > controls, $p = 0.0679$	correl - t-test -
TPJ (post)	correl - t-test abnormal VMP > normal VMP, $p = 0.027^*$ abnormal VMP > controls, $p = 0.0111^*$	correl - t-test -	correl normal VMP to Sway, $p = 0.0044^{**}$ t-test abnormal VMP > normal VMP, $p = 0.0886$ abnormal VMP > controls, $p = 0.0399^*$	correl normal Sway to Sway, $p = 0.0026^{**}$ t-test abnormal Sway > normal Sway, $p = 0.002^{**}$ abnormal Sway > controls, $p = 0.0012^{**}$

Table. 17. Summary for ROI voxelwise analysis – AD and RD (2/2).

TPJ (ant + post)

Research suggests that the TPJ might be a brain region responsible for the encoding of motion duration and travelled distance (Kaski et al., 2016) during angular movements in the dark. Another possibility is that the TPJ plays the role of a velocity integrator over time to derive position, thus implicating the abnormal timing perception as a potential reason for spatial disorientation (Kaski et al., 2016). This

suggests the TPJ is a crucial region for vestibular-guided spatial orientation. Here, I divided the TPJ into two parts – anterior and posterior and discussed them separately.

The mean value analysis for TPJ (ant) showed a main effect of the patient/control group for FA and RD, in addition to the Sway-based division for FA. On the other hand, TPJ (post) showed a statistically meaningful difference between patients/controls for MD only but more notable results for Sway division (FA, MD and RD). Still, neither of the TPJ regions achieved a significant effect of group for VMP division, possibly because of the predominantly more “moderate” cases from this “moderate-severe” patient cohort and the already subtle vestibular spatial signal in this acute TBI cohort.

Voxelwise DTI analysis for TPJ (ant) showed no statistically important results. On the other side, the TPJ (post) showed a statistically notable correlation for “patients FA to Sway”, followed by a “normal to Sway” correlation for both VMP and Sway divisions (FA, MD and RD). These non-vestibular-based correlations might have underestimated the role of TPJ (post) in central vestibular processing. Importantly, however, this analysis gave a reason for further investigation by showing (1) a statistical difference between “*abnormally performing patients ~ controls*” for FA, MD and RD for both VMP and Sway divisions and (2) a critical discrimination within patients for vestibular Sway - “*abnormal Sway patients ~ normal Sway patients*” (for FA and RD).

C. DTI ROI voxelwise analysis – vestibular spatial and postural processing - Summary

In this DTI ROI voxelwise analysis, I looked at how the brain mechanism of vestibular spatial dysfunction or vestibular imbalance were affected during acute TBI in a selected group of eleven vestibular regions. In addition, I investigated if these results could point to the suggested link between spatial and postural processing via the central vestibular system. My main findings are that (1) vestibular spatial and vestibular postural processing showed decreased performance in some of the selected vestibular regions but not in all, (2) rarely could a vestibular region be attributed as “more VMP” or “more vestibular Sway”. More often, it was both modalities that showed an effect in a specific vestibular region, thus supporting the suggested link between them. Lastly, (3) in comparison to DTI whole-brain analysis, for this ROI analysis Vestibular Sway/VMP were able to establish multiple individual links to WM structure abnormalities during acute TBI, alongside multiple mutual links such as the “abnormal VMP to Sway” or “abnormal Sway to VMP”.

DTI Vestibular spatial processing

Figure 90. presents my idea of a summary of the findings of this vestibular-guided spatial study and other vestibular studies that were able to suggest important brain regions implicated by vestibular-driven spatial processing. The three-step vestibular-guided spatial model presented my *II hypothesis*

that discusses the idea of the vestibular-guided spatial orientation comprising *VMP*, *egocentric* and *allocentric* (egocentric+) navigation. This idea, I discussed in great detail in Chapter V.

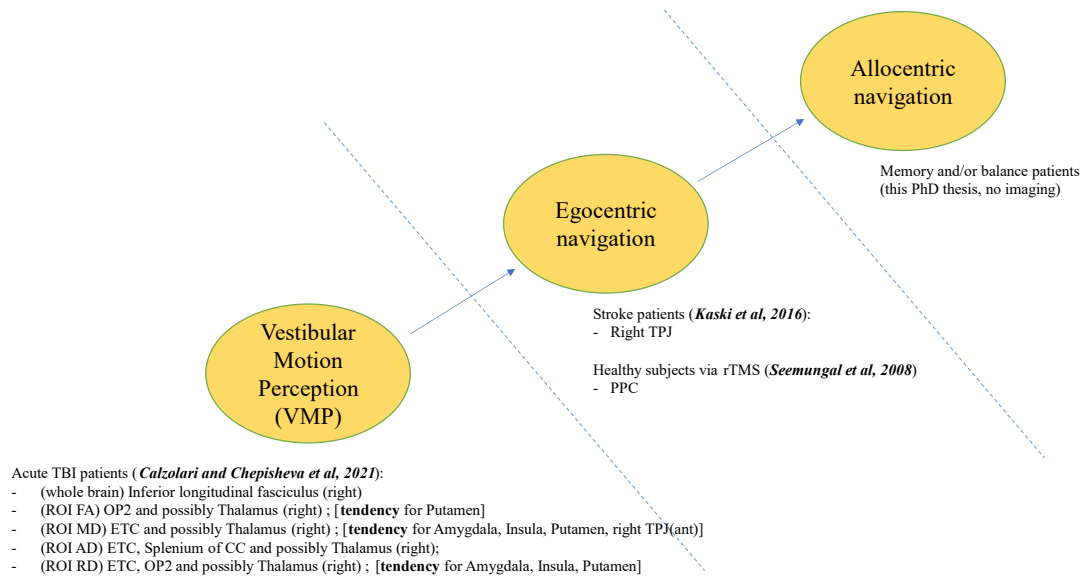


Figure. 90. Overview of vestibular-guided spatial orientation for a suggested three-step model that I discuss in Chapter VIII with the help of a small cohort of memory and/or balance patients.

The first level of the diagram displays the achieved findings of this TBI study (Chapters VI and VII), stressing the importance of the Right Inferior longitudinal fasciculus (as evidenced by the DTI whole-brain voxelwise analysis). The ROI investigation of white matter atrophy in a selection of highly grey matter structures in this Chapter was no easy task, even if DTI analysis of these structures is common in the literature. Still, the results about the link between the subtle vestibular signal and these vestibular implicated regions during the acute state of TBI proved this initiative worth it.

My analysis suggested that the **OP2**, the **ETC** and possibly **THALAMUS (Right)** and **TPJ (post)** might be regions more tightly connected with vestibular-driven spatial perception in contrast to the other vestibular areas selected for this ROI analysis. In addition, I also observed a tendency towards significance in the **AMYGDALA**, **INSULA** and **PUTAMEN**, all of which deserve more detailed attention in a future bigger cohort of patients/longitudinal design study or a study group that based on Mayo criteria (Malec et al., 2007) qualifies the patients as more “severe” TBI within the “moderate-severe” classification.

Importantly, as compared to the whole-brain analysis whose main finding about the rILF pointed to the right hemisphere, the ROI analysis gave additional information about the brain networks involved in vestibular self-motion perception. It suggested that this brain network is bi-hemispheric comprising regions located also in the left hemisphere. Indeed, based on my analysis, the maximum intensity voxels of the statistically significant and highly important correlation “abnormal VMP to VMP” in the ETC and OP2 pointed to the left ETC and left OP2, respectively. In addition, there was some left-sided significance also in the PUTAMEN and INSULA.

The second level of the diagram presents findings from other studies, where authors were able to contribute towards the literature discussing vestibular egocentric navigation and distinguish the TPJ and PPC as crucial areas. The last level, I have populated with the ‘memory and/or balance patients’ cohort from Chapter V. Even if this cohort of patients presented interesting scientific findings, I did not have data about imaging and thus left this section empty. Still, based on my results from Chapter V, I believe that these patients could have shed light on the allocentric level of the three-step spatial model.

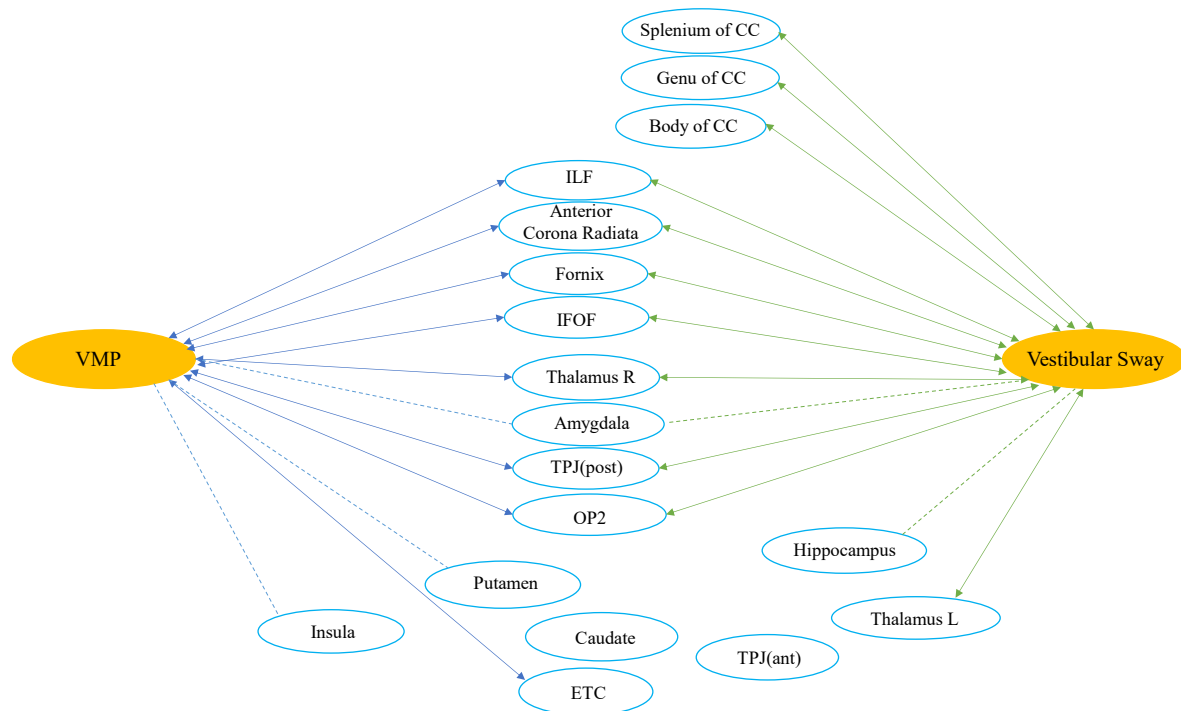


Figure. 91. DTI voxelwise analysis results – summary of brain regions and their links to VMP and vestibular Sway based on whole brain and ROI DTI analyses.

DTI Vestibular postural processing

Vestibular-driven posturography has shown a wider bi-hemispheric spread of areas implicated with vestibular postural processing after acute TBI via a much greater number of statistically significant results than vestibular-guided spatial processing. Voxelwise DTI ROI analysis pointed to an even more widespread effect of the vestibular-guided postural control (in comparison to mean value analysis), which considering the already seen widespread of the whole-brain DTI analysis for vestibular Sway was not unexpected. In fact, ROI analysis provided some detailed information about this previously observed spread across the brain, managing to point to several specific brain areas, which made the interpretation of the results less ambiguous. Some vestibular regions more tightly linked to vestibular Sway damage were **both THALAMI (Right and Left), the TPJ (post) and OP2** and possibly also AMYGDALA and HIPPOCAMPUS.

Still, as discussed throughout the analysis, for both the VMP and vestibular Sway divisions, statistically notable results with non-vestibular aetiology were also present in some of the selected regions. Thus, addition research is needed to establish the role of the suggested brain areas for VMP and vestibular Sway-based processing (Fig.91).

E. EOG – Vestibular Ocular reflex (VOR) (Please check Appendix)

6. Conclusions – TBI study

Vestibular dysfunction after TBI plays a detrimental role in the normal spatial orientation and postural control of patients, sometimes long after the acute phase of their TBI insult. However, the vestibular system makes multiple connections throughout the brain, as witnessed by the variety of crucial structures investigated in this Chapter VII, including also limbic structures. It follows that a vestibular loss is expected to be implicated not only in functional and cognitive but also in emotional disorders (Smith & Darlington, 2013). In addition, as discussed in (Hummel et al., 2014), vestibular dysfunction has been linked to the decrease in glucocorticoids, whose reduction was shown to affect the hippocampal volume in some neuropsychiatric diseases, among which posttraumatic stress disorder (Sapolsky, 2000). Consequently, patients enter an ‘environment’ that is difficult for them not only from a physical (e.g. pain, falls, disorientation) but also from a psychological point of view (e.g. loss of independence, depression because of the inability to orientate or maintain balance). This makes the lack of information about how exactly traumatic brain injury affects the vestibular-guided spatial and postural functions even more pressing, as these two ecological modalities constitute an important part of our independence and ability to function as self-supporting individuals.

Chapter VIII

Summary of Findings and Future Work

While extensive research has been advancing our understanding about the spatial and postural decline in patients with central nervous system dysfunction, much less is known about how the vestibular system contributes to the spatial and postural processing in these patients. So, even if the vestibular system takes part in a complex network of connections throughout the brain, scientific evidence about the neural mechanisms of these crucial ecological processes under vestibular guidance is sparse.

The vestibular signal is especially relevant during turning movements in the dark such as while walking in our garden or at home at night, where the vestibular signal becomes central. As the prevention of falls and disorientation are of serious concern for the medical service, more vestibular-driven knowledge is necessary, as to decrease the burden for patients with vestibular disabilities. Two groups of neurological patients that are prominent with their spatial and postural dysfunction and where vestibular research is lacking are acute traumatic brain injury (TBI) patients and also patients with memory impairments, such as those with Alzheimer's disease (AD).

My aim for this thesis was to investigate the contribution of the vestibular signal in the spatial orientation and postural control of patients with acute traumatic brain injury or patients with memory and (balance) impairment. Consequently, I hoped to improve our understanding about how the vestibular-guided mechanisms of spatial navigation and postural control were affected in these two patient groups and increase awareness about the importance of the vestibular-based diagnosis that could lead to the improvement of the subsequent prognostication and outcome for the patients. Clinical and non-clinical research-based behavioural testing was the basis of my research, along with brain imaging analysis (DTI and VBM) for the acute TBI cohort.

In this study my hypotheses and objectives were:

HYPOTHESIS I - Central nervous system dysfunction due to TBI or memory impairment affecting the processing of vestibular signals will manifest with spatial disorientation and postural imbalance.

- To investigate how the brain mechanisms of vestibular spatial orientation or vestibular balance are affected during acute TBI and what WM/GM regions are implicated based on DTI and VBM analyses? Alternatively, how such mechanisms are affected in patients with acute TBI or patients with memory and (balance) complaints based on behavioural testing alone?
- To investigate if vestibular-guided spatial and postural modalities share a common neuronal network and where these network regions are located?
- To investigate whether the cortical/subcortical morphology (i.e. volume, thickness, local gyrification index) links to vestibular spatial and vestibular postural impairment in acute TBI using VBM analysis?
- To investigate if the integrity of the Corpus Callosum is linked to loss of vestibular motion perception or vestibular imbalance during acute TBI using DTI and VBM analyses?

- To investigate if the integrity of cortical and subcortical regions known to receive vestibular input, is linked to loss of vestibular motion perception/vestibular imbalance during acute TBI using DTI and VBM analyses?

HYPOTHESIS II - Vestibular-guided spatial orientation can be viewed as a continuous and hierarchically organised three-step process (vestibular self-motion, egocentric and allocentric level), where each step is incorporated in the subsequent one.

- To investigate if it is feasible to look at the vestibular-guided spatial navigation as a three-step process testing healthy controls from three age groups?
- To investigate how vestibular spatial navigation (i.e. the three-step model) is affected during passive navigation in patients with memory impairment?

HYPOTHESIS III - Patients experiencing greater cognitive load will not find the information from the vestibular cues helpful but rather burdensome during spatial navigation or balance.

- To investigate how the computational burden in the brain of acute TBI patients or patients with memory and (balance) impairment links to/affects their spatial orientation and postural control under vestibular guidance while using a set of cognitive tests that patients performed?
- To investigate the link between cognitive dysfunction (using the MMSE/ACE III-R tests) and vestibular-mediated spatial navigation via the three-step spatial model in patients with memory impairment?

Based on these hypotheses and their objectives, my main findings were:

I. Acute TBI study

In this study, I investigated (1) how vestibular spatial orientation and vestibular postural control changed during the acute state of TBI (i.e. HYPOTHESIS I). In addition, I looked at (2) the effect of cognitive load on vestibular spatial/postural modalities during acute TBI (i.e. HYPOTHESIS III). Importantly, this was the first study that attempted to link vestibular-driven spatial and postural central processing with acute WM/GM damage due to TBI.

I found that acute TBI patients showed a decreased perception of vestibular self-motion (VMP). Indeed, 15 out of 37 acute TBI patients had an abnormal VMP threshold, i.e. this condition was not rare among acute TBI. In addition, VMP threshold in TBI patients was significantly higher as compared to their EOG thresholds (i.e. VOR). Irrespective of whether TBI patients' VMP was decreased or not, they presented with a preserved vestibular-ocular reflex (VOR), thus suggesting uncoupling between VMP/VOR (perception/reflex) for those with abnormal VMP.

In addition, postural impairment in acute TBI was mainly and most significantly of a vestibular nature, although it was present *by observation* in all four posturography conditions (i.e. HO, HC, SO and SC). There are 14 out of 37 acute TBI patients presenting with impaired vestibular-driven Sway performance. There was a link between VMP and vestibular Sway in these patients confirmed via a significant positive correlation between them. Interestingly, compared to patients without attenuated VMP, those TBI patients with the condition were more unbalanced. This coincides with previous research stressing the crucial role that vestibular loss takes during acute TBI. Indeed, whereas 75% of mild TBI survivors without any vestibular features (e.g. dizziness) were likely to return to work after six months post-injury, only 33% of those with accompanying vestibular dysfunction were able to do so (Chamelian & Feinstein, 2004), (Calzolari and Chepishcheva et al., 2021). What is more, vestibular dysfunction seems to be highly present in TBI patients irrespective of the type of trauma, i.e. blunt (59%), blast (47%) or combined between blunt and blast (83%) injury (Denby et al., 2020).

With respect to the “vestibular system – cognition” relationship, in my study, TBI patients with abnormal VMP performance showed decreased ACE memory, ACE fluency and ACE attention scores, Trail making A and B tests scores, along with a decreased self-reported balance confidence via the ABC balance test. In addition, the mean VMP threshold of TBI patients correlated significantly with the ACE total score (and almost all of its sub-components) and Trail making test A and B. On the other hand, there was no correlation for TBI patients between any of the vestibular Sway measures investigated in this study (i.e. the 95% confidence ellipse SC, RMS SC or GAIN SC/SO) and their cognitive tests’ performance– ACE total and its sub-components or the Trail making A and B tests. Thus, my analysis suggested that vestibular input during acute TBI might be reduced and thus might play a minimal role, i.e. as a shield mechanism of the brain against overload.

Importantly, posttraumatic stress disorder, anxiety, depression (Fife & Kalra, 2015), (L. Smith et al., 2019) depersonalization or derealization (Kolev et al., 2014) may often accompany vestibular dysfunction. In addition, vestibular dysfunction has been associated with changes in mood, fatigue and sleep hygiene (L. Smith et al., 2019). Thus, these patients are not only in physical danger of losing their balance and getting lost, but also in danger on a psychological level that may have unknown deteriorative effects on their psyche as well as on their wellbeing and desire to recover. In my study, I measured the DHI, PHQ-9 and GAD-7 and found that patients showed significant decrease in all their measures (self-perceived dizziness, depression and anxiety, respectively) compared to the baseline. However, no difference between abnormal VMP/normal VMP or abnormal Sway/normal Sway was achieved for any of the three tests.

DTI whole-brain voxelwise analysis showed that TBI patients exhibiting abnormal vestibular postural performance showed a correlation between their DTI-derived parameters (MD and RD) in the Right Inferior longitudinal fasciculus and the degree to which their vestibular self-motion perception was impaired as a result of TBI. Importantly, this significant correlation between vestibular-based postural

stability and VMP performance was driven by patients with abnormal vestibular Sway balance (i.e. on a soft surface, eyes-closed condition), but no such correlation was present for normally performing vestibular Sway patients or controls. What was more, MD and RD analyses did not establish any statistically notable correlations between abnormally performing patients for the vestibular Sway task and vestibular motion perception in the Left Inferior longitudinal fasciculus. This important result contributed to the idea of the Right-hemispheric dominance for the vestibular system (Dieterich et al., 2003) as based on DTI whole-brain analysis.

Whole-brain DTI analysis showed the dynamic nature of WM changes during the acute state of TBI reflecting on the biology behind my findings. Importantly, FA, MD and RD were sensitive DTI parameters towards vestibular-driven spatial and postural deficits in this cohort of acute TBI patients thus suggesting that VMP and vestibular Sway were linked to WM atrophy in acute TBI. Many examples throughout the analysis were given. However, interestingly, VMP and/or vestibular Sway didn't manage to establish any significant correlations on their own, but it was rather the combination between them, i.e. "abnormal Sway to VMP" or "abnormal VMP to Sway" that showed results closer to significance or were indeed statistically meaningful with respect to WM abnormalities.

A further interesting finding was that vestibular-driven postural damage was spread widely across the white matter of both brain hemispheres (as per whole-brain DTI and VBM and ROI DTI and VBM analyses), whereas VMP deficits seemed to be more concentrated to the right of the brain based on whole-brain DTI analysis even if some left-sided regions were also present for axial diffusivity analysis. Importantly, the ROI VBM and DTI analyses suggested also the role of the left-hemispheric regions in the neural network of vestibular spatial processing by indicating some left-hemispheric significance for the regions of the CC (Chapter VI, section A) or some of the eleven vestibular regions (Chapter VI, section B).

The mean value WM tract analyses showed WM tracts that were mutual between VMP/vestibular Sway or specific for each of them. In particular, mutual tracts were (1) Forceps minor, (2) Inferior fronto-occipital fasciculus R, (3) Inferior longitudinal fasciculus R, (4) Fornix and (5) Anterior corona radiata R. Other WM tracts were only Sway-based specific (1) Anterior thalamic radiation L, (2) Inferior fronto-occipital fasciculus L, (3) Inferior longitudinal fasciculus L, (4) Anterior corona radiata L, (5) Stria terminalis R and (6) Forceps major or VMP specific - Posterior thalamic radiation R.

Still, this analysis also drew my attention to four WM tracts that were mutual for both types of vestibular processing and showed the most significant results. These four tracts were: (1) the Right Inferior longitudinal fasciculus (rILF), (2) the Right Inferior Fronto-occipital fasciculus (rIFOF), (3) the Anterior Corona Radiata R and (4) the Fornix. All these tracts have been previously implicated with TBI damage and all of them play a central role for the intercommunication in the brain. Importantly, however, was that Fornix showed statistically significant results with both VMP and Sway which were not entirely vestibular-based, as was the case with the other three tracts – the rILF, rIFOF and the Anterior Corona radiata R. One possible reason for this decreased sensitivity towards vestibular-based

processing in the Fornix, was its smaller size and the lack of more “severe” cases in this “moderate-severe” acuter TBI cohort (Malec et al., 2007).

Research highly supports the idea that multi-neuroimaging studies are capable of achieving better and more robust results as they promote a more holistic approach. Consequently, my study was also a multi-neuroimaging effort comprising VBM analysis alongside DTI analysis. Based on VBM whole-brain analysis (analysis in Appendix), when dividing the patients based on their VMP/Sway performance (as per whole-brain mean value analysis), there was a clear hierarchical trend for “controls GM volume > normal performance patients > abnormal performance patients” and also for CSF volume “controls CSF < normal performance patients CSF < abnormal performance patients CSF”.

Importantly, whole-brain voxelwise GM investigation showed practically no statistically notable results for any of the contrasts linked to vestibular spatial and vestibular postural processing in comparison to WM VBM analysis. However, these statistically meaningful results about WM VBM analysis, I interpreted with caution, as VBM WM analysis has shown to be inferior compared to DTI analysis (Whitwell, 2009).

Further, whole-brain VBM analysis showed that volumetric changes might be sensitive at detecting differences between TBI sub-groups but were less specific in their relationships with spatial orientation and postural control under vestibular guidance. What was more, Sway division showed a difference not only between the whole-brain WM volume of abnormally performing Sway patients and controls but also within patients themselves (i.e. abnormal/normal Sway), which was an important finding. In addition, patients with poor balance showed a notable link to vestibular Sway.

Further, mean thickness was lowest in patients with abnormal VMP/Sway, whereas ventricular volume (3rd, 4th and both lateral ventricles) was highest in patients with abnormal Sway. The volumetric investigation of my specific regions of interest, showed that GM volumetric analysis showed a more expressed preference of the Left Caudate (as part of the basal ganglia) for vestibular Sway, whereas the same analysis showed the preference of the Left Insula for the VMP division. Lastly, my acute TBI cohort showed a difference between groups' local gyrification index (LGI), which was, however, not statistical, irrespective of the division method.

Further, I concentrated on specific regions of interest via ROI DTI and VBM analyses by performing mean value and voxelwise analyses (ROI VBM analysis is available in Appendix).

First, I looked at the Corpus Callosum, as the biggest commissural WM tract in the brain, often reported to be damaged after TBI (Tomaiuolo et al., 2004), (Ham & Sharp, 2012), (Edlow et al., 2016). Sway-based FA and RD analyses for all three Corpus Callosum regions were consistently significant for the discrimination between “abnormal Sway patients and controls”. Further, for Vestibular Sway, but not for VMP, there was clear discrimination among patients' groups, with this suggestion being strongest for Splenium, followed by Body and Genu. For the latter two, there were some non-vestibular links that

might have interfered. Most importantly, significant correlations of non-vestibular nature were hardly registered for the Splenium analysis (both for DTI and not at all for VBM analyses), as the main callosal region implicated with the vestibular system (Kirsch et al., 2016).

Whereas the DTI ROI voxelwise analysis showed that WM integrity in abnormal VMP patients differed from controls, specifically via FA (Body and Genu), the association between callosal damage and vestibular imbalance was stronger. Thus, my Corpus Callosum analysis revealed a link between vestibular-guided Sway performance and DTI WM atrophy in all three callosal regions during the acute TBI.

The ROI DTI analysis of the eleven vestibular regions reflected the dynamic nature of WM changes during acute TBI by showing that based on axial diffusivity analysis some of the investigated vestibular regions were already undergoing reparation processes, while others showed no signs of a commenced remyelination/repair processes. When looking at the VMP/Sway division for these vestibular regions, my analysis suggested that some regions were more tightly implicated with the vestibular spatial and/or vestibular postural processing than others. In particular, for VMP division, I noted the OP2, the ETC and possibly the Thalamus (right) and TPJ (post) might have been brain areas more tightly connected with vestibular-driven spatial perception. A tendency towards significance was noted in the Amygdala, Insula and Putamen. On the other hand, some vestibular regions that were more tightly linked to vestibular Sway damage were both Thalami, the TPJ (post) and OP2. A tendency was seen in the Amygdala and the Hippocampus.

Interestingly, with respect to ROI analysis (including mean value WM ROI analysis and mean value and voxelwise analyses for CC and the eleven vestibular regions), the VMP and vestibular Sway managed to also establish individual notable correlation to WM abnormalities during acute TBI whereas this was not the case for whole-brain DTI analysis. In addition, the ‘abnormal Sway to VMP’ and ‘abnormal VMP to Sway’ correlations showing a tendency towards significance or statistical significance were also present, as in the whole brain DTI analysis, contributing to the idea of the suggested link between spatial and postural modalities via the central vestibular system.

Lastly, as previously indicated, ROI analysis pointed to both vestibular spatial and vestibular postural processing being bi-hemispheric modalities. Even if literature has greatly contributed to the idea of spatial and postural modalities being predominantly right-hemispheric, there are also data about the crucial role of left-hemispheric regions (Burgess et al., 2002), (Paillard & Noé, 2020). A review article about postural balance put this idea together discussing that based on previous research “cerebral hemisphere specialization should not be understood as an absolute dominance of the right over the left cerebral hemisphere for balance control, but as a functional superiority of the right hemisphere at processing functions relevant for balance control leading to its greater proportional influence on stabilization and recovery of upright balance” (Paillard & Noé, 2020). This statement can well apply to spatial orientation as well. Whereas the bi-hemispheric spread of the vestibular-Sway was confirmed

by whole-brain and ROI analyses, for VMP – the bi-hemispheric idea was hinted during the whole-brain analysis and confirmed during the ROI analysis. In particular, left OP2 and left ETC were two regions more tightly implicated with VMP processing, alongside a suggestion for left-sided importance in the Putamen and Insula. Two recent studies confirmed the idea of the inclusion of the left OP2 as part of the putative human vestibular cortex – a compilation of brain atlases for vestibular functional MRI research (J. L. Smith et al., 2023) and an in-depth investigation of the role of the OP2 in the human vestibular cortex (Ibitoye et al., 2023).

II. Memory and (balance) patients – pilot study

In this study, I investigated (1) how vestibular spatial orientation and vestibular postural control changed in patients with memory and (balance) complaints (i.e. HYPOTHESIS I). Further, (2) I concentrated specifically on vestibular spatial navigation looking at a continuous three-step model comprising of three tasks and the performance of memory patients on these vestibular spatial tasks (i.e. HYPOTHESIS II). Lastly, (3) I explored how the computational burden affected patients' vestibular spatial and vestibular postural processing (i.e. HYPOTHESIS III).

This was the first study where a vestibular motion perception task was performed by patients with memory and (balance) impairment. Memory and (balance) patients showed elevated (i.e. worsened) VMP threshold. Notably, VMP thresholds and EOG thresholds were significantly different for memory and (balance) patients, with EOG being lower. EOG thresholds showed a capacity to remain preserved even when VMP thresholds were not intact in these memory and (balance) patients.

In addition, patients also displayed decreased vestibular Sway performance, but there was no correlation between vestibular spatial and vestibular postural control for these patients. Further, patients displayed more vestibular-mediated postural impairment than VMP impairment. What was more, their vestibular-driven imbalance (i.e. SC) was the most impaired posturography measure among the different sway conditions, even if *by observation* there was increased Sway for all posturography conditions (i.e. HO, HC, SO and SC). These findings contribute to our better understanding of vestibular-based imbalance in patients with memory impairment considering that people with AD have an increased risk of falls and are two to three times more likely to fall and get injured in comparison to healthy elderly (Cronin et al., 2017), (Agrawal et al., 2019), (Yesantharao et al., 2022). Still, their imbalance is a less recognised feature of early Alzheimer's disease (Cronin et al., 2017), possibly because falls often come before cognitive decline and thus may remain “unnoticed”. Lastly, as concurrent with previous research (Leandri et al., 2009), for the posturography test, my cohort of memory and (balance) patients showed a slightly increased vestibular Sway in the antero-posterior plane (RMS AP) as compared to lateral Sway (RMS L).

With respect to the “vestibular system – cognition” relationship, the vestibular motion perception was

able to correlate to MMSE but not to ACE (only Left-sided VMP threshold linked to ACE-attention). In addition, the results showed that patients with decreased cognitive skills displayed attenuation of their vestibular self-motion perception. These patients performed almost 6.4 times worse as compared to healthy elderly controls > 60yrs and almost 5 times worse when compared to patients with normal cognition.

On the other hand, no notable correlations were established between MMSE/ACE and the posturography components not only for vestibular Sway SC but for all four sway conditions for the three measures of interest (i.e. Area 95% confidence ellipse, RMS AP and RMS L). However, patients with decreased cognition showed impaired balance for all three posturography measures for the SC condition (i.e. 95% confidence ellipse, RMS AP and RMS L) and differed significantly from patients with preserved cognition and healthy elderly controls. What was more, two of the four patients with decreased cognitive skills “fell” during the vestibular Sway condition.

Further, I explored a three-step model comprising VMP, vestibular egocentric and vestibular allocentric tasks. The hypothesised continuous mechanism involves a smooth flow of acceleration and, consequently, velocity derived information from the peripheral vestibular system to the central vestibular system and the cerebral cortex, where the transition from “velocity to location” occurs. This mechanism suggests that the skills used in the first stage (i.e. vestibular self-motion perception) will further contribute to the second, i.e. egocentric level, and the egocentric skills in their turn will be used in the third level, i.e. the allocentric task (Fig.46). Thus, the continuous model assumes that any disability/damage in one of the steps will consequently impair or at least influence the tasks that follow, as complexity rises with every following task. For instance, this model expects that abnormality on the egocentric level will affect the allocentric level. Still, the continuous model allows for people to have abnormal vestibular motion perception and intact egocentric performance, as the anatomical correlates of vestibular self-motion and vestibular egocentric navigation are suggested to be distinct (Kaski et al., 2016).

Based on the testing of 60 healthy controls separated in three age groups, I concluded that it was feasible to look at the vestibular-guided spatial navigation as a three-step process comprising the vestibular self-motion perception test, vestibular egocentric and vestibular allocentric (egocentric+) tasks. After successfully completing the healthy controls testing, I was able to invite memory and (balance) patients to take part in my study. This was the first study where a comprehensive three-step testing battery comprising three vestibular tasks (VMP, egocentric and allocentric (egocentric+) tasks) was administered not only in healthy controls but also in patients with memory and (balance) impairment. The results showed that patients with decreased cognition showed further impaired spatial behaviour during both the egocentric and the allocentric (egocentric+) tasks. Interestingly, the patients with decreased VMP and decreased cognition tended to perform worse on the allocentric (egocentric+) task, forming a plateau. Two of these patients forming the plateau had hippocampal volume loss, based on

their clinical MRI scans, as a possible explanation for their performance. Importantly, all four patients with decreased cognition had elevated (= impaired) VMP threshold.

Vestibular system-driven correction for the egocentric task played a more significant role in the analysis of patients with decreased cognitive control ($MMSE \leq 24$) but did not show such an effect on patients performing within a normal cognitive range ($MMSE > 24$). Patients with preserved cognitive skills ($MMSE > 24$) had a less varied and more predictable behaviour on the egocentric task, especially for the initial egocentric analysis. Further, for the main analysis of the egocentric task, patients with preserved cognition and healthy elderly controls showed similar performance, even if $MMSE > 24$ patients experienced more variability of individual responses. However, a difference between the cognitively intact patients and healthy controls > 60 yrs was noted in their allocentric (egocentric+) performance.

What was more, the allocentric (egocentric+) task discriminated better between patients and controls than the egocentric task. Still, at this point, the allocentric (egocentric+) task discriminated statistically between patients and controls but not within patients. On the other hand, the egocentric task discriminated better between healthy controls groups than the allocentric (egocentric+) task. Specifically, the egocentric task was sensitive to show the difference between the younger healthy controls (<40 yrs, and between $(40-60)$ yrs) as compared to the healthy elderly > 60 yrs.

With respect to the cognitive tests, the vestibular self-motion perception threshold showed a strong negative correlation to a widely established cognitive test such as the MMSE and thus emerged as an alternative way to divide patients into groups. Still, there was no 100% match – while all patients with decreased cognition had decreased VMP, not all impaired VMP patients had impaired cognition. With other words, patients with normal VMP had also $MMSE > 24$, but not all patients with $MMSE > 24$ had a normal VMP performance. With respect to the second cognitive test, VMP did not manage to establish a notable correlation to ACE.

Lastly, whereas patients' allocentric (egocentric+) task showed a significant correlation to MMSE, ACE memory and ACE attention, the patients' egocentric performance achieved no notable correlations with any of the memory tests.

In Appendix, I attach a table comparing the loss of the skills for AD patients at every pathological stage based on Braak's classification (Braak & Braak, 1991), (Braak et al., 2006) compared with the skills that my patients needed for the successful completion of the VMP, egocentric and allocentric tasks. The pathological process makes it clear of how tightly implicated the skills are, that are required for spatial navigation and the areas that are affected by the Alzheimer's disease. Based on (Nelson et al., 2009), my patients were approximately at stage III and maybe slightly IV, considering I set a MMSE of 20 points as the minimum threshold allowed for patients to be included in the study. Unfortunately, around stage III and maybe IV, most of the functions needed for a successful spatial navigation are either impaired or have started to drastically deteriorate. Thus, as spatial testing of memory patients hints to become more challenging with time, the results from such an initiative are extremely valuable.

III. Implications/Future work

As seen throughout this thesis, vestibular information is essential for our proper spatial and postural processing during health and disease. The vestibular system is (1) crucial for maintaining our sense of balance/equilibrium, (2) for the stability of our gaze, (3) presents as a contributor to our self-motion perception and spatial orientation, (4) contributes to crucial reflexes such as the VOR, VSR, VCR, (5) important for place and HD cells of the spatial cognitive map, (6) links to limbic structures and consequently links to decreased self-esteem, increased anxiety, sleep disturbance, (7) links to decreased level of glucocorticoids leading to decreased hippocampal volume, (8) essential for our orientation in the dark and (9) answering essential question for our orientation (“Am I moving?”, “How much of a distance have I travelled/covered?”, “Where am I?”) (Stackman & Taube, 1997), (Stackman et al., 2002), (Angelaki & Cullen, 2008), (Kolev et al., 2014), (Seemungal, 2014), (Bronstein et al., 2015), (Fife & Kalra, 2015), (Bear et al., 2016), (Kaski et al., 2016), (Brandt & Dieterich, 2017), (Cullen, 2019), (L. Smith et al., 2019). However, my literature research indicated the current gaps in the management of patients with central affections of the nervous system suffering vestibular impairment and the lack of knowledge about the neural mechanisms behind their decline. Even if the vestibular system is only one of many contributors to spatial and postural processing, the loss of vestibular function in patients with central affections of the nervous system has been shown to significantly decrease their quality of life and incur “a substantial societal cost” (Agrawal et al., 2017). While for healthy individuals, the vestibular system presents as a crucial resource ensuring precise and coordinated navigation and postural control, it is unclear how the diseased brain evaluates this extra sensory information and if it is an additional chance for a compensatory mechanism or rather a “noisy” burden to the already “computationally” overloaded pathological brain.

Whereas alone the knowledge about how the vestibular loss contributes to spatial and postural processing is unlikely to solve the whole ambiguity surrounding these conditions, the vestibular system and its importance in the overall solution of this issue should not be underestimated. As already stated, a more holistic approach, coming from all possible contributors, including the vestibular system, should weigh the importance of all systems involved. Indeed, research has shown that combined treatment strategies and multifaceted approaches might show more promise for complex medical conditions such as Alzheimer’s disease and acute TBI.

Thus, the goal of this PhD study was to concentrate on one of the often underrated but crucial contributors to the general solution of this ambiguity, i.e. the vestibular system. As seen throughout this study, even if there is some human-based expertise about the peripheral vestibular system and its link to spatial and postural impairment, the studies attempting central vestibular research are very few. Even so, these few central vestibular studies presented certain unclarities about their results, making it impossible for us to gain further knowledge about central vestibular dysfunction in the navigation/balance of patients with memory impairments or acute TBI.

Given the immense effect disorientation and balance loss/falls can play in one's life, alongside the many physical, mental and financial implications connected with them, more research is needed. One possible way the medical practice might take to better address the high percentage of vestibular dysfunction, is [1] the implementation of more vestibular-based examinations and vestibular-based rehabilitation therapies. For instance, although postural instability and falls have been a great risk for the AD population, scientists revealed that out of 801 AD patients at a tertiary AD referral center, only 0.62% (i.e. 5 patients) were referred to vestibular physical therapy (Gandhi et al., 2020). However, such a change can only happen with the help of more vestibular studies and robust scientific evidence discussing the crucial role of the vestibular system.

Another path for the medical service involves [2] the “vestibular implants”. Vestibular implants have been successfully developed not only for animals (Karmali et al., 2021) but also for humans (Chow et al., 2021). In the human-based study, patients improved their balance and gait, but all of them experienced some hearing loss. This was an expected side effect leading to the vestibular implant being placed only unilaterally instead of bilaterally (Chow et al., 2021). Thus, many questions about the nature of the vestibular system and its involvement in spatial orientation and postural control remain open. Consequently, much work is ahead aiming at better facilitation of neurological diagnoses and improved treatment schemes (Montero-Odasso, Manuel et al., 2017) for patients with vestibular disabilities.

[My personal contribution to the further collection of vestibular based spatial and postural data](#)

During my imaging analysis for the [acute TBI cohort](#) (Chapters VI, VII, alongside a lot of information available in Appendix), I provided extremely detailed information about my vestibular-based findings with MNI coordinates of the maximum intensity voxels and cluster information. Information was collected not only about significant contrasts but also about those showing a close tendency towards significance. These data can significantly contribute to the collection of further information about vestibular-driven spatial and postural processing and guide prospective vestibular-based research in the investigation of the regions of interest pointed out in this study. To confirm or refute my current findings, one possible step is a (1) tractography-based analysis of the WM tracts that my analysis implicated as statistically notable, and even those showing only a tendency towards significance. In addition, to investigate further the effect of acute TBI on the vestibular spatial and vestibular postural processing, one could consider a few more examples (2) bigger cohort with more severe cases based on the Mayo classification criteria (Malec et al., 2007), (3) blood sampling, (4) more in depth investigation of DAI, which was also performed for this study but was not included in the thesis due to a low number of more severe DAI cases. However, it showed that DAI analysis with a higher number of severe cases can greatly facilitate the central vestibular spatial/postural investigation during acute TBI. Further, (5) proper cerebellum/brainstem images for DTI that would allow for additional and crucial vestibular regions to be included in the analysis, (6) acceptable image quality for rfMRI (which were not available

for this study and did not allow for a reliable analysis), (7) further segmentation of the suggested vestibular regions (e.g. more in-depth investigation of the Insula). Please check “possible limitations of the acute TBI study” for further ideas.

With respect to the questions investigated with the help of my second cohort of patients, i.e. [the memory and \(balance\) patients](#), a few examples on how this analysis could be taken further are (1) establishing a well-controlled and good-sized cohort of different neurological groups (e.g. MCI, Alzheimer’s patients, Parkinson’s patients), (2) performing blood sampling and brain imaging, (3) considering a longitudinal design, (4) more vestibular-based tests (e.g. testing of individual time constants (perceptual and ocular), (5) finer adjustment of the JOYSTICK task as to be able to pick up differences between patients’ groups and be vestibular-controlled at the same time. Please check “possible limitations of the acute Memory and (balance) patients study” for further ideas.

In addition, instead of simply suggesting prospective vestibular-based spatial studies for healthy controls and patients, in Appendix I provided information on some small studies I already performed for several different vestibular tests that I developed. These have the potential to be expanded in bigger cohorts of healthy participants and later also – in different neurological cohorts. A few examples that can be taken further, include (1) Vestibular-guided Adaptation task – this was a VR task (with a headset) while participants were seated in a rotation chair experiencing passive chair rotations (healthy controls only) ($n = 13$). Here, I applied a variety of rotational velocities in a variation of an allocentric task similar to the MOUNTAIN task presented in this thesis. I provided false feedback after specific passive angular rotations, hoping to learn more about the mechanisms of encoding at velocities typical for “outside of the laboratory” environments. Further, I also tested (2) six Parkinson’s patients to learn more about their vestibular-guided spatial navigation and (3) six chronic TBI patients on the same three-step spatial model as presented in this thesis (i.e. the three-step model). This allowed for a comparison among memory and (balance) patients and the two new neurological cohorts.

Next, (4) I developed a vestibular-guided Mental transformation task – this was again a VR task (with a headset) while participants were seated in a rotation chair experiencing passive chair rotations (healthy controls only) ($n = 20$). In this task, I combined mental transformation and vestibular spatial memory predicting that there was a relationship between the function of complexity of the presented scene and the spatial deficit of working memory under vestibular guidance. In addition, I developed (5) a human-based MWM task to assess if active locomotion under vestibular guidance (and rotations) may impose a burden in the navigation of brain impaired patients. This was a VR task (with a headset) while participants were actively moving in a laboratory environment. A testing procedure comprising a pure egocentric, a pure allocentric and a combined “egocentric and allocentric” task was developed.

In addition, a few more suggestions are available on how to test patients under vestibular guidance with a variety of rotational tests (passive chair rotations). Lastly, a virtual maze/virtual forest spatial environments were also developed to facilitate more varied testing under vestibular guidance (active locomotion).

Possible Limitations of the acute TBI study:

- The laboratory testing was long (4h) and sometime tiring for acute TBI patients. Therefore, testing sessions were often divided into 2x2h to help prevent tiredness and stress. In addition, the brain scan sessions accounted for additional 1.5 – 2h.
- No blood sampling was performed. However, it is crucial to consider that blood and other tissue sampling (e.g. CSF, saliva, urine) could have a high potential to contribute to this vestibular study (R. Smith, M. Chepishcheva et al., 2019).
- The inclusion criteria were very strict (e.g. intact peripheral and brainstem reflex vestibular functioning and a closed head injury), limiting the number and severity of patients that could take place. This was done with the idea that patients should be able to perform some testing.
- The restriction in the severity of patients did not allow for the testing of more severe cases, possibly leading to the miss of significant vestibular-based findings.
- Imaging data was shared among 2 different research groups, which led to compromises in the scanning protocols (inclusion/exclusion of cortical or brainstem/cerebellum regions). This led to insufficient data for the cerebellum/brainstem for DTI (and the exclusion of important vestibular-related WM tracts and other brain areas) and unreliable data for rfMRI analysis.
- Sharing patients between the 2 research groups led to increased burden/tiredness for patients. Still, even if brain scans were shared, no other experimental data was shared between groups which was not a practical solution.
- Vestibular regions that are less amenable to the ROI technique (e.g. segmentation of the perirhinal cortex is a notoriously difficult task) were not investigated.

Possible Limitations of the Memory and (balance) patients – pilot study:

- Recruiting Alzheimer's patients without an established cohort or multi-centre collaboration was a highly challenging task.
- Generally, testing of memory patients is not an easy task itself. Patients tended to get tired despite their best desire to participate. This involved several visits to the Laboratory, which became difficult with time as patients did not always feel well.
- Studies that are proud to test memory patients with extremely short tests are usually not collecting enough data to make more solid conclusions. However, studies that require longer testing batteries run slower. Thus, a balance is needed, which is often hard to find.
- The tests were done in a randomised order to avoid bias. Therefore, although it might have been linked to tiredness, there were cases when people performed with more technical mistakes for the less complex tasks.

- Recruitment at this stage of the disease (early to middle) was not straightforward as some potential participants who were already stepping over to the middle stage felt unsure about taking part in research studies, especially with a piece of a virtual reality (VR) equipment.
- Finding a person with an intact peripheral vestibular system tends to become more difficult with age, and I also lost several Alzheimer's participants because of this.
- No blood sampling and brain imaging were available for this study, as there was insufficient financial support.
- The velocity restriction I imposed on the joystick tool itself, as discussed during the initial Joystick analysis. The stimulus that patients perceived was within 30 -120°/sec peak velocity range for 30°-180° angles with timings varying from 1- 4 seconds. Still, to avoid a kinetic strategy, I decreased the allowed peak velocity of the joystick, so patients had to use their perceived rotation as an indicator of how to respond. It is important to note that both patients and healthy controls underwent a training session until they felt confident using the joystick, and I felt confident that they could manipulate the joystick freely and within the allowed 7s for rotation.

Still, 4 out of 51 healthy participants were excluded from the analysis because of longer than 7s responses. Possible factors such as (1) tiredness and (2) lack of attention could have contributed to these exclusions, while other factors could not be ruled out. Later, some of them reported having performed slower than instructed as they started overthinking their answers. Still, most of my patients and healthy participants managed to complete the task with the allowed velocity limitation of the joystick, some even without any errors at all.

However, considering my patients had memory impairment, I sometimes needed to remind them of the instructions of the task, also during the real testing. Therefore, the speed I imposed on the joystick might have posed a possible limitation that I need to improve for future experiments in order to accommodate the needs of my participants in the best possible way. Still, this shall also be done with caution. During the development of the JOYSTICK task, while looking for the best maximum speed to impose on the joystick, some memory patients tested got scared when they realised that the chair could move quicker than 60°/sec.

- A potential limitation of the MOUNTAIN task might have been the use of the Virtual Reality concerning its tolerability by the patients. My literature research indicated an enormous variety of tasks used for the exploration of spatial orientation in Alzheimer's patients: the 4 Mountain Task, the Supermarket trolley task, the Floor maze, the Start maze, the Y-maze, the Corsi block test, the MWM task, the Triangle task, the route learning test, the heading orientating test and multiple others whose mechanisms are based on these several cornerstone tasks. Some of these tasks were performed with pencil and paper, others with real active navigation involved, and a third group was performed in front of a computer or with the help of a Virtual Reality (either active or passive). While some claim that 'pencil and paper' and computer-based (screen-based)

2D experiments are not realistic, others are also against the 3D Virtual reality as a possible contributor to intimidation of older participants, and even more so for pathological individuals while dealing with the advanced machinery/equipment. Another potential issue might be the induced dizziness or motion sickness after using Virtual Reality (da Costa et al., 2018). Still, real-world versus virtual-world data have shown comparable results (Cushman et al., 2008), (Laczó, Jan et al., 2012), (Nedelska et al., 2012). Therefore, researchers support the use of this virtual modality in the research setting as a tool that is able to provide safe and varied environmental conditions for participants while being able to accurately detect and measure performance, which is not always possible and often very difficult when in the real world (Weniger et al., 2011), (Cogné et al., 2017), (Clay et al., 2020). Interestingly, the brain compensatory mechanisms via the optic flow can ensure a speed signal by triggering activity in the vestibular nuclei even if the vestibular system is itself inactivated (Jacob et al., 2014). Consequently, this could elicit why during passive virtual reality testing in front of a computer with no real vestibular signal production, grid cell firing is still recorded (Jacob et al., 2014). Consequently, based on safety reasons and the possibility of achieving high-quality and comparable performance results, I decided that Virtual Reality would be used in my MOUNTAIN task. In addition, it was superior to the “Curtain task” (i.e. = the initial allocentric task used), where patients’ tolerability towards the task was very low, mainly due to the uncomfortable general set of the task.

- This was an ongoing study at the time when the COVID-19 pandemic started, and some tasks were not completed by all participants.

IV. Concluding remarks

Vestibular spatial and vestibular postural deficits present a huge disadvantage and are felt not only on a physical but also on a psychological level by all those affected. Still, there is a clear need for more (central) vestibular-driven knowledge that can better facilitate the understanding of the aetiology of these dysfunctions.

A possible change can start with the more frequent implementation of the vestibular system examination/ rehabilitation/ therapy in the clinic. However, such a change can only happen with the help of more feasibility studies and solid scientific evidence stressing the crucial role that the vestibular system plays in the long-term solution and the better understanding of the neural mechanisms of the spatial and postural modalities during health and disease.

Chapter IX

Appendix

NOTA BENE! Most of the Appendix sections and live links available throughout were removed to help with the long-term storage of my PhD thesis on the Imperial Spiral website. Importantly, all information listed in the Appendix (e.g. discussion sections, detailed analysis, images) that is not directly presented here is available upon reasonable request to anyone interested in studying the vestibular-guided spatial and postural processing in patients with central affections of the nervous system.

Thank you,

Mariya Chepishева

Table of content:

1. APPENDIX TO CHAPTER II. Materials and Methods.
2. APPENDIX TO CHAPTER III. Psychophysics, behaviour, neurophysiology and neuropsychology – acute TBI.
3. APPENDIX TO CHAPTER IV. Psychophysics, behaviour, neurophysiology and neuropsychology – Memory and (balance) patients – a pilot study.
4. APPENDIX TO CHAPTER V. Vestibular spatial navigation – Memory and (balance) patients – a pilot study.
5. APPENDIX to the TBI study - Voxel-based Morphometry – whole brain analysis in acute TBI.
6. APPENDIX TO CHAPTER VI. Vestibular regions and CC – DTI and VBM – acute TBI.
7. APPENDIX TO CHAPTER VII. Diffusion Tensor Imaging in acute TBI.
8. APPENDIX TO CHAPTER VIII. Conclusions and Future work.

Appendix to Chapter II

- 1) Development of the Mountain Task
- 2) Fig.A1.VBM pipeline (SPM/FSL GLM) + separate Freesurfer analysis scheme

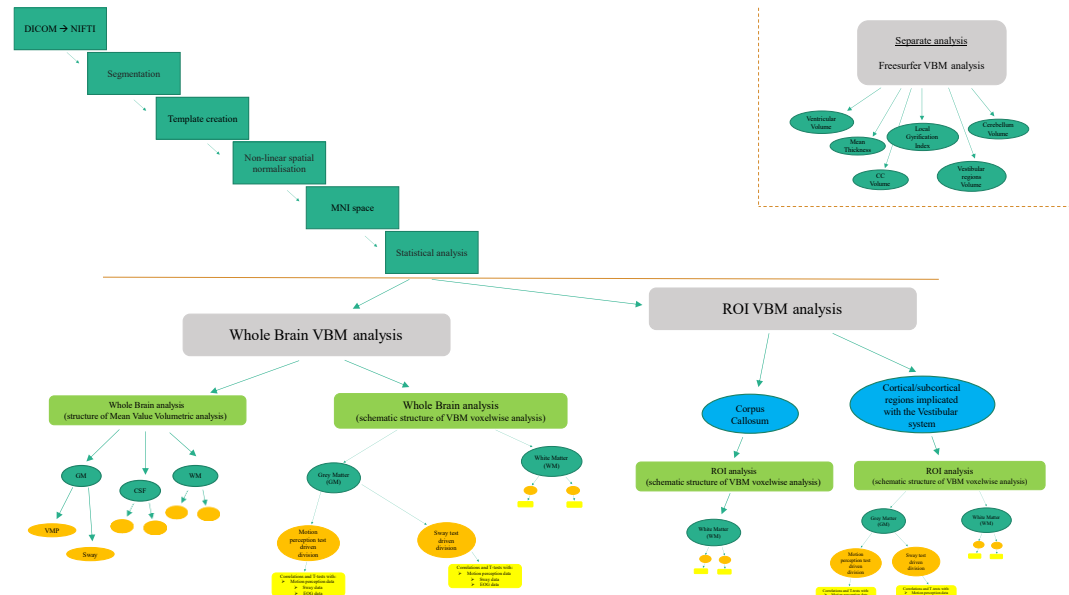


Figure. A1. VBM pipeline (above the orange line) and statistical analysis (below the orange line) (volumetric exploration and voxelwise analysis) + separate Freesurfer analysis scheme.

Appendix to Chapter III

- 1) Postural control exploration in cerebellar or brainstem stroke patients, vestibular neuritis and bilateral vestibular failure patients – unpublished data – a BRC final report/article.

Expert Diagnostics in Acute stroke with Vertigo – EnDeAVOr

https://drive.google.com/file/d/1jKndSLDb640qI5LU_3lIR96rWboyZNQ9/view?usp=sharing

- 1) Healthy controls for TBI study – demographics.
- 2) Acute TBI - ABC balance test – performance based on VMP and Sway performance.
- 3) Acute TBI - ABC balance test – correlations.
- 4) Acute TBI - Reaction Time Test (RT) – control/patients, VMP and Sway division.
- 5) Acute TBI - EOG - VMP and Sway division.
- 6) Acute TBI – Posturography – individual ANOVAs - table
- 7) Acute TBI - Sway performance based on RMS (SC) and the Sway 95% ellipse GAIN SC/SO.
- 8) Acute TBI - Perceptual threshold (non-visual RT task) performance – VMP and Sway division.

Appendix to Chapter IV

- 1) Memory patients – Sway performance – MMSE division.
- 2) Memory patients – Sway performance – VMP division.

Appendix to Chapter V

- 1) Healthy controls – demographics.
- 1) Healthy controls – Joystick task (analysis) – a detailed table of content follows in this section.
- 2) Healthy controls – Mountain task (analysis) – a detailed table of content follows in this section.
- 3) Memory patients – Joystick task (analysis) – descriptive statistics; a detailed table of content follows in this section.
- 4) Memory patients – Mountain task (analysis) – descriptive statistics; a detailed table of content follows in this section.
- 5) Memory patients – Extended Discussion sections.

Healthy CONTROLS – JOYSTICK task – TABLE OF CONTENT

- 1) Descriptive statistics and distribution plots.
- 2) Error (ABS) – Joystick task – Healthy Controls.
- 3) GAIN (ABS) – Joystick task – Healthy Controls.
- 4) GROUP - XY scatter plots displaying Joystick performance (MEDIAN + IQR) based on AGE division (<40yrs, <(40-60)>yrs, >60yrs) - right/left-sided rotations, right/left-sided rotations divided by beep delay, averaged performance and averaged performance divided by beep delay (phase II).
- 5) Slope and R^2 plots.

Healthy CONTROLS – MOUNTAIN task – TABLE OF CONTENT

- 1) Descriptive statistics and distribution plots.
- 2) Error (ABS) – Mountain task – Healthy Controls.
- 3) GAIN (ABS) – Mountain task – Healthy Controls.
- 4) GROUP - XY scatter plots displaying Mountain performance (MEDIAN + IQR) based on AGE division (<40yrs, <(40-60)>yrs, >60yrs) - right/left-sided rotations, right/left-sided rotations divided by beep delay, averaged performance and averaged performance divided by beep delay (phase V).
- 5) Slope and R^2 plots.
- 6) Healthy controls – age groups – Group Joystick/Mountain task SLOPE versus AGE
- 7) Healthy controls who completed both the JOYSTICK and the MOUNTAIN task – correlations

MEMORY PATIENTS - JOYSTICK task - TABLE OF CONTENT

- 1) Descriptive statistics and distribution plots.
- 2) Error (ABS) – Joystick task – (Controls >60yrs, MMSE $\leq$ 24, MMSE > 24) - (VMP, MMSE).
- 3) GAIN (ABS) – Joystick task – (Controls >60yrs, MMSE $\leq$ 24, MMSE > 24) - (VMP, MMSE).
- 4) GROUP - XY scatter plots displaying Joystick performance (MEDIAN + IQR) based on MMSE division (Controls >60yrs, MMSE $\leq$ 24, MMSE > 24) - right/left-sided rotations, right/left-sided rotations divided by beep delay, averaged performance and averaged performance divided by beep delay (phase II).
- 5) INITIAL analysis for Memory patients for Joystick task (8 panels + table).
- 6) SLOPE and R^2 – GROUP plots based on VESTIBULAR MOTION PERCEPTION division (healthy controls > 60yrs, patients with abnormal motion perception performance, patients within normal range motion perception performance).

- 7) SLOPE performance based on MMSE or Vestibular Motion Perception performance.
- 8) Effect size, sample size and Bayesian estimates.
- 9) Figure.A2. Memory and (balance) patients – Number of JOYSTICK task errors completed during the task.
- 10) Figure.A3. Memory and (balance) patients – Group JOYSTICK performance – the difference in performance based on a Right and Left rotation – INITIAL JOYSTICK analysis.

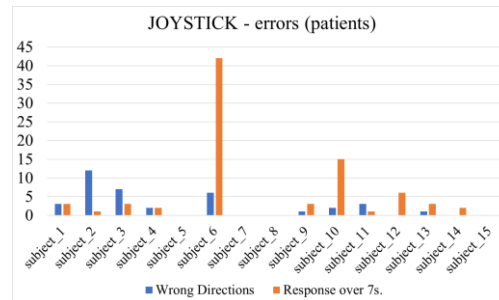
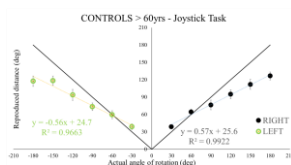


Figure.A2. Memory and (balance) patients – Number of JOYSTICK task errors completed during the task. The X-axis displays the individual participants, whereas the Y-axis represents the number of errors. When patients completed trials in contrast to the instructions given, their trials were excluded from the analysis. This type of error is displayed in blue colour, with subject Nr.2 displaying the highest number of this type of error. However, responses over 7s. account for a more significant number of errors and are marked with orange colour. Subject Nr.6 was excluded from the analysis because of the high number of over 7s responses. Subjects Nr.5, 7, 8 and 15 did not make any type of errors at all.

Panel 3



The plots present the difference in performance of a right and left rotation for patients divided in two groups based on their MMSE score: MMSE > 24 are considered with “normal cognition”, whereas MMSE ≤ 24 indicates “mild/early functional impairment”.

On the left side, there is the performance of the age matched controls > 60yrs and on the right side, the patients are presented at three levels of “analysis correction”: (1) raw data without any corrections; (2) wrong directions during response are removed; (3) data is corrected for the working of the vestibular system and thus any rotations over 7s are removed.

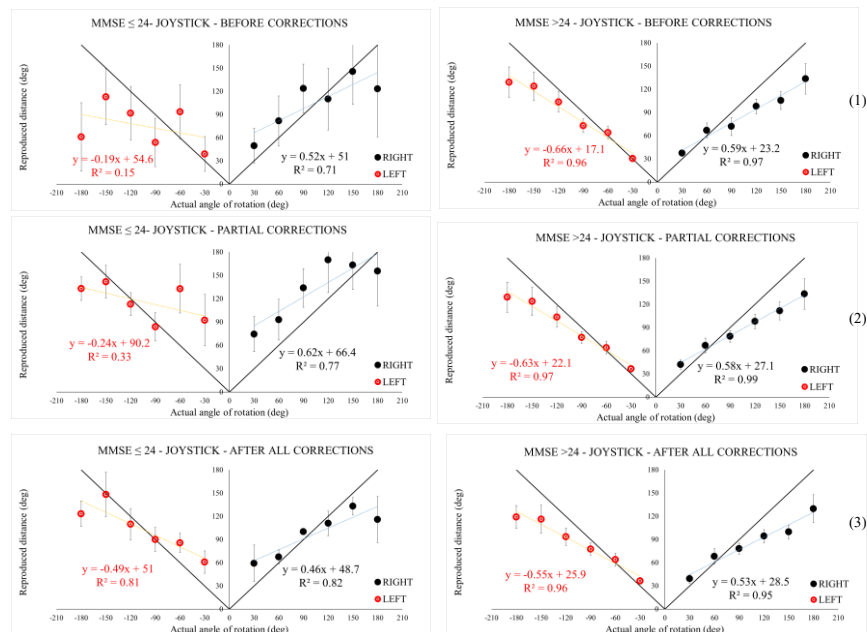


Figure.A3. Memory and (balance) patients – Group JOYSTICK performance – the difference in performance based on a Right and Left rotation. This panel presents patients separated based on MMSE score in three correction levels: (1) BEFORE, (2) PARTIAL and (3) AFTER ALL correction (average + standard error).

MEMORY PATIENTS - MOUNTAIN task - TABLE OF CONTENT

- 1) Descriptive statistics and distribution plots.
- 2) Error (ABS) – Mountain task – (Controls > 60yrs, MMSE ≤ 24, MMSE > 24) - (MMSE, VMP).
- 3) GAIN (ABS) – Mountain task – (Controls > 60yrs, MMSE ≤ 24, MMSE > 24) – (MMSE, VMP).
- 4) GROUP – XY scatter plots displaying Mountain performance (MEDIAN + IQR) based on MMSE division (Controls > 60yrs, MMSE ≤ 24, MMSE > 24) – right/left-sided rotations,

- right/left-sided rotations divided by beep delay, averaged performance and averaged performance divided by beep delay (phase V).
- 5) SLOPE and R2 – GROUP plots based on VESTIBULAR MOTION PERCEPTION division (healthy controls > 60yrs, patients with abnormal motion perception performance, patients within normal range motion perception performance).
 - 6) SLOPE performance based on MMSE or Vestibular Motion Perception performance.
 - 7) Effect size, sample size and Bayesian estimates.
 - 8) K-means, Hierarchical clustering analysis and PCA for patients only.

MEMORY PATIENTS – Extended DISCUSSION sections

- 1) 5.3. VMP is not an accepted way to divide patients into groups, but it shows its potential.
- 2) 5.4. The anatomical correlates of vestibular-guided spatial disorientation in Alzheimer's disease + Table.A4.

Alzheimer's pathological stages as per Braak et al. (1991, 2006) and functions of the affected regions	Joystick and Mountains - skills needed to successfully complete the tasks
I stage - transentorhinal cortex directly for memory functions; affected area part of a structure for detection of novel objects (perirhinal cortex); Affected area close to areas for declarative memory (Brodmann 36);	- short term memory (neural basis in the hippocampus and the diencephalon, both part of the limbic system): • visual memory • temporal (i.e., time) memory • spatial memory • vestibular memory
II stage - layer II of entorhinal cortex (+layer III) projects to dentate gyrus, responsible for new episodic memories, spontaneous exploration of new environments; Lesions start in hippocampus (long-term memory, spatial processing and orientation)	- attention/concentration (neural basis in the reticular activating system - brainstem and thalamic nuclei; + multimodal association areas (prefrontal, posterior parietal, temporal lobes)
III stage - anterior portions of the parahippocampal gyrus for scene recognition, for topographical scene stimuli (landscapes, in short images of places). Occipitotemporal gyrus for colour information; face and body recognition. The lingual gyrus (= medial occipitotemporal gyrus) for processing of vision (related to letters), analysis of logical conditions (i.e. logical order of events) and encoding of visual memory.	- self- motion perception
IV stage - further parts of the hippocampus; Insula receives sensory information from the environment; Medial temporal gyrus for contemplating distance, face and word recognition; Medial temporal gyrus together with others - language and semantic memory processing.	- reaction times
V stage - peristriate area 19 (together with 18) visual feature extracting, shape recognition, attentional and multimodal integrating functions. Area 19 thought to be the differentiation point of the "what" and "where" visual pathways.	- path integration → velocity to position
VI stage - affected areas for vision and sound	- to know how much have I moved (uncalibrated, i.e., egocentric task)
	- to link the amount of travelled distance to a remembered visual scene (allocentric, i.e., calibrated task) = mapping
	- reasoning, logic

Table.A4. A direct comparison between the functions affected by Alzheimer's pathology as per Braak et al. (1991, 2006) and the skills needed to complete the three tasks: self-motion perception task, egocentric (JOYSTICK) and allocentric (egocentric+) (MOUNTAIN) task.

Appendix to acute TBI study – whole brain VBM analysis

NOTE: Detailed information, plots and results available upon reasonable request.

- A. Section I – VBM WHOLE-BRAIN MEAN VALUE – statistical analysis
- B. Section II – WHOLE-BRAIN VOXELWISE ANALYSIS
- C. Section III – VOLUMETRIC/THICKNESS/LGI - statistical analysis

In this sub-Chapter, I performed a detailed volumetric/thickness analysis (using Freesurfer) and calculated the LGI (local gyrification index) during the acute state of TBI. The analysis resulted in multiple results that are available upon request. These results include volumetric and thickness information concerning patient/control, VMP and Sway division discussing (1) the visual cortex, primary somatosensory cortex, primary motor cortex,

premotor and supplementary motor cortex, (2) all gyri and sulci of the brain (separated by Right/Left hemisphere), (3) WM hypointensities and (4) defect surface holes (separated by Right/Left hemisphere). Here, I attempted to summarise some findings concerning (1) ventricles, (2) mean thickness, (3) the Corpus Callosum (discussed in more detail in Chapter VII), (4) the selected Vestibular regions (discussed in more detail in Chapter VII), (5) local gyrification index (LGI) and the differences within groups based on factors such as gender and age.

VBM - Summary/Discussion

[Mean value analysis.](#)

[Whole-brain Voxelwise analysis \(Figure A5 and A6 \(summary plots\)\).](#)

[Volumetric/Thickness/LGI analysis.](#)

<i>GM (VMP division)</i> correl normal VMP to VMP, $p = 0.0667$ abnormal VMP to EOG, $p = 0.0681$ normal VMP to EOG, $p = 0.0266^*$ t-test -	<i>WM (VMP division)</i> correl abnormal VMP to Sway, $p = 0.0385^*$ normal VMP to Sway, $p = 0.0223^*$ t-test abnormal VMP > controls, $p = 0.0244^*$
<i>GM (Sway division)</i> correl normal Sway to VMP, $p = 0.0835$ normal Sway to EOG, $p = 0.006^{**}$ t-test -	<i>WM (Sway division)</i> correl abnormal Sway to Sway, $p = 0.0111^*$ t-test abnormal Sway > normal Sway, $p = 0.0464^*$ abnormal Sway > controls, $p = 0.0046^{**}$
GM correl patients to VMP, $p = 0.0963$ t-test -	WM correl patients to Sway, $p = 0.0031^{**}$ t-test patients > controls, $p = 0.032^*$

Table.A5. Voxelwise VBM analysis – summary of significant GM and WM correlation and comparison (t-test) contrasts while dividing into VMP (first row), Sway performance (second row) or patient-control (third row) division method.

Additional VBM analysis:

- 1) LGI – gender and age differences – controls only.
- 2) ANCOVA (age and gender analysis for WM and GM).

Appendix to Chapter VI

- 1) DTI parameters - AGE - GENDER (patients and controls and controls only analyses).
- 2) Whole-Brain DTI analysis – detailed report.
- 3) Corona Radiata – correlations.
- 4) White matter tracts table with Vestibular Input (parts 1 and 2).
- 5) DTI Fornix analysis - (patient/control, VMP, vestibular Sway and DAI divisions).
- 6) ANOVA – White matter tracts (5 tables) + Corona radiata ANOVA.
- 7) Corona radiate – white matter tracts – (patient/control, VMP, vestibular Sway and DAI divisions).

VBM

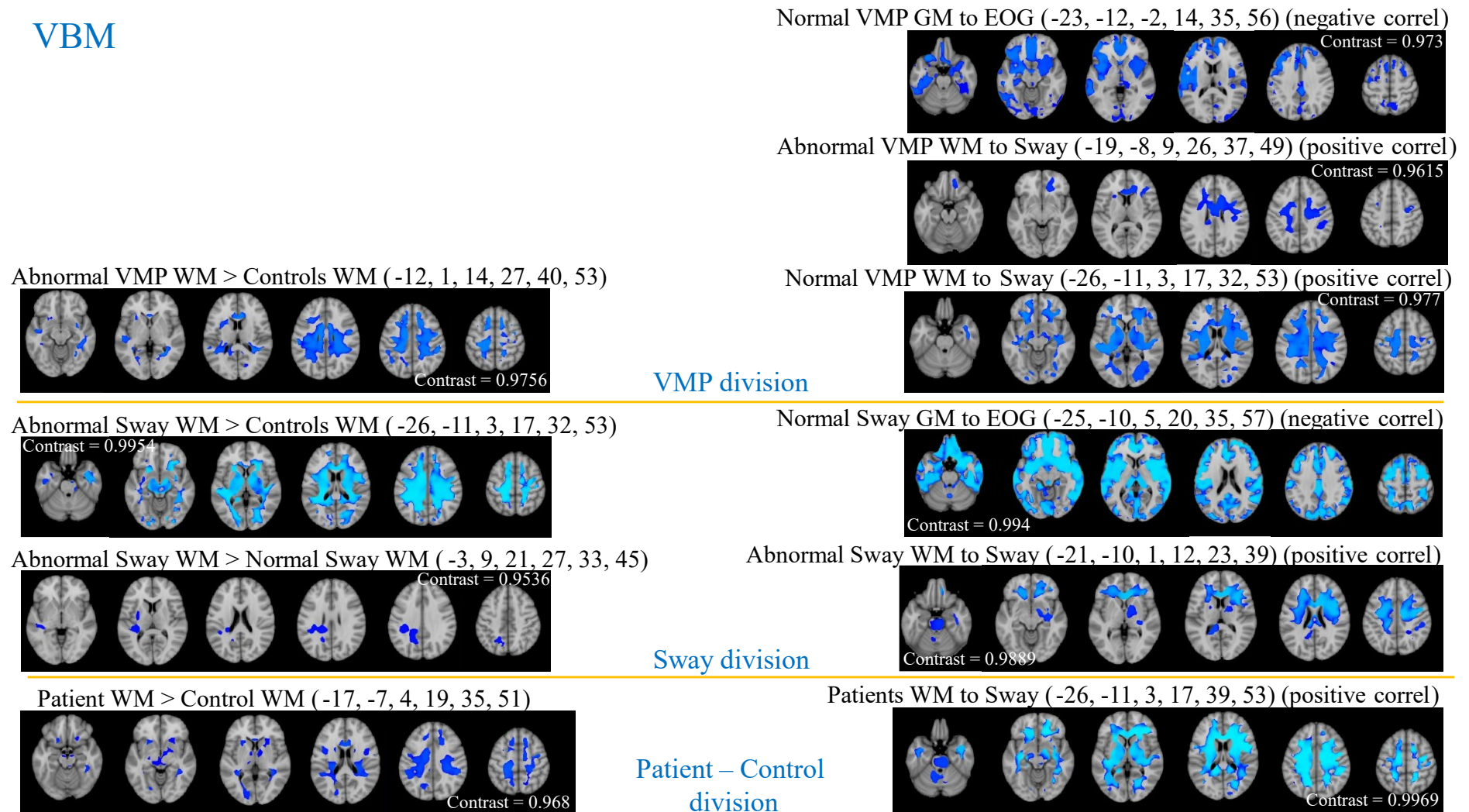
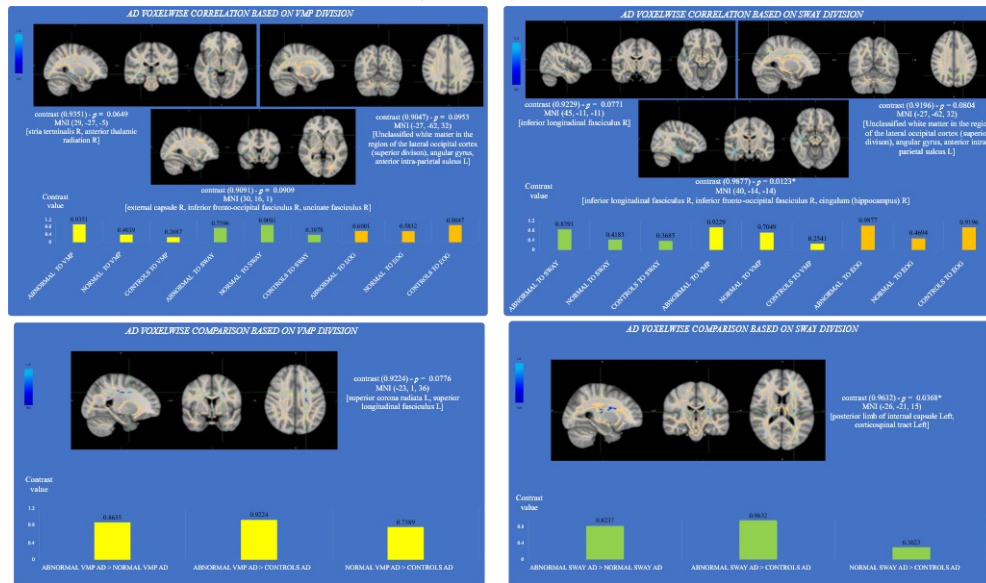


Figure. A6. VBM whole-brain voxelwise analysis – summary of statistically notable findings (axial view). Images are overlaid upon a standard MNI 152 T1 brain atlas. I present VMP division data in the upper section of the plot (above the orange line), Sway division in the middle section of the plot (between the orange lines) and patients-control division in the lower section of the plot (below the orange line). In addition, I present t-tests on the left side and correlations – on the right side. After the contrast description, in the brackets, I present the # of each slice in the image. The contrast values of each contrast are included for easier interpretation. Lastly, for the correlations, I show whether it is a positive/negative correlation.

- 8) A detailed report about the WM tracts analysis – Results section.
- 9) DTI whole brain Axial Diffusivity analysis – Summary Figure A7.
- 10) Sum. Figure A8. Summary of significant DTI comparison (t-test) analysis for VMP division.
- 11) Sum. Figure A8. Summary of DTI correlation analysis for Sway division (1/2).
- 12) Sum. Figure A8. Summary of DTI comparison (t-test) analysis for Sway division (2/2).
- 13) Sum. Figure A8. Summary of DTI correlation and comparison (t-test) analysis for Patient-Control division.
- 14) Figure. A9. DTI WM Tracts – patient/control division.

DTI whole brain - Axial Diffusivity analysis



Summary Figure A7. – Figure. Axial Diffusivity (AD) Voxelwise Correlation based on VESTIBULAR MOTION perception division (panel – top row – left); Figure. Axial Diffusivity (AD) Voxelwise Comparison based on VESTIBULAR MOTION perception division (panel – bottom row – left); Figure. Axial Diffusivity (AD) Voxelwise Correlation based on SWAY 95% confidence ellipse division (panel – top row – right); Figure. Axial Diffusivity (AD) Voxelwise Comparison based on SWAY 95% confidence ellipse division (panel – bottom row – right).

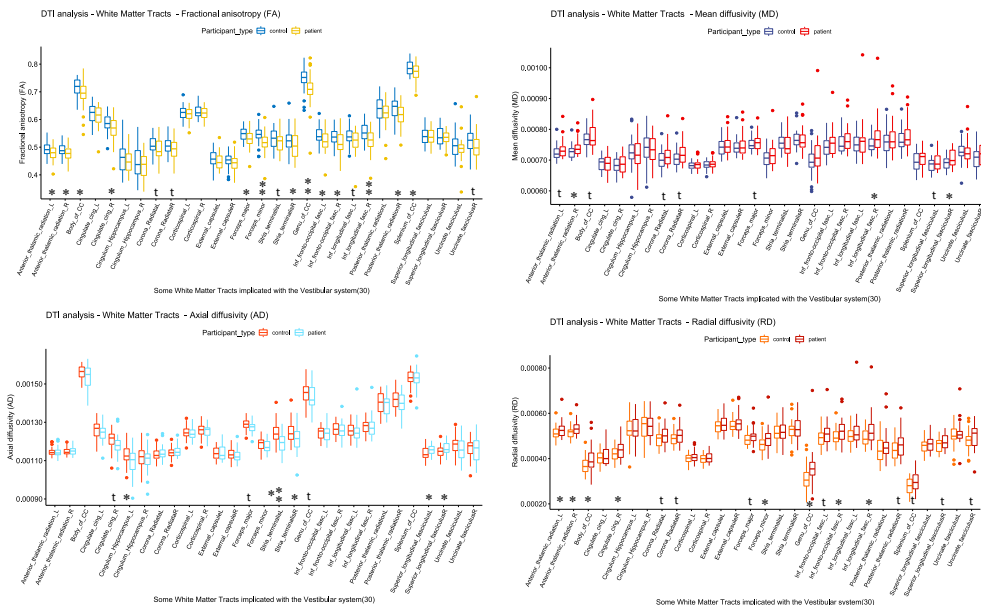
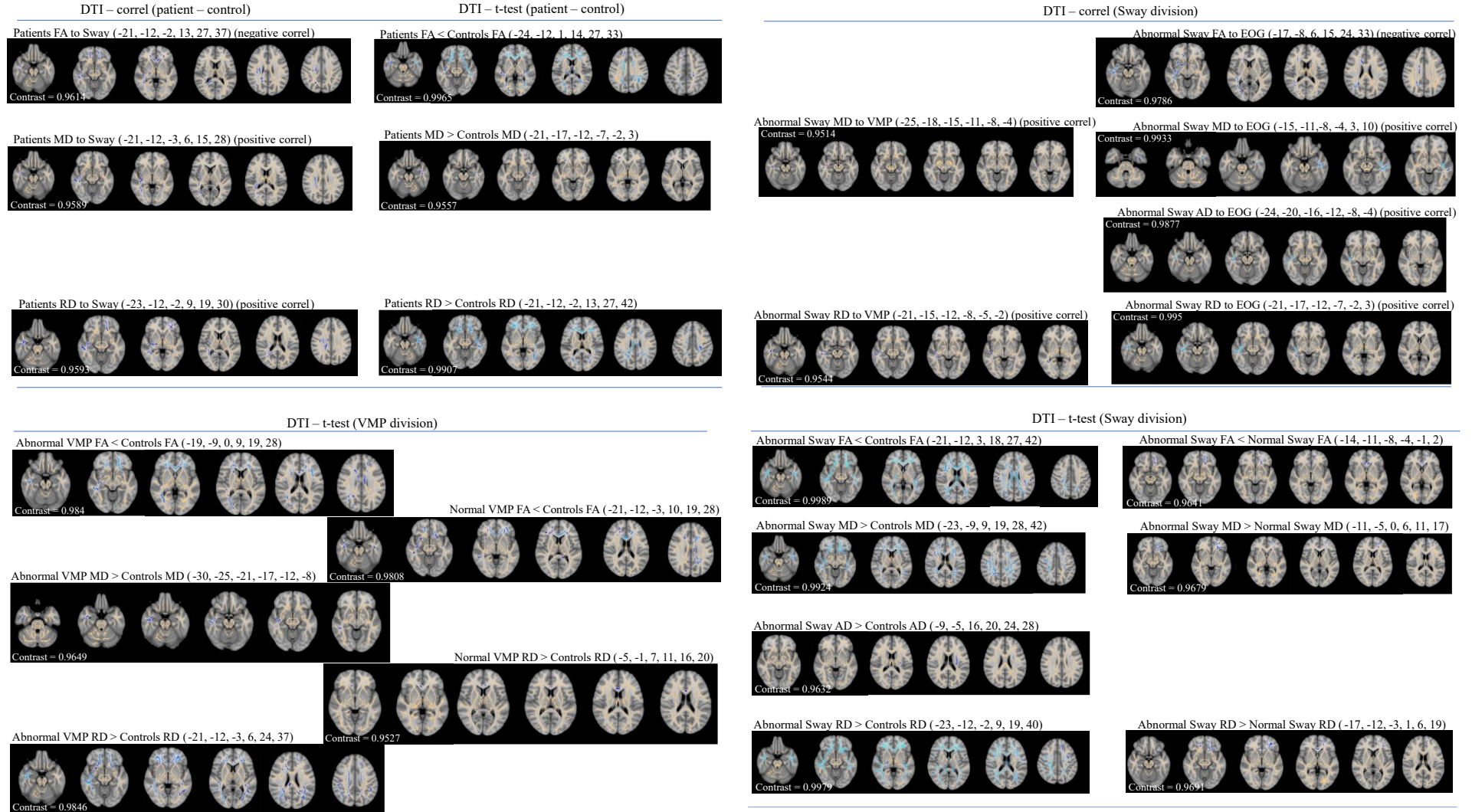


Figure. A9. DTI WM Tracts – patient/control division. Legend – an asterisk “*” indicates a statistically significant result, whereas “t”- a tendency towards significance (I consider tendency any p -value between [0.1 - 0.051]).



Summary Figure A8. - MNI slice sequence Nr. is listed in the brackets from left to right to mirror the sequence of the axial slices presented in the images. For correlations, I also show whether it is a positive/negative correlation. **Figure.** Summary of significant DTI comparison (t-test) analysis for VMP division (panel – bottom row – left); **Figure.** Summary of DTI correlation analysis for Sway division (1/2) (panel – top row – right); **Figure.** Summary of DTI comparison (t-test) analysis for Sway division (2/2) (panel – bottom row – right); **Figure.** Summary of DTI correlation and comparison (t-test) analysis for Patient-Control division (panel – top row – left).

Appendix to Chapter VII

- 1) Vestibular regions – Comparison between ‘patient/control’ for DTI parameters.
- 2) DTI analysis - Vestibular regions – correlation to VMP/Vestibular Sway (tables).
- 3) DTI analysis – Vestibular regions – detailed ANOVA tables (part 1, 2).
- 4) Corpus Callosum – Mean value DTI analysis – patient/control division (Fig.A10).
- 5) Vestibular regions – Mean value DTI analysis – patient/control division (Fig.A11).
- 6) Corpus Callosum – DTI voxelwise analysis – detailed report.
 - Splenium
 - Body
 - Genu
- 7) Corpus Callosum – VBM voxelwise analysis – detailed report.
 - Splenium
 - Body
 - Genu
- 8) Vestibular regions – voxel-based DTI analysis – detailed report.
 - Amygdala
 - Caudate
 - ETC
 - Hippocampus
 - Insula
 - Thalamus (left)
 - OP2
 - Putamen
 - Thalamus (right)
 - TPJ (ant)
 - TPJ (post)
- 9) Vestibular regions – voxel-based VBM analysis – detailed report.
 - Amygdala
 - Caudate
 - ETC
 - Hippocampus
 - Insula
 - Thalamus (left)
 - OP2
 - Putamen
 - Thalamus (right)
 - TPJ (ant)
 - TPJ (post)
- 10) Voxelwise VBM analysis – Corpus Callosum and Vestibular regions.
- 11) EOG - Vestibular-ocular reflex (VOR).

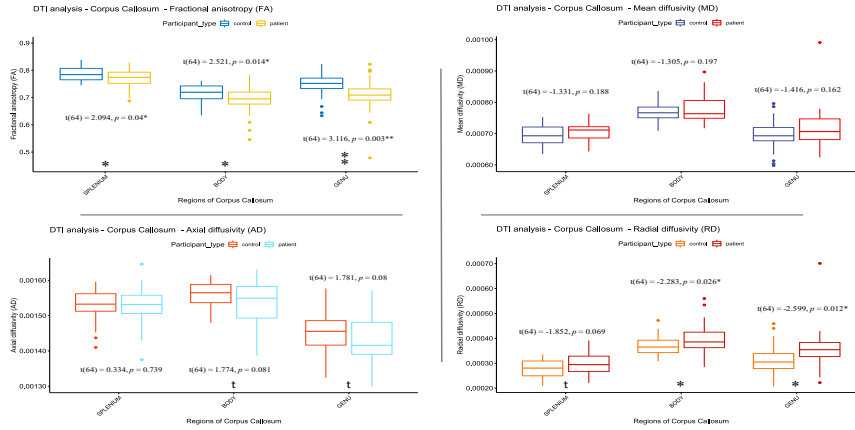


Fig. A10. DTI analysis – Corpus Callosum with its three regions SPLENIUM, BODY and GENU – patient – control division (medians + IQR). Legend – an asterisk “*” indicates a statistically significant result, whereas “t” – a tendency towards significance (I consider tendency any p -value between [0.1 - 0.051]).

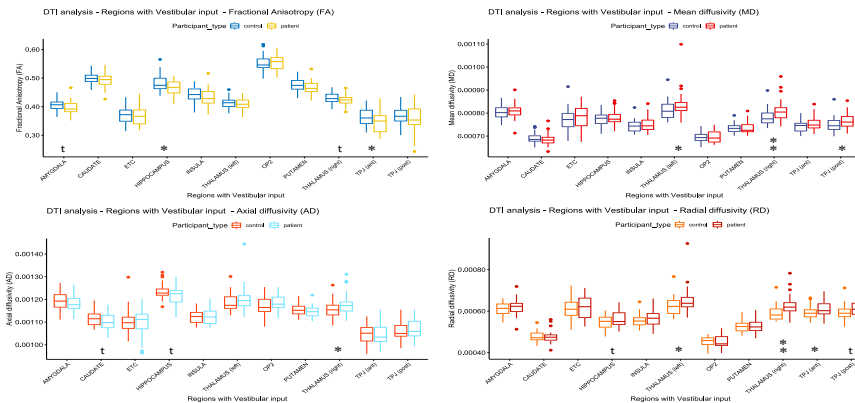


Figure. A11. DTI analysis - Vestibular regions - mean values (patient – control division). Legend – an asterisk “*” indicates a statistically significant effect of group, whereas “t” displays a tendency towards a statistically significant result (I consider tendency any p -value between [0.1 and 0.051]).

VOXELWISE ANALYSIS – VBM – Corpus Callosum and Vestibular Regions

NOTE: All individual Vestibular regions plots for WM and GM (similar to those presented for DTI analysis) are available upon reasonable request. The same applies to the individual WM CC plots.

VBM analysis – Corpus Callosum - Summary

The data from the Corpus Callosum VBM analysis are summarised in Table. A12.

Region of the Corpus Callosum	WM (VMP division)	WM (Sway division)
SPLENIUM	correl abnormal VMP to VMP, $p = 0.0713$ abnormal VMP to Sway, $p = 0.0509$ t-test normal VMP > controls, $p = 0.0615$	correl abnormal Sway to Sway, $p = 0.0538$ abnormal Sway to VMP, $p = 0.0376^*$ t-test abnormal Sway > normal Sway, $p = 0.0569$ abnormal Sway > controls, $p = 0.0192^*$
BODY	correl abnormal VMP to Sway, $p = 0.0094^{**}$ normal VMP to Sway, $p = 0.0321^*$ t-test abnormal VMP > controls, $p = 0.0105^*$ normal VMP > controls, $p = 0.0672$	correl abnormal Sway to Sway, $p = 0.0011^{**}$ abnormal Sway to VMP, $p = 0.0185^*$ t-test abnormal Sway > normal Sway, $p = 0.06$ abnormal Sway > controls, $p = 0.0032^{**}$
GENU	correl abnormal VMP to Sway, $p = 0.0093^{**}$ normal VMP to Sway, $p = 0.0347^*$ t-test abnormal VMP > controls, $p = 0.0313^*$	correl abnormal Sway to Sway, $p = 0.0008^{***}$ abnormal Sway to VMP, $p = 0.0334^*$ t-test abnormal Sway > normal Sway, $p = 0.0894$

Table. A12. Summary for CC voxelwise VBM analysis.

VBM analysis – Vestibular Regions - Summary

Brain region with Vestibular Input	GM (VMP division)	GM (Sway division)	WM (VMP division)	WM (Sway division)
AMYGDALA	correl normal VMP to VMP, $p = 0.0898$ normal VMP to EOG, $p = 0.0149^*$ t-test -	correl normal Sway to VMP, $p = 0.0897$ normal Sway to EOG, $p = 0.0046^{**}$ t-test -	correl normal VMP to Sway, $p = 0.04^*$ t-test abnormal VMP > controls, $p = 0.0597$ normal VMP > controls, $p = 0.0314^*$	correl abnormal Sway to Sway, $p = 0.0322^*$ t-test abnormal Sway > normal Sway, $p = 0.0185^*$ abnormal Sway > controls, $p = 0.0015^{***}$
CAUDATE	correl normal VMP to VMP, $p = 0.0284^*$ t-test -	correl normal Sway to EOG, $p = 0.0498^*$ t-test abnormal Sway < normal Sway, $p = 0.0932$ abnormal Sway < controls, $p = 0.0704$	correl abnormal VMP to Sway, $p = 0.0281^*$ normal VMP to Sway, $p = 0.0128^*$ t-test abnormal VMP > controls, $p = 0.0424^*$ normal VMP > controls, $p = 0.065$	correl abnormal Sway to Sway, $p = 0.0039^{**}$ t-test abnormal Sway > normal Sway, $p = 0.0189^*$ abnormal Sway > controls, $p = 0.0048^{***}$
ETC	correl normal VMP to VMP, $p = 0.0911$ abnormal VMP to EOG, $p = 0.0668$ normal VMP to EOG, $p = 0.0147^*$ t-test -	correl abnormal Sway to EOG, $p = 0.084$ normal Sway to EOG, $p = 0.0122^*$ t-test -	correl - t-test abnormal VMP > controls, $p = 0.0205^*$ normal VMP > controls, $p = 0.0266^*$	correl - t-test abnormal Sway > normal Sway, $p = 0.0073^{**}$ abnormal Sway > controls, $p = 0.0004^{***}$
HIPPOCAMPUS	correl normal VMP to VMP, $p = 0.0781$ normal VMP to EOG, $p = 0.0416^*$ t-test -	correl normal Sway to EOG, $p = 0.0316^*$ t-test -	correl normal VMP to Sway, $p = 0.0164^*$ t-test abnormal VMP > controls, $p = 0.0429^*$ normal VMP > controls, $p = 0.0978$	correl abnormal Sway to Sway, $p = 0.0916$ t-test abnormal Sway > normal Sway, $p = 0.0103^*$ abnormal Sway > controls, $p = 0.0034^{**}$
INSULA	correl abnormal VMP to EOG, $p = 0.0721$ normal VMP to EOG, $p = 0.0083^{**}$ t-test abnormal VMP < normal VMP, $p = 0.073$ abnormal VMP < controls, $p = 0.0392^*$	correl abnormal Sway to EOG, $p = 0.0509$ normal Sway to EOG, $p = 0.0025^{**}$ t-test abnormal Sway < controls, $p = 0.0931$	correl normal VMP to Sway, $p = 0.0116^*$ t-test abnormal VMP > normal VMP, $p = 0.098$ abnormal VMP > controls, $p = 0.0117^*$ normal VMP > controls, $p = 0.0443^*$	correl abnormal Sway to Sway, $p = 0.0593$ t-test abnormal Sway > normal Sway, $p = 0.0244^*$ abnormal Sway > controls, $p = 0.0023^{***}$ normal Sway > controls, $p = 0.0975$

Table. A13. Summary for VBM ROI voxelwise analysis – GM and WM.

Brain region with Vestibular Input	GM (VMP division)	GM (Sway division)	WM (VMP division)	WM (Sway division)
THALAMUS (left)	correl normal VMP to VMP, $p = 0.061$ t-test abnormal VMP < normal VMP, $p = 0.0458^*$ abnormal VMP < controls, $p = 0.012^*$	correl normal Sway to VMP, $p = 0.0841$ abnormal Sway to EOG, $p = 0.0809$ normal Sway to EOG, $p = 0.0182^*$ t-test abnormal Sway < normal Sway, $p = 0.0278^*$ abnormal Sway < controls, $p = 0.0175^*$	correl normal VMP to Sway, $p = 0.0193^*$ t-test abnormal VMP > controls, $p = 0.0614$ normal VMP > controls, $p = 0.0918$	correl - t-test abnormal Sway > normal Sway, $p = 0.0403^*$ abnormal Sway > controls, $p = 0.0076^{**}$
OP2	correl abnormal VMP to EOG, $p = 0.0298^*$ normal VMP to EOG, $p = 0.0167^*$ t-test -	correl abnormal Sway to EOG, $p = 0.053$ normal Sway to EOG, $p = 0.0064^{**}$ t-test -	correl normal VMP to Sway, $p = 0.0124^*$ t-test abnormal VMP > controls, $p = 0.0246^*$ normal VMP > controls, $p = 0.0842$	correl abnormal Sway to Sway, $p = 0.0672$ t-test abnormal Sway > normal Sway, $p = 0.02^*$ abnormal Sway > controls, $p = 0.0039^{**}$
PUTAMEN	correl abnormal VMP to EOG, $p = 0.0176^*$ normal VMP to EOG, $p = 0.003^{**}$ t-test -	correl abnormal Sway to EOG, $p = 0.0432^*$ normal Sway to EOG, $p = 0.0014^{**}$ t-test -	correl normal VMP to Sway, $p = 0.0076^{**}$ t-test abnormal VMP > controls, $p = 0.0413^*$ normal VMP > controls, $p = 0.0408^*$	correl abnormal Sway to Sway, $p = 0.0469^*$ t-test abnormal Sway > normal Sway, $p = 0.0177^*$ abnormal Sway > controls, $p = 0.0042^{**}$
THALAMUS (right)	correl normal VMP to VMP, $p = 0.0813$ normal VMP to EOG, $p = 0.045^*$ t-test abnormal VMP < normal VMP, $p = 0.0126^*$ abnormal VMP < controls, $p = 0.0069^{**}$	correl normal Sway to VMP, $p = 0.0937$ abnormal Sway to EOG, $p = 0.0635$ t-test -	correl normal VMP to Sway, $p = 0.0203^*$ t-test abnormal VMP > controls, $p = 0.0961$	correl abnormal Sway to Sway, $p = 0.0872$ t-test abnormal Sway > normal Sway, $p = 0.0429^*$ abnormal Sway > controls, $p = 0.0117^*$
TPJ (ant)	correl normal VMP to VMP, $p = 0.0733$ normal VMP to Sway, $p = 0.0623$ t-test -	correl normal Sway to VMP, $p = 0.0242^*$ normal Sway to EOG, $p = 0.0114^*$ t-test -	correl - t-test abnormal VMP > controls, $p = 0.0621$	correl normal Sway to Sway, $p = 0.0209^*$ t-test -
TPJ (post)	correl normal VMP to Sway, $p = 0.0868$ abnormal VMP to EOG, $p = 0.064$ t-test abnormal VMP < normal VMP, $p = 0.0655$	correl normal Sway to VMP, $p = 0.0412^*$ normal Sway to EOG, $p = 0.0128^*$ t-test abnormal Sway < normal Sway, $p = 0.0543$	correl - t-test abnormal VMP > normal VMP, $p = 0.0303^*$	correl normal Sway to Sway, $p = 0.0165^*$ abnormal Sway to VMP, $p = 0.0213^*$ abnormal Sway to EOG, $p = 0.0528$ t-test -

Table. A14. Summary for VBM ROI voxelwise analysis – GM and WM.

Appendix to Chapter VIII

1. Vestibular-guided Adaptation task (controls) – spatial testing (n = 13).
2. Parkinson's patients' spatial testing (n = 6).
3. Comparison between patients with Memory and (Balance) complaints and Parkinson's patients.
4. Chronic TBI patients spatial testing (n = 6).
5. Vestibular-guided Mental transformation task (n = 20).
6. Morris Water Maze task – structure for a future experiment.
7. Some further suggestions to test spatial orientation under vestibular guidance.

NOTE: All suggestions for future tasks and current design ideas/results are available upon reasonable request.

Chapter X

References

- 2020 Alzheimer's disease facts and figures. (2020). *Alzheimer's and Dementia*, 16(3), 391–460. <https://doi.org/10.1002/alz.12068>
- Agrawal, Y., Carey, J. P., Della Santina, C. C., Schubert, M. C., & Minor, L. B. (2009). Disorders of Balance and Vestibular Function in US Adults. *Archives of Internal Medicine*, 169(10), 938. <https://doi.org/10.1001/archinternmed.2009.66>
- Agrawal, Y., Pineault, K. G., & Semenov, Y. R. (2017). Health-related quality of life and economic burden of vestibular loss in older adults. *Laryngoscope Investigative Otolaryngology*, 3(1), 8–15. <https://doi.org/10.1002/liv2.129>
- Agrawal, Y., Smith, P. F., & Rosenberg, P. B. (2020). Vestibular impairment, cognitive decline and Alzheimer's disease: balancing the evidence. *Aging and Mental Health*, 24(5), 705–708. <https://doi.org/10.1080/13607863.2019.1566813>
- Aitken, P., Zheng, Y., & Smith, P. F. (2018). The modulation of hippocampal theta rhythm by the vestibular system. *Journal of Neurophysiology*, 119(2), 548–562. <https://doi.org/10.1152/jn.00548.2017>
- Akin, F. W., & Murnane, O. D. (2011). Head injury and blast exposure: Vestibular consequences. *Otolaryngologic Clinics of North America*, 44(2), 323–334. <https://doi.org/10.1016/j.otc.2011.01.005>
- Alexander, A. L., Hurley, S. A., Samsonov, A. A., Adluru, N., Hosseinbor, A. P., Mossahebi, P., Tromp, do P. m., Zakszewski, E., & Field, A. S. (2011). Characterization of Cerebral White Matter Properties Using Quantitative Magnetic Resonance Imaging Stains. *Brain Connectivity*, 1(6), 423–446. <https://doi.org/10.1089/brain.2011.0071>
- Alexander, A. L., Lee, J. E., Lazar, M., & Field, A. S. (2007). Diffusion Tensor Imaging of the Brain. *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics*, 4(July), 316–329. <https://www.sciencedirect.com/science/article/pii/S1933721307000955>
- Alhilali, L. M., Yaeger, K., Collins, M., & Fakhra, S. (2014). Detection of central white matter injury underlying vestibulopathy after mild traumatic brain injury. *Radiology*, 272(1), 224–232. <https://doi.org/10.1148/radiol.14132670>
- Allison, S. L., Fagan, A. M., Morris, J. C., & Head, D. (2016). Spatial Navigation in Preclinical Alzheimer's Disease. *Journal of Alzheimer's Disease*, 52(1), 77–90. <https://doi.org/10.3233/JAD-150855>
- Alzheimer's & Dementia: Global Resources. (2021). Alzheimer's Association - report. *Alzheimer's Association*. <https://www.alz.org/global/overview.asp>
- Angelaki, D. E., & Cullen, K. E. (2008). Vestibular system: The many facets of a multimodal sense. *Annual Review of Neuroscience*, 31, 125–150. <https://doi.org/10.1146/annurev.neuro.31.060407.125555>
- Angelaki, D. E., & Yakusheva, T. A. (2009). How Vestibular Neurons Solve the Tilt/Translation Ambiguity. *Ann N Y Acad Sci*, 1164, 19–28. <https://doi.org/10.1111/j.1749-6632.2009.03939.x>
- Anson, E., Ehrenburg, M. R., Simonsick, E. M., & Agrawal, Y. (2021). Association between vestibular function and rotational spatial orientation perception in older adults. *Journal of Vestibular Research: Equilibrium and Orientation*, 31(6), 469–478. <https://doi.org/10.3233/VES-201582>
- Anson, E., Ehrenburg, M. R., Wei, E. X., Bakar, D., Simonsick, E., & Agrawal, Y. (2019). Saccular function is associated with both angular and distance errors on the triangle completion test. *Clinical Neurophysiology*,

- 130(11), 2137–2143. <https://doi.org/10.1016/j.clinph.2019.08.027>
- Arenth, P., Russel, K., Scanlon, J., Kessler, L., & Ricker, J. (2014). Corpus Callosum integrity and neuropsychological performance after TBI: a diffusion tensor imaging study. *J Head Trauma Rehabil*, 29(2), E1–E10. <https://doi.org/10.1097/HTR.0b013e318289ede5>.Corpus
- Armstrong, R. A. (2018). Visual problems associated with traumatic brain injury. *Clinical and Experimental Optometry*, 101(6), 716–726. <https://doi.org/10.1111/cxo.12670>
- Arshad, Q., & Seemungal, B.M. (2016). Age-related vestibular loss: Current understanding and future research directions. *Frontiers in Neurology*, 7(DEC), 1–6. <https://doi.org/10.3389/fneur.2016.00231>
- Arshad, Q., Roberts, R. E., Ahmad, H., Lobo, R., Patel, M., Ham, T., Sharp, D. J., & Seemungal, B M. (2017). Patients with chronic dizziness following traumatic head injury typically have multiple diagnoses involving combined peripheral and central vestibular dysfunction. *Clinical Neurology and Neurosurgery*, 155, 17–19. <https://doi.org/10.1016/j.clineuro.2017.01.021>
- Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry - The methods. *NeuroImage*, 11(6 I), 805–821. <https://doi.org/10.1006/nimg.2000.0582>
- Atkinson, J., & Egeth, H. (1973). Right hemisphere superiority in visual orientation matching. *Canad.J.Psychol.*, 27(2), 152–158. <https://doi.org/10.1037/h0082464>
- Avillac, M., Denève, S., Olivier, E., Pouget, A., & Duhamel, J. R. (2005). Reference frames for representing visual and tactile locations in parietal cortex. *Nature Neuroscience*, 8(7), 941–949. <https://doi.org/10.1038/nn1480>
- Basser, P. J., Mattiello, J., & LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophysical Journal*, 66(1), 259–267. [https://doi.org/10.1016/S0006-3495\(94\)80775-1](https://doi.org/10.1016/S0006-3495(94)80775-1)
- Basta, D., Todt, I., Scherer, H., Clarke, A., & Ernst, A. (2005). Postural control in otolith disorders. *Human Movement Science*, 24(2), 268–279. <https://doi.org/10.1016/j.humov.2005.04.002>
- Bear, M., Connors, B., & Paradiso, M. (2016). *Neuroscience: Exploring the brain* (Fourth Edi). Walters Kluwer.
- Behrens, T. E. J., Woolrich, M. W., Jenkinson, M., Johansen-Berg, H., Nunes, R. G., Clare, S., Matthews, P. M., Brady, J. M., & Smith, S. M. (2003). Characterization and Propagation of Uncertainty in Diffusion-Weighted MR Imaging. *Magnetic Resonance in Medicine*, 50(5), 1077–1088. <https://doi.org/10.1002/mrm.10609>
- Benton, A. & Tranel, D. (1993). Visuo-perceptual, visuospatial, and visuoconstructive disorders. In *Clinical neuropsychology* (pp. 165–213).
- Berthoz, A., & Viaud-Delmon, I. (1999). Multisensory integration in spatial orientation. *Current Opinion in Neurobiology*, 9(6), 708–712. [https://doi.org/10.1016/S0959-4388\(99\)00041-0](https://doi.org/10.1016/S0959-4388(99)00041-0)
- Bertolini, G., Ramat, S., Bockisch, C. J., Marti, S., Straumann, D., & Palla, A. (2012). Is vestibular self-motion perception controlled by the velocity storage? insights from patients with chronic degeneration of the vestibulo-cerebellum. *PLoS ONE*, 7(6), 1–10. <https://doi.org/10.1371/journal.pone.0036763>
- Besnard, S., Lopez, C., Brandt, T., Denise, P., & Smith, P. F. (2015). Editorial: The vestibular system in cognitive and memory processes in mammals. *Frontiers in Integrative Neuroscience*, 9(November), 1–4. <https://doi.org/10.3389/fnint.2015.00055>
- Bigelow, R. T., & Agrawal, Y. (2015). Vestibular involvement in cognition: Visuospatial ability, attention, executive function, and memory. *Journal of Vestibular Research: Equilibrium and Orientation*, 25(2), 73–89. <https://doi.org/10.3233/VES-150544>
- Bigelow, R. T., Semenov, Y. R., Trevino, C., Ferrucci, L., Resnick, S. M., Simonsick, E. M., Xue, Q. L., & Agrawal, Y. (2015). Association between visuospatial ability and vestibular function in the Baltimore Longitudinal Study of Aging. *Journal of the American Geriatrics Society*, 63(9), 1837–1844. <https://doi.org/10.1111/jgs.13609>

- Bigler, E. D., Blatter, D. D., Gale, S. D., Ryser, D. K., Macnamara, S. E., Bailey, B. J., Hopkins, R. O., Johnson, S. C., Anderson, C. V., Russo, A. A., & Abildskov, T. J. (1996). Traumatic brain injury and memory: The role of hippocampal atrophy. *Neuropsychology*, 10(3), 333–342. <https://doi.org/10.1037/0894-4105.10.3.333>
- Biju, K., Oh, E., Rosenberg, P., Xue, Q. L., Dash, P., Haroon Burhanullah, M., & Agrawal, Y. (2022). Vestibular Function Predicts Balance and Fall Risk in Patients with Alzheimer’s Disease. *Journal of Alzheimer’s Disease*, 86(3), 1159–1168. <https://doi.org/10.3233/JAD-215366>
- Blanke, O., Perrig, S., Thut, G., Landis, T., & Seeck, M. (2000). Simple and complex vestibular responses induced by electrical cortical stimulation of the parietal cortex in humans. *Journal of Neurology Neurosurgery and Psychiatry*, 69(4), 553–556. <https://doi.org/10.1136/jnnp.69.4.553>
- Bourke, N. J., Yanez Lopez, M., Jenkins, P. O., De Simoni, S., Cole, J. H., Lally, P., Mallas, E.-J., Zhang, H., & Sharp, D. J. (2021). Traumatic brain injury: a comparison of diffusion and volumetric magnetic resonance imaging measures. *Brain Communications*, 3(2), 1–12. <https://doi.org/10.1093/braincomms/fcab006>
- Braak, H., & Braak, E. (1991). Neuropathological staging of Alzheimer-related changes. *Acta Neuropathologica*, 82(4), 239–259. <https://doi.org/10.1007/BF00308809>
- Braak, H., Alafuzoff, I., Arzberger, T., Kretschmar, H., & Del Tredici, K. (2006). Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathologica*, 112(4), 389–404. <https://doi.org/10.1007/s00401-006-0127-z>
- Braak, H., & Del Tredici, K. (2015). The preclinical phase of the pathological process underlying sporadic Alzheimer’s disease. *Brain*, 138(10), 2814–2833. <https://doi.org/10.1093/brain/awv236>
- Brandt, T., Dieterich, M., & Danek, A. (1994). Vestibular cortex lesions affect the perception of verticality. *Annals of Neurology*, 35(4), 403–412. <https://doi.org/10.1002/ana.410350406>
- Brandt, T., & Dietrich, M. (1999). The vestibular cortex. Its locations, functions, and disorders. *Annals New York Academy of Sciences*, 871, 293–312.
- Brandt, T., Schautzer, F., Hamilton, D. A., Brüning, R., Markowitsch, H. J., Kalla, R., Darlington, C., Smith, P., & Strupp, M. (2005). Vestibular loss causes hippocampal atrophy and impaired spatial memory in humans. *Brain*, 128(11), 2732–2741. <https://doi.org/10.1093/brain/awh617>
- Brandt, T., & Dieterich, M. (2017). The dizzy patient: Don’t forget disorders of the central vestibular system. *Nature Reviews Neurology*, 13(6), 352–362. <https://doi.org/10.1038/nrneurol.2017.58>
- Brandt, T., Zwergal, A., & Glasauer, S. (2017). 3-D spatial memory and navigation: Functions and disorders. *Current Opinion in Neurology*, 30(1), 90–97. <https://doi.org/10.1097/WCO.0000000000000415>
- Brevern, M. von, Faldon, M. E., Brookes, G. B., & Gresty, M. A. (1997). Evaluating 3D Semicircular Canal Function by Perception of Rotation. *The American Journal of Otology*, 18, 484–493.
- Britten, K. H. (2008). Mechanisms of self-motion perception. *Annual Review of Neuroscience*, 31, 389–410. <https://doi.org/10.1146/annurev.neuro.29.051605.112953>
- Bronstein, A. M., Grunfeld, E. A., Faldon, M., & Okada, T. (2008). Reduced self-motion perception in patients with midline cerebellar lesions. *NeuroReport*, 19(6), 91–93.
- Bronstein, A. M., Patel, M., & Arshad, Q. (2015). A brief review of the clinical anatomy of the vestibular-ocular connections - How much do we know? *Eye (Basingstoke)*, 29(2), 163–170. <https://doi.org/10.1038/eye.2014.262>
- Buckley, T., Murray, N. G., Munkasy, B. A., Oldham, J. R., Evans, K. M., & Clouse, B. (2021). Impairments in Dynamic Postural Control across Concussion Clinical Milestones. *Journal of Neurotrauma*, 38(1), 86–93. <https://doi.org/10.1089/neu.2019.6910>
- Burgess, N., Becker, S., King, J. A., & O’Keefe, J. (2001). Memory for events and their spatial context: Models and experiments. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 356(1413), 1493–1503. <https://doi.org/10.1098/rstb.2001.0948>

- Burgess, N., Maguire, E. A., & O'Keefe, J. (2002). The human hippocampus and spatial and episodic memory. *Neuron*, 35(4), 625–641. [https://doi.org/10.1016/S0896-6273\(02\)00830-9](https://doi.org/10.1016/S0896-6273(02)00830-9)
- Byrne, P., Becker, S., & Burgess, N. (2007). Remembering the past and imagining the future: A neural model of spatial memory and imagery. *Psychological Review*, 114(2), 340–375. <https://doi.org/10.1037/0033-295X.114.2.340>
- Calzolari, E., Chepishcheva, M., Smith, R. M., Mahmud, M., Hellyer, P. J., Tahtis, V., Arshad, Q., Jolly, A., Wilson, M., Rust, H., Sharp, D. J., & Seemungal, B. M. (2021). Vestibular agnosia in traumatic brain injury and its link to imbalance. *Brain : A Journal of Neurology*, 144(1), 128–143. <https://doi.org/10.1093/brain/awaa386>
- Camicioli, R., Howieson, D., Lehman, S., & Kaye, J. (1997). Talking while walking: The effect of a dual task in aging and Alzheimer's disease. *Neurology*, 48(4), 955–958. <https://doi.org/10.1212/WNL.48.4.955>
- Carriot, J., Jamali, M., & Cullen, K. E. (2015). Rapid adaptation of multisensory integration in vestibular pathways. *Frontiers in Systems Neuroscience*, 9(April), 1–5. <https://doi.org/10.3389/fnsys.2015.00059>
- Catena, R. D., Van Donkelaar, P., Halterman, C. I., & Chou, L. S. (2009). Spatial orientation of attention and obstacle avoidance following concussion. *Experimental Brain Research*, 194(1), 67–77. <https://doi.org/10.1007/s00221-008-1669-1>
- Chamelian, L., & Feinstein, A. (2004). Outcome after mild to moderate traumatic brain injury: The role of dizziness. *Archives of Physical Medicine and Rehabilitation*, 85(10), 1662–1666. <https://doi.org/10.1016/j.apmr.2004.02.012>
- Chan, D., Gallaher, L. M., Moodley, K., Minati, L., Burgess, N., & Hartley, T. (2016). The 4 mountains test: A short test of spatial memory with high sensitivity for the diagnosis of pre-dementia Alzheimer's disease. *Journal of Visualized Experiments*, 2016(116), 1–11. <https://doi.org/10.3791/54454>
- Chen, A., DeAngelis, G. C., & Angelaki, D. E. (2011). Representation of vestibular and visual cues to self-motion in ventral intraparietal cortex. *Journal of Neuroscience*, 31(33), 12036–12052. <https://doi.org/10.1523/JNEUROSCI.0395-11.2011>
- Chen, G. (2018). Identifying posture cells in the brain. *Science*, 362(6414), 520–521. <https://doi.org/10.1126/science.aav3819>
- Chen, G., Lu, Y., King, J. A., Cacucci, F., & Burgess, N. (2019). Differential influences of environment and self-motion on place and grid cell firing. *Nature Communications*, 10, 630.
- Cheng, Z., & Gu, Y. (2018). Vestibular system and self-motion. *Frontiers in Cellular Neuroscience*, 12(November), 1–9. <https://doi.org/10.3389/fncel.2018.00456>
- Chepishcheva, M. K. (2021). The Vestibular system and its implications in spatial orientation and postural control. *SSRN Neuroscience, Sensory & Motor Neurobiology EJournal*. <https://doi.org/http://dx.doi.org/10.2139/ssrn.3988338> (pre-print)
- Chepishcheva, M. K. (2022). Spatial Orientation, Postural Control and the Vestibular System in Healthy Elderly and Alzheimer's Dementia. *SSRN Neurodegeneration & Nervous System Aging EJournal*. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4007515 (pre-print)
- Chepishcheva, M. K. (2023). Spatial Orientation, Postural Control and the Vestibular System in Healthy Elderly and Alzheimer's Dementia. *PeerJ*, May 2 (11:e15040). <https://doi.org/10.7717/peerj.15040>
- Chong, R. K. Y., Horak, F. B., Frank, J., & Kaye, J. (1999). Sensory organization for balance: Specific deficits in Alzheimer's but not in Parkinson's disease. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, 54(3). <https://doi.org/10.1093/gerona/54.3.M122>
- Chow, M. R., Ayiotis, A. I., Schoo, D. P., Gimmon, Y., Lane, K. E., Morris, B. J., Rahman, M. A., Valentin, N. S., Boutros, P. J., Bowditch, S. P., Ward, B. K., Sun, D. Q., Treviño Guajardo, C., Schubert, M. C., Carey, J. P., & Della Santina, C. C. (2021). Posture, Gait, Quality of Life, and Hearing with a Vestibular Implant. *New England Journal of Medicine*, 384(6), 521–532. <https://doi.org/10.1056/nejmoa2020457>

- Chrastil, E. R., & Warren, W. H. (2017). Rotational error in path integration: encoding and execution errors in angle reproduction. *Experimental Brain Research*, 235(6), 1885–1897. <https://doi.org/10.1007/s00221-017-4910-y>
- Churchill, N. W., Hutchison, M. G., Graham, S. J., & Schweizer, T. A. (2021). Insular Connectivity Is Associated With Self-Appraisal of Cognitive Function After a Concussion. *Frontiers in Neurology*, 12(May), 1–14. <https://doi.org/10.3389/fneur.2021.653442>
- Clark, B. J., & Harvey, R. E. (2016). Do the anterior and lateral thalamic nuclei make distinct contributions to spatial representation and memory? *Neurobiology of Learning and Memory*, 133, 69–78. <https://doi.org/10.1016/j.nlm.2016.06.002>
- Clay, F., Howett, D., FitzGerald, J., Fletcher, P., Chan, D., & Price, A. (2020). Use of Immersive Virtual Reality in the Assessment and Treatment of Alzheimer’s Disease: A Systematic Review. *Journal of Alzheimer’s Disease*, 75(1), 23–43. <https://doi.org/10.3233/jad-191218>
- Cogné, M., Taillade, M., N’Kaoua, B., Tarruella, A., Klinger, E., Larrue, F., Sauzéon, H., Joseph, P. A., & Sorita, E. (2017). The contribution of virtual reality to the diagnosis of spatial navigation disorders and to the study of the role of navigational aids: A systematic literature review. *Annals of Physical and Rehabilitation Medicine*, 60(3), 164–176. <https://doi.org/10.1016/j.rehab.2015.12.004>
- Cole, J. H., Jolly, A., De Simoni, S., Bourke, N., Patel, M. C., Scott, G., & Sharp, D. J. (2018). Spatial patterns of progressive brain volume loss after moderate-severe traumatic brain injury. *Brain*, 141(3), 822–836. <https://doi.org/10.1093/brain/awx354>
- Cole, J. H., Leech, R., & Sharp, D. J. (2015). Prediction of brain age suggests accelerated atrophy after traumatic brain injury. *Annals of Neurology*, 77(4), 571–581. <https://doi.org/10.1002/ana.24367>
- Colombo, D., Serino, S., Tuena, C., Pedrolì, E., Dakanalis, A., Cipresso, P., & Riva, G. (2017). Egocentric and allocentric spatial reference frames in aging: A systematic review. *Neuroscience and Biobehavioral Reviews*, 80(February), 605–621. <https://doi.org/10.1016/j.neubiorev.2017.07.012>
- Coughlan, G., Laczó, J., Hort, J., Minihane, A. M., & Hornberger, M. (2018). Spatial navigation deficits — Overlooked cognitive marker for preclinical Alzheimer disease? *Nature Reviews Neurology*, 14(8), 496–506. <https://doi.org/10.1038/s41582-018-0031-x>
- Coughlan, G., Plumb, W., Zhukovsky, P., Aung, M. H., & Hornberger, M. (2022). Vestibular contribution to path integration deficits in ‘at-genetic-risk’ for Alzheimer’s disease. *MedRxiv*, 2022.04.29.22274496. <http://medrxiv.org/content/early/2022/05/02/2022.04.29.22274496.abstract>
- Crétual, A. (2015). Which biomechanical models are currently used in standing posture analysis? *Neurophysiologie Clinique*, 45(4–5), 285–295. <https://doi.org/10.1016/j.neucli.2015.07.004>
- Cronin, T., Arshad, Q., & Seemungal, B. M. (2017). Vestibular deficits in neurodegenerative disorders: Balance, dizziness, and spatial disorientation. *Frontiers in Neurology*, 8(OCT). <https://doi.org/10.3389/fneur.2017.00538>
- Cullen, K. E. (2011). The neural encoding of self-motion. *Current Opinion in Neurobiology*, 21(4), 587–595. <https://doi.org/10.1016/j.conb.2011.05.022>
- Cullen, K. E. (2012). The vestibular system: multimodal integration and encoding of self-motion for motor control. *Trends in Neurosciences*, 35(3), 185–196. <https://doi.org/10.1016/j.tins.2011.12.001>
- Cullen, K. E. (2019). Vestibular processing during natural self-motion: implications for perception and action. *Nature Reviews Neuroscience*, 20(June). <https://doi.org/10.1038/s41583-019-0153-1>
- Cullen, K. E., Brooks, J. X., Jamali, M., Carriot, J., & Massot, C. (2011). Internal models of self-motion: Computations that suppress vestibular reafference in early vestibular processing. *Experimental Brain Research*, 210(3–4), 377–388. <https://doi.org/10.1007/s00221-011-2555-9>
- Cullen, K. E., & Roy, J. E. (2004). Signal Processing in the Vestibular System during Active Versus Passive Head Movements. *Journal of Neurophysiology*, 91(5), 1919–1933. <https://doi.org/10.1152/jn.00988.2003>

- Cushman, L. A., Stein, K., & Duffy, C. J. (2008). Detecting navigational deficits in cognitive aging and Alzheimer disease using virtual reality. *Neurology*, 71(12), 888–895. <https://doi.org/10.1212/01.wnl.0000326262.67613.fe>
- da Costa RQM, Pompeu JE, de Mello DD, Moretto E, Rodrigues FZ, Dos Santos MD, Nitrini R, Morganti F, Brucki SMD. Two new virtual reality tasks for the assessment of spatial orientation Preliminary results of tolerability, sense of presence and usability. *Dement Neuropsychol*. 2018 Apr-Jun;12(2):196-204. doi: 10.1590/1980-57642018dn12-020013. PMID: 29988338; PMCID: PMC6022991.
- Davies, R. A., & Luxon, L. M. (1995). Dizziness following head injury: A neuro-otological study. *Journal of Neurology*, 242(4), 222–230. <https://doi.org/10.1007/BF00919595>
- Davis, AE, Gimenez, AM & Therrien, B. (2001). Effects of Entorhinal Cortex Lesions on Sensory Integration and Spatial Learning. *Nursing Research*, 50(2), 77–85.
- Denby, E., Murphy, D., Busuttil, W., Sakel, M., & Wilkinson, D. (2020). Neuropsychiatric outcomes in UK military veterans with mild traumatic brain injury and vestibular dysfunction. *Journal of Head Trauma Rehabilitation*, 35(1), 57–65. <https://doi.org/10.1097/HTR.0000000000000468>
- Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, 31(3), 968–980. <https://doi.org/10.1016/j.neuroimage.2006.01.021>
- Destrieux, C., Fischl, B., Dale, A., & Halgren, E. (2010). Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *NeuroImage*, 53(1), 1–15. <https://doi.org/10.1016/j.neuroimage.2010.06.010>
- Dieterich, M., Bense, S., Lutz, S., Drzezga, A., Stephan, T., Bartenstein, P., & Brandt, T. (2003). Dominance for vestibular cortical function in the non-dominant hemisphere. *Cerebral Cortex*, 13(9), 994–1007. <https://doi.org/10.1093/cercor/13.9.994>
- Dieterich, M., & Brandt, T. (2018). Global orientation in space and the lateralization of brain functions. *Current Opinion in Neurology*, 31(1), 96–104. <https://doi.org/10.1097/WCO.0000000000000516>
- Douaud, G., Smith, S., Jenkinson, M., Behrens, T., Johansen-Berg, H., Vickers, J., James, S., Voets, N., Watkins, K., Matthews, P. M., & James, A. (2007). Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. *Brain*, 130(9), 2375–2386. <https://doi.org/10.1093/brain/awm184>
- Dijkoningen, D., Leunissen, I., Caeyenberghs, K., Hoogkamer, W., Sunaert, S., Duysens, J., & Swinnen, S. P. (2015). Regional volumes in brain stem and cerebellum are associated with postural impairments in young brain-injured patients. *Human Brain Mapping*, 36(12), 4897–4909. <https://doi.org/10.1002/hbm.22958>
- Dubois, B., Feldman, H. H., Jacova, C., Hampel, H., Molinuevo, J. L., Blennow, K., Dekosky, S. T., Gauthier, S., Selkoe, D., Bateman, R., Cappa, S., Crutch, S., Engelborghs, S., Frisoni, G. B., Fox, N. C., Galasko, D., Habert, M. O., Jicha, G. A., Nordberg, A., ... Cummings, J. L. (2014). Advancing research diagnostic criteria for Alzheimer's disease: The IWG-2 criteria. *The Lancet Neurology*, 13(6), 614–629. [https://doi.org/10.1016/S1474-4422\(14\)70090-0](https://doi.org/10.1016/S1474-4422(14)70090-0)
- Duffy, C. J. (1998). MST neurons respond to optic flow and translational movement. *Journal of Neurophysiology*, 80(4), 1816–1827. <https://doi.org/10.1152/jn.1998.80.4.1816>
- Eatock, R. A., & Songer, J. E. (2011). Vestibular hair cells and afferents: Two channels for head motion signals. In *Annual Review of Neuroscience* (Vol. 34). <https://doi.org/10.1146/annurev-neuro-061010-113710>
- Edlow, B. L., Copen, W. A., Izzy, S., Bakhadirov, K., van der Kouwe, A., Glenn, M. B., Greenberg, S. M., Greer, D. M., & Wu, O. (2016). Diffusion tensor imaging in acute-to-subacute traumatic brain injury: A longitudinal analysis. *BMC Neurology*, 16(1), 1–11. <https://doi.org/10.1186/s12883-015-0525-8>
- Eichenbaum, H. (2014). Time cells in the hippocampus: A new dimension for mapping memories. *Nature Reviews Neuroscience*, 15(11), 732–744. <https://doi.org/10.1038/nrn3827>

- Eickhoff, S. B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R., Amunts, K., & Zilles, K. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage*, 25(4), 1325–1335. <https://doi.org/10.1016/j.neuroimage.2004.12.034>
- Eickhoff, S. B., Weiss, P. H., Amunts, K., Fink, G. R., & Zilles, K. (2006). Identifying human parieto-insular vestibular cortex using fMRI and cytoarchitectonic mapping. *Human Brain Mapping*, 27(7), 611–621. <https://doi.org/10.1002/hbm.20205>
- Ekstrom, A. D., Huffman, D. J., & Starrett, M. (2017). Interacting networks of brain regions underlie human spatial navigation: A review and novel synthesis of the literature. *Journal of Neurophysiology*, 118(6), 3328–3344. <https://doi.org/10.1152/jn.00531.2017>
- Epstein, R. A., Patai, E. Z., Julian, J. B., & Spiers, H. J. (2017). The cognitive map in humans: Spatial navigation and beyond. *Nature Neuroscience*, 20(11), 1504–1513. <https://doi.org/10.1038/nn.4656>
- Fagerholm, E. D., Hellyer, P. J., Scott, G., Leech, R., & Sharp, D. J. (2015). Disconnection of network hubs and cognitive impairment after traumatic brain injury. *Brain*, 138(6), 1696–1709. <https://doi.org/10.1093/brain/awv075>
- Farrell, M. J., & Robertson, I. H. (2000). The automatic updating of egocentric spatial relationships and its impairment due to right posterior cortical lesions. *Neuropsychologia*, 38(5), 585–595. [https://doi.org/10.1016/S0028-3932\(99\)00123-2](https://doi.org/10.1016/S0028-3932(99)00123-2)
- Feldman, H. M., Yeatman, J. D., Lee, E. S., Barde, L. H. F., & Gaman-Bean, S. (2010). Diffusion Tensor Imaging: A Review for Pediatric Researchers and Clinicians. *Journal of Developmental and Behavioral Pediatrics*, 31(4), 346–356. <https://doi.org/10.1097/DBP.0b013e3181dcaa8b>
- Fernandez-Baizan, C., Diaz-Caceres, E., Arias, J. L., & Mendez, M. (2019). Egocentric and allocentric spatial memory in healthy aging: Performance on real-world tasks. *Brazilian Journal of Medical and Biological Research*, 52(4), 1–7. <https://doi.org/10.1590/1414-431x20198041>
- Fernandez, C., & Goldberg, J. M. (1971). Physiology of peripheral neurons innervating semicircular canals of the squirrel monkey. II. Response to sinusoidal stimulation and dynamics of peripheral vestibular system. *Journal of Neurophysiology*, 34(4), 661–675. <https://doi.org/10.1152/jn.1971.34.4.661>
- Fernandez, C., & Goldberg, J. M. (1976). Physiology of peripheral neurons innervating otolith organs of the squirrel monkey. I. Response to static tilts and to long-duration centrifugal force. *J. Neurophysiol.*, 39, 985–995. <https://doi.org/10.1152/jn.1976.39.5.985>
- Ferrè, E. R., Longo, M. R., Fiori, F., & Haggard, P. (2013). Vestibular modulation of spatial perception. *Frontiers in Human Neuroscience*, 7(OCT), 1–7. <https://doi.org/10.3389/fnhum.2013.00660>
- Fife, T. D., & Kalra, D. (2015). Persistent vertigo and dizziness after mild traumatic brain injury. *Annals of the New York Academy of Sciences*, 1343(1), 97–105. <https://doi.org/10.1111/nyas.12678>
- Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., & Dale, A. M. (2002). Whole Brain Segmentation. *Neuron*, 33(3), 341–355. [https://doi.org/10.1016/s0896-6273\(02\)00569-x](https://doi.org/10.1016/s0896-6273(02)00569-x)
- Fischl, B., Sereno, M. I., & Dale, A. M. (1999a). Cortical surface-based analysis. I. Segmentation and Surface Reconstruction. *NeuroImage*, 9(2), 195–207. <http://www.ncbi.nlm.nih.gov/pubmed/9931269>
- Fischl, B., Sereno, M. I., & Dale, A. M. (1999b). Cortical Surface-Based Analysis. II: Inflation, Flattening, and a Surface-Based Coordinate System. *NeuroImage*, 207, 195–207.
- Fischl, B., Van Der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D. H., Busa, E., Seidman, L. J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B., & Dale, A. M. (2004). Automatically Parcellating the Human Cerebral Cortex. *Cerebral Cortex*, 14(1), 11–22. <https://doi.org/10.1093/cercor/bhg087>
- Folstein, M., Folstein, S., & McHugh, P. (1975). "MINI-MENTAL STATE" - A PRACTICAL METHOD FOR GRADING THE COGNITIVE STATE OF PATIENTS FOR THE CLINICIAN*. *Journal of Psychiatric*

- Frank, S. M., & Greenlee, M. W. (2018). The parieto-insular vestibular cortex in humans: More than a single area? *Journal of Neurophysiology*, 120(3), 1438–1450. <https://doi.org/10.1152/jn.00907.2017>
- Frank, S. M., Wirth, A. M., & Greenlee, M. W. (2016). Visual-vestibular processing in the human Sylvian fissure. *Journal of Neurophysiology*, 116(2), 263–271. <https://doi.org/10.1152/jn.00009.2016>
- Franke, L. M., Walker, W. C., Cifu, D. X., Ochs, A. L., & Lew, H. L. (2012). Sensorintegrative dysfunction underlying vestibular disorders after traumatic brain injury: A review. *Journal of Rehabilitation Research and Development*, 49(7), 985–994. <https://doi.org/10.1682/JRRD.2011.12.0250>
- Gale, S. D., Baxter, L., Roundy, N., & Johnson, S. C. (2005). Traumatic brain injury and grey matter concentration: A preliminary voxel based morphometry study. *Journal of Neurology, Neurosurgery and Psychiatry*, 76(7), 984–988. <https://doi.org/10.1136/jnnp.2004.036210>
- Gale, S. D., Burr, R. B., Bigler, E. D., & Blatter, D. (1993). Fornix degeneration and memory in traumatic brain injury. *Brain Research Bulletin*, 32(4), 345–349. [https://doi.org/10.1016/0361-9230\(93\)90198-K](https://doi.org/10.1016/0361-9230(93)90198-K)
- Gandhi, P., Klatt, B. N., & Agrawal, Y. (2020). Physical and Vestibular Physical Therapy Referrals in People With Alzheimer's Disease. *Alzheimer Disease & Associated Disorders, Publish Ah*(00), 1–3. <https://doi.org/10.1097/wad.0000000000000390>
- Ghajari, M., Hellyer, P. J., & Sharp, D. J. (2017). Computational modelling of traumatic brain injury predicts the location of chronic traumatic encephalopathy pathology. *Brain*, 140(2), 333–343. <https://doi.org/10.1093/brain/aww317>
- Goldberg, J. M., Wilson, V. J., Cullen, K. E., Angelaki, D. E., Broussard, D. M., Buttner-Ennever, J., Fukushima, K., & Minor, L. B. (2012). *The Vestibular System: A Sixth Sense*.
- Grabherr, L., Nicoucar, K., Mast, F. W., & Merfeld, D. M. (2008). Vestibular thresholds for yaw rotation about an earth-vertical axis as a function of frequency. *Experimental Brain Research*, 186(4), 677–681. <https://doi.org/10.1007/s00221-008-1350-8>
- Graham, N. S. N., Jolly, A., Zimmerman, K., Bourke, N. J., Scott, G., Cole, J. H., Schott, J. M., & Sharp, D. J. (2020). Diffuse axonal injury predicts neurodegeneration after moderate-severe traumatic brain injury. *Brain*, 143(12), 3685–3698. <https://doi.org/10.1093/brain/awaa316>
- Green, A. M., & Angelaki, D. E. (2003). Resolution of Sensory Ambiguities for Gaze Stabilization Requires a Second Neural Integrator. *Journal of Neuroscience*, 23(28), 9265–9275. <https://doi.org/10.1523/jneurosci.23-28-09265.2003>
- Grüsser, O. J., Pause, M., & Schreier, U. (1990). Vestibular neurones in the parieto-insular cortex of monkeys (Macaca fascicularis): visual and neck receptor responses. *The Journal of Physiology*, 430(1), 559–583. <https://doi.org/10.1113/jphysiol.1990.sp018307>
- Gu, X., Hof, P. R., Friston, K. J., & Fan, J. (2013). Anterior insular cortex and emotional awareness. *Journal of Comparative Neurology*, 521(15), 3371–3388. <https://doi.org/10.1002/cne.23368>
- Guedry, F. E. (1974). Psychophysics of Vestibular Sensation. In *Handbook of Sensory Physiology, Part 2, Chapter 1* (pp. 3–154). https://doi.org/10.1007/978-3-642-65920-1_1
- Guldin, W. O., & Grüsser, O. J. (1998). Is there a vestibular cortex? *Trends in Neurosciences*, 21(6), 254–259. [https://doi.org/10.1016/S0166-2236\(97\)01211-3](https://doi.org/10.1016/S0166-2236(97)01211-3)
- Guskiewicz, K. M., Perrin, D. H., & Gansneder, B. M. (1996). Effect of mild head injury on postural stability in athletes. *Journal of Athletic Training*, 31(4), 300–306.
- Haddad, J. M., Rietdyk, S., Claxton, L. J., & Huber, J. E. (2013). Task-dependent postural control throughout the lifespan. *Exercise and Sport Sciences Reviews*, 41(2), 123–132. <https://doi.org/10.1097/JES.0b013e3182877cc8>
- Ham, T. E., & Sharp, D. J. (2012). How can investigation of network function inform rehabilitation after

- traumatic brain injury? *Current Opinion in Neurology*, 25(6), 662–669.
<https://doi.org/10.1097/WCO.0b013e328359488f>
- Han, K., Chapman, S. B., & Krawczyk, D. C. (2015). Altered amygdala connectivity in individuals with chronic traumatic brain injury and comorbid depressive symptoms. *Frontiers in Neurology*, 6(NOV), 1–22.
<https://doi.org/10.3389/fneur.2015.00231>
- Harris, M. A., & Wolbers, T. (2013). How age-related strategy switching deficits affect wayfinding in complex environments. *Neurobiology of Aging*, 35(5), 1095–1102.
<https://doi.org/10.1016/j.neurobiolaging.2013.10.086>
- Hartley, T., Lever, C., Burgess, N., & O’Keefe, J. (2014). Space in the brain: How the hippocampal formation supports spatial cognition. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 369(1635). <https://doi.org/10.1098/rstb.2012.0510>
- Hartley, T., Maguire, E. A., Spiers, H. J., & Burgess, N. (2003). The well-worn route and the path less traveled: Distinct neural bases of route following and wayfinding in humans. *Neuron*, 37(5), 877–888.
[https://doi.org/10.1016/S0896-6273\(03\)00095-3](https://doi.org/10.1016/S0896-6273(03)00095-3)
- Harun, A., Oh, E. S., Bigelow, R. T., Studenski, S., & Agrawal, Y. (2016). Vestibular Impairment in Dementia. *Otology and Neurotology*, 37(8), 1137–1142. <https://doi.org/10.1097/MAO.0000000000001157>
- Hellström, T., Westlye, L. T., Kaufmann, T., Trung Doan, N., Søbørg, H. L., Sigurdardottir, S., Nordhøy, W., Helseth, E., Andreassen, O. A., & Andelic, N. (2017). White matter microstructure is associated with functional, cognitive and emotional symptoms 12 months after mild traumatic brain injury. *Scientific Reports*, 7(1), 1–14. <https://doi.org/10.1038/s41598-017-13628-1>
- Henderson, Victor W., Mack, Wendy, & Williams, B. W. (1989). Spatial Disorientation in Alzheimer’s Disease. *Arch Neurol.*, 46(4), 391–394.
- Herbet, G., Zemmoura, I., & Duffau, H. (2018). Functional Anatomy of the Inferior Longitudinal Fasciculus: From Historical Reports to Current Hypotheses. *Frontiers in Neuroanatomy*, 12(September), 1–15.
<https://doi.org/10.3389/fnana.2018.00077>
- Hitier, M., Besnard, S., & Smith, P. F. (2014). Vestibular pathways involved in cognition. *Frontiers in Integrative Neuroscience*, 8(JUL), 1–16. <https://doi.org/10.3389/fnint.2014.00059>
- Hodgetts, C. J., Postans, M., Shine, J. P., Jones, D. K., Lawrence, A. D., & Graham, K. S. (2015). Dissociable roles of the inferior longitudinal fasciculus and fornix in face and place perception. *ELife*, 4(AUGUST2015), 1–25. <https://doi.org/10.7554/eLife.07902>
- Hodgetts, C. J., Postans, M., Warne, N., Varnava, A., Lawrence, A. D., & Graham, K. S. (2017). Distinct contributions of the fornix and inferior longitudinal fasciculus to episodic and semantic autobiographical memory. *Cortex*, 94, 1–14. <https://doi.org/10.1016/j.cortex.2017.05.010>
- Holden, H. M., & Gilbert, P. E. (2012). Less efficient pattern separation may contribute to age-related spatial memory deficits. *Frontiers in Aging Neuroscience*, 4(MAY), 1–6.
<https://doi.org/10.3389/fnagi.2012.00009>
- Hua, K., Zhang, J., Wakana, S., Jiang, H., Li, X., Reich, D. S., Calabresi, P. A., Pekar, J. J., van Zijl, P. C. M., & Mori, S. (2008). Tract probability maps in stereotaxic spaces: Analyses of white matter anatomy and tract-specific quantification. *NeuroImage*, 39(1), 336–347. <https://doi.org/10.1016/j.neuroimage.2007.07.053>
- Hulkower, M. B., Poliak, D. B., Rosenbaum, S. B., Zimmerman, M. E., & Lipton, M. L. (2013). A decade of DTI in traumatic brain injury: 10 years and 100 articles later. *American Journal of Neuroradiology*, 34(11), 2064–2074. <https://doi.org/10.3174/ajnr.A3395>
- Hummel, N., Hüfner, K., Stephan, T., Linn, J., Kremmyda, O., Brandt, T., & Flanagan, V. L. (2014). Vestibular loss and balance training cause similar changes in human cerebral white matter fractional anisotropy. *PLoS ONE*, 9(4), 1–11. <https://doi.org/10.1371/journal.pone.0095666>
- Hwang, K., Bertolero, M. A., Liu, W. B., & D’Esposito, M. (2017). The human thalamus is an integrative hub

- for functional brain networks. *Journal of Neuroscience*, 37(23), 5594–5607. <https://doi.org/10.1523/JNEUROSCI.0067-17.2017>
- Iaria, G., Palermo, L., Committeri, G., & Barton, J. J. S. (2009). Age differences in the formation and use of cognitive maps. *Behavioural Brain Research*, 196(2), 187–191. <https://doi.org/10.1016/j.bbr.2008.08.040>
- Iaria, G., Petrides, M., Dagher, A., Pike, B., & Bohbot, V. D. (2003). Cognitive strategies dependent on the hippocampus and caudate nucleus in human navigation: Variability and change with practice. *Journal of Neuroscience*, 23(13), 5945–5952. <https://doi.org/10.1523/jneurosci.23-13-05945.2003>
- Ibitoye, R. T., Mallas, E. J., Bourke, N. J., Kaski, D., Bronstein, A. M., & Sharp, D. J. (2023). The human vestibular cortex: functional anatomy of OP2, its connectivity and the effect of vestibular disease. *Cerebral Cortex (New York, N.Y. : 1991)*, 33(3), 567–582. <https://doi.org/10.1093/cercor/bhac085>
- Jacob, A., Tward, D. J., Resnick, S., Smith, P. F., Lopez, C., Rebello, E., Wei, E. X., Tilak Ratnanather, J., & Agrawal, Y. (2020). Vestibular function and cortical and sub-cortical alterations in an aging population. *Heliyon*, 6(8). <https://doi.org/10.1016/j.heliyon.2020.e04728>
- Jacob, P., Poucet, B., Liberge, M., Save, E., & Sargolini, F. (2014). Vestibular control of entorhinal cortex activity in spatial navigation. *Frontiers in Integrative Neuroscience*, 8(June), 1–9. <https://doi.org/10.3389/fnint.2014.00038>
- Ji, L., & Zhai, S. (2018). Aging and the peripheral vestibular system. *Journal of Otology*, 13(4), 138–140. <https://doi.org/10.1016/j.joto.2018.11.006>
- Johnson, D. K., Storandt, M., Morris, J. C., & Galvin, J. E. (2009). Longitudinal Study of the Transition From Healthy Aging to Alzheimer's Disease. *Arch Neurol.*, 66(10), 1254–1259.
- Johnson, V.E., Stewart, W., & Smith, D. H. (2013). Axonal Pathology in Traumatic Brain Injury. *Experimental Neurology*, 246, 35–43. <https://doi.org/10.1016/j.expneurol.2012.01.013>
- Jolly, A. (2020). *Investigating working memory impairment after traumatic brain injury*, PhD thesis
- Jolly, A., Balaet, M., Azor, A., Friedland, D., Sandrone, S., Graham, N., Zimmerman, K., & Sharp, D. J. (2021). Detecting axonal injury in individual patients after traumatic brain injury. *Brain : A Journal of Neurology*, 144(1), 92–113. <https://doi.org/10.1093/brain/awaa372>
- Kahane, P., Hoffmann, D., Minotti, L., & Berthoz, A. (2003). Reappraisal of the Human Vestibular Cortex by Cortical Electrical Stimulation Study. *Annals of Neurology*, 54(5), 615–624. <https://doi.org/10.1002/ana.10726>
- Kalová, E., Vlček, K., Jarolímová, E., & Bureš, J. (2005). Allothetic orientation and sequential ordering of places is impaired in early stages of Alzheimer's disease: Corresponding results in real space tests and computer tests. *Behavioural Brain Research*, 159(2), 175–186. <https://doi.org/10.1016/j.bbr.2004.10.016>
- Kamil, R. J., Jacob, A., Ratnanather, J. T., Resnick, S. M., & Agrawal, Y. (2018). Vestibular Function and Hippocampal Volume in the Baltimore Longitudinal Study of Aging (BLSA). *Otology and Neurotology*, 39(6), 765–771. <https://doi.org/10.1097/MAO.0000000000001838>
- Karmali, F., Haburcakova, C., Gong, W., Della Santina, C. C., Merfeld, D. M., & Lewis, R. F. (2021). An implanted vestibular prosthesis improves spatial orientation in animals with severe vestibular damage. *Journal of Neuroscience*, 41(17), 3879–3888. <https://doi.org/10.1523/JNEUROSCI.2204-20.2021>
- Kaski, D., Quadir, S., Nigmatullina, Y., Malhotra, P. A., Bronstein, A. M., & Seemungal, B.M. (2016). Temporoparietal encoding of space and time during vestibular-guided orientation. *Brain*, 139(2), 392–403. <https://doi.org/10.1093/brain/awv370>
- Katz, E., de Jong, J. M. B. V., Buettner-Ennever, J., & Cohen, B. (1991). Effects of midline medullary lesions on velocity storage and the vestibulo-ocular reflex. *Experimental Brain Research*, 87(3), 505–520. <https://doi.org/10.1007/BF00227076>
- Killiany, R. J., Gomez-Isla, T., Moss, M., Kikinis, R., Sandor, T., Jolesz, F., Tanzi, R., Jones, K., Hyman, B. T.,

- & Albert, M. S. (2000). Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. *Annals of Neurology*, 47(4), 430–439. [https://doi.org/10.1002/1531-8249\(200004\)47:4<430::AID-ANA5>3.0.CO;2-I](https://doi.org/10.1002/1531-8249(200004)47:4<430::AID-ANA5>3.0.CO;2-I)
- Kinnunen, K. M., Greenwood, R., Powell, J. H., Leech, R., Hawkins, P. C., Bonnelle, V., Patel, M. C., Counsell, S. J., & Sharp, D. J. (2011). White matter damage and cognitive impairment after traumatic brain injury. *Brain*, 134(2), 449–463. <https://doi.org/10.1093/brain/awq347>
- Kirsch, V., Keeser, D., Hergenroeder, T., Erat, O., Ertl-Wagner, B., Brandt, T., & Dieterich, M. (2016). Structural and functional connectivity mapping of the vestibular circuitry from human brainstem to cortex. *Brain Structure and Function*, 221(3), 1291–1308. <https://doi.org/10.1007/s00429-014-0971-x>
- Kleinschmidt, A., Thilo, K. V., Büchel, C., Gresty, M. A., Bronstein, A. M., & Frackowiak, R. S. J. (2002). Neural correlates of visual-motion perception as object- or self-motion. *NeuroImage*, 16(4), 873–882. <https://doi.org/10.1006/nimg.2002.1181>
- Kolev, O. I., Georgieva-Zhostova, S. O., & Berthoz, A. (2014). Anxiety changes depersonalization and derealization symptoms in vestibular patients. *Behavioural Neurology*, 2014. <https://doi.org/10.1155/2014/847054>
- Kotapka, M. J., Graham, D. I., Adams, J. H., & Gennarelli, T. A. (1992). Hippocampal pathology in fatal non-missile human head injury. *Acta Neuropathologica*, 83(5), 530–534. <https://doi.org/10.1007/BF00310031>
- Kraus, M. F., Susmaras, T., Caughlin, B. P., Walker, C. J., Sweeney, J. A., & Little, D. M. (2007). White matter integrity and cognition in chronic traumatic brain injury: A diffusion tensor imaging study. *Brain*, 130(10), 2508–2519. <https://doi.org/10.1093/brain/awm216>
- Lackner, J. R., & DiZio, P. (2005). Vestibular, proprioceptive, and haptic contributions to spatial orientation. *Annual Review of Psychology*, 56, 115–147. <https://doi.org/10.1146/annurev.psych.55.090902.142023>
- Laczó, Jan, Andel, R., Vyhnalek, M., Vlček, K., Magerova, H., Varjassyova, A., Nedelska, Z., Gazova, I., Bojar, M., Sheardova, K., & Hort, J. (2012). From morris water maze to computer tests in the prediction of Alzheimer's disease. *Neurodegenerative Diseases*, 10(1–4), 153–157. <https://doi.org/10.1159/000333121>
- Langlois, J. A., Rutland-Brown, W., & Wald, M. M. (2006). The epidemiology and impact of traumatic brain injury: A brief overview. *Journal of Head Trauma Rehabilitation*, 21(5), 375–378. <https://doi.org/10.1097/00001199-200609000-00001>
- Leandri, M., Cammisuli, S., Cammarata, S., Baratto, L., Campbell, J., Simonini, M., & Tabaton, M. (2009). Balance features in Alzheimer's disease and amnesic mild cognitive impairment. *Journal of Alzheimer's Disease*, 16(1), 113–120. <https://doi.org/10.3233/JAD-2009-0928>
- Lehning, M., Leplow, B., Ekroll, V., Benz, B., Ritz, A., Mehdorn, M., & Ferstl, R. (2003). Recovery of spatial memory and persistence of spatial orientation deficits after traumatic brain injury during childhood. *Brain Injury*, 17(10), 855–869. <https://doi.org/10.1080/0269905031000089369>
- Leigh, R. J., & Zee, D. S. (2015). Chapter III: The Vestibular-Optokinetic System. In *The Neurology of Eye Movements (5 ed.)* (5th ed.). <https://doi.org/10.1093/med/9780199969289.003.0003>
- Lester, A. W., Moffat, S. D., Wiener, J. M., Barnes, C. A., & Wolbers, T. (2017). The Aging Navigational System. *Neuron*, 95(5), 1019–1035. <https://doi.org/10.1016/j.neuron.2017.06.037>
- Levin, H. S., Meyers, C. A., Grossman, R. G., & Sarwar, M. (1981). Ventricular Enlargement After Closed Head Injury. *JAMA Neurology*, 38(10), 623–629. <https://doi.org/10.1001/archneur.1981.00510100051007>
- Lindemer, E. R., Salat, D. H., Leritz, E. C., McGlinchey, R. E., & Milberg, W. P. (2013). Reduced cortical thickness with increased lifetime burden of PTSD in OEF/OIF Veterans and the impact of comorbid TBI. *NeuroImage: Clinical*, 2(1), 601–611. <https://doi.org/10.1016/j.nicl.2013.04.009>
- Lopez, C., & Blanke, O. (2011). The thalamocortical vestibular system in animals and humans. *Brain Research Reviews*, 67(1–2), 119–146. <https://doi.org/10.1016/j.brainresrev.2010.12.002>

- Maas, A. I. R., Menon, D. K., David Adelson, P. D., Andelic, N., Bell, M. J., Belli, A., Bragge, P., Brazinova, A., Büki, A., Chesnut, R. M., Citerio, G., Coburn, M., Jamie Cooper, D., Tamara Crowder, A., Czeiter, E., Czosnyka, M., Diaz-Arrastia, R., Dreier, J. P., Duhaime, A. C., ... Zemek, R. (2017). Traumatic brain injury: Integrated approaches to improve prevention, clinical care, and research. *The Lancet Neurology*, 16(12), 987–1048. [https://doi.org/10.1016/S1474-4422\(17\)30371-X](https://doi.org/10.1016/S1474-4422(17)30371-X)
- Mac Donald, C. L., Dikranian, K., Bayly, P., Holtzman, D., & Brody, D. (2007). Diffusion tensor imaging reliably detects experimental traumatic axonal injury and indicates approximate time of injury. *Journal of Neuroscience*, 27(44), 11869–11876. <https://doi.org/10.1523/JNEUROSCI.3647-07.2007>
- Maguire, E., Franckowiak, R. S. J., & Frith, C. D. (1996). Learning to find your way - a role for the human hippocampal formation. *Proceedings of the Royal Society*, 1745–1750.
- Maguire, E. A. (2001). The retrosplenial contribution to human navigation: a review of lesion and neuroimaging findings. *Scandinavian Journal of Psychology*, 42, 225–238.
- Malec, J. F., Brown, A. W., Leibson, C. L., Flaada, J. T., Mandrekar, J. N., Diehl, N. N., & Perkins, P. K. (2007). The mayo classification system for traumatic brain injury severity. *Journal of Neurotrauma*, 24(9), 1417–1424. <https://doi.org/10.1089/neu.2006.0245>
- Manckoundia, P., Pfitzenmeyer, P., & Athis, P. (2006). *Impact of Cognitive Task on the Posture of Elderly Subjects With Alzheimer's Disease Compared to Healthy Elderly Subjects*. 21(2), 236–241. <https://doi.org/10.1002/mds.20649>
- Manohar, S. G., Pertzov, Y., & Husain, M. (2017). Short-term memory for spatial, sequential and duration information. *Current Opinion in Behavioral Sciences*, 17, 20–26. <https://doi.org/10.1016/j.cobeha.2017.05.023>
- Marcus, H. J., Paine, H., Sargeant, M., Wolstenholme, S., Collins, K., Marroney, N., Arshad, Q., Tsang, K., Jones, B., Smith, R., Wilson, M. H., Rust, H. M., & Seemungal, BM. (2019). Vestibular dysfunction in acute traumatic brain injury. *Journal of Neurology*, 266(10), 2430–2433. <https://doi.org/10.1007/s00415-019-09403-z>
- Mars, R. B., Sallet, J., Schüffelen, U., Jbabdi, S., Toni, I., & Rushworth, M. F. S. (2012). Connectivity-based subdivisions of the human right “temporoparietal junction area”: Evidence for different areas participating in different cortical networks. *Cerebral Cortex*, 22(8), 1894–1903. <https://doi.org/10.1093/cercor/bhr268>
- Mast, F. W., Preuss, N., Hartmann, M., & Grabherr, L. (2014). Spatial cognition , body representation and affective processes : the role of vestibular information beyond ocular reflexes and control of posture. *Frontiers in Neuroscience*, 8(May), 1–14. <https://doi.org/10.3389/fnint.2014.00044>
- Mayne, R. (1974). A Systems Concept of the Vestibular Organs. In *Handbook of Sensory Physiology, Part 2, Chapter 1* (pp. 493–580).
- McCorkle, T. A., Barson, J. R., & Raghupathi, R. (2021). A Role for the Amygdala in Impairments of Affective Behaviors Following Mild Traumatic Brain Injury. *Frontiers in Behavioral Neuroscience*, 15(March), 1–14. <https://doi.org/10.3389/fnbeh.2021.601275>
- McFarlane, L. H., Burles, F., Yeates, K. O., Schneider, K., & Iaria, G. (2020). A pilot study evaluating the effects of concussion on the ability to form cognitive maps for spatial orientation in adolescent hockey players. *Brain Injury*, 34(8), 1112–1117. <https://doi.org/10.1080/02699052.2020.1773537>
- McNaughton, B. L., Battaglia, F. P., Jensen, O., Moser, E.I., & Moser, M.B. (2006). Path integration and the neural basis of the “cognitive map.” *Nature Reviews Neuroscience*, 7(8), 663–678. <https://doi.org/10.1038/nrn1932>
- Meade, M., Meade, J., Sauzeon, H., & Fernandes, M. (2019). Active Navigation in Virtual Environments Benefits Spatial Memory in Older Adults. *Brain Sciences*, 9(3), 47. <https://doi.org/10.3390/brainsci9030047>
- Meilinger, T., Frankenstein, J., & Bühlhoff, H. H. (2013). Learning to navigate: Experience versus maps. *Cognition*, 129(1), 24–30. <https://doi.org/10.1016/j.cognition.2013.05.013>

- Merfeld, D.M., Young, L. R., Oman, C. M., & Shelhamer, M. J. (1993). 'A multidimensional model of the effect of gravity on the spatial orientation of the monkey. *Journal of Vestibular Research*, 3, 141–161.
- Merfeld, D.M., Zupan, L., & Peterka, R. J. (1999). Humans use internal models to estimate gravity and linear acceleration. *Nature*, 398(6728), 615–618. <https://doi.org/10.1038/19303>
- Mesbah, N., Perry, M., Hill, K. D., Kaur, M., & Hale, L. (2016). Postural stability in older adults with Alzheimer's disease. *Physical Therapy*, 97(3), 290–309. <https://doi.org/10.2522/ptj.20160115>
- Micarelli, A., Viziano, A., Della-Morte, D., Augimeri, I., & Alessandrini, M. (2018). Degree of functional impairment associated with vestibular hypofunction among older adults with cognitive decline. *Otology and Neurotology*, 39(5), e392–e400. <https://doi.org/10.1097/MAO.0000000000001746>
- Mimica, B., Dunn, B. A., Tombaz, T., Srikanth Bojja, V. P. T. N., & Whitlock, J. R. (2018). Efficient cortical coding of 3D posture in freely behaving rats. *Science*, 362(6414), 584–589. <https://doi.org/10.1126/science.aau2013>
- Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., & Hodges, J. R. (2006). The Addenbrooke's Cognitive Examination revised (ACE-R): A brief cognitive test battery for dementia screening. *International Journal of Geriatric Psychiatry*, 21(11), 1078–1085. <https://doi.org/10.1002/gps.1610>
- Moffat, S. D. (2009). Aging and spatial navigation: What do we know and where do we go? *Neuropsychology Review*, 19(4), 478–489. <https://doi.org/10.1007/s11065-009-9120-3>
- Moffat, S. D., Zonderman, A. B., & Resnick, S. M. (2001). Age differences in spatial memory in a virtual environment navigation task. *Neurobiology of Aging*, 22(5), 787–796. [https://doi.org/10.1016/S0197-4580\(01\)00251-2](https://doi.org/10.1016/S0197-4580(01)00251-2)
- Molloy, D. W., & Clamette, R. (1999). *Standardised Mini-mental State Examination. A user's guide*.
- Molloy, D. W., & Standish, T. I. M. (1997). A guide to the standardized Mini-Mental State Examination. *International Psychogeriatrics*, 9(SUPPL. 1), 87–94. <https://doi.org/10.1017/S1041610297004754>
- Monacelli, A. M., Cushman, L. A., & Kavcic, V. (2003). Spatial disorientation in Alzheimer's disease. *Neurology*, 61(11).
- Montchal, M. E., Reagh, Z. M., & Yassa, M. A. (2019). Precise temporal memories are supported by the lateral entorhinal cortex in humans. *Nature Neuroscience*, 22(2), 284–288. <https://doi.org/10.1038/s41593-018-0303-1>
- Montello, D. R. (1998). A new framework for understanding the acquisition of spatial knowledge in large-scale environments. *Spatial and Temporal Reasoning in Geographic Information Systems*, 143–154.
- Montero-Odasso, Manuel, Sarquis-Adamson, Y., Speechley, M., Borrie, M. J., Hachinski, V. C., Wells, J., Riccio, P. M., Schapira, M., Sejdic, E., Camicioli, R. M., Bartha, R., McIlroy, W. E., & Muir-Hunter, S. (2017). Association of dual-task gait with incident dementia in mild cognitive impairment: Results from the gait and brain study. *JAMA Neurology*, 74(7), 857–865. <https://doi.org/10.1001/jamaneurol.2017.0643>
- Mori, S., Oishi, K., Jiang, H., Jiang, L., Li, X., Akhter, K., Faria, A. V., Mahmood, A., Woods, R., Toga, A., Pike, B., Neto, R., Evans, A., Zhang, J., Huang, H., Miller, M. I., Van, P., & Mazziotta, J. (2008). Stereotaxic White Matter Atlas Based on Diffusion Tensor Imaging in an ICBM Template. *NeuroImage*, 40(2), 570–582.
- Mori, S., & Zhang, J. (2006). Principles of Diffusion Tensor Imaging and Its Applications to Basic Neuroscience Research. *Neuron*, 51(5), 527–539. <https://doi.org/10.1016/j.neuron.2006.08.012>
- Moser, E.I., Kropff, E., & Moser, M.B. (2008). Place cells, grid cells, and the brain's spatial representation system. *Annual Review of Neuroscience*, 31, 69–89. <https://doi.org/10.1146/annurev.neuro.31.061307.090723>
- Moser, M.B., Rowland, D. C., & Moser, E.I. (2015). Place Cells, Grid Cells, and Memory. *Cold Spring Harb Perspect Biol*, 1–16.

- Murray, N. G., Szekely, B., Moran, R., Ryan, G., Powell, D., Munkasy, B. A., Buckley, T. A., & Guskiewicz, K. (2019). Concussion history associated with increased postural control deficits after subsequent injury. *Physiological Measurement*, 40(2), aafcd8. <https://doi.org/10.1088/1361-6579/aafcd8>
- Murugavel, M., Cubon, V., Putukian, M., Echemendia, R., Osherson, D., & Dettwiler, A. (2014). A longitudinal diffusion tensor imaging study assessing white matter fiber tracts after sports related concussion. *Journal of Neurotrauma*, 31(22), 1860–1871.
- Nakamagoe, K., Fujimiya, S., Koganezawa, T., Kadono, K., Shimizu, K., Fujizuka, N., Takiguchi, S., Ueno, T., Monzen, T., & Tamaoka, A. (2015). Vestibular Function Impairment in Alzheimer's Disease. *Journal of Alzheimer's Disease*, 47(1), 185–196. <https://doi.org/10.3233/JAD-142646>
- Nakayama, N., Okumura, A., Shinoda, J., Yasokawa, Y. T., Miwa, K., Yoshimura, S. I., & Iwama, T. (2006). Evidence for white matter disruption in traumatic brain injury without macroscopic lesions. *Journal of Neurology, Neurosurgery and Psychiatry*, 77(7), 850–855. <https://doi.org/10.1136/jnnp.2005.077875>
- Narayana, P. A., Yu, X., Hasan, K. M., Wilde, E. A., Levin, H. S., Hunter, J. V., Miller, E. R., Patel, V. K. S., Robertson, C. S., & McCarthy, J. J. (2015). Multi-modal MRI of mild traumatic brain injury. *NeuroImage: Clinical*, 7, 87–97. <https://doi.org/10.1016/j.nicl.2014.07.010>
- Nedelska, Z., Andel, R., Laczo, J., Vlček, K., Horinek, D., Lisy, J., Sheardova, K., Bures, J., & Hort, J. (2012). Spatial navigation impairment is proportional to right hippocampal volume. *Proceedings of the National Academy of Sciences*, 109(7), 2590–2594. <https://doi.org/10.1073/pnas.1121588109>
- Nelson, P. T., Braak, H., & Markesbery, W. R. (2009). Neuropathology and Cognitive Impairment in Alzheimer Disease: A Complex but Coherent Relationship. *J Neuropathol Exp Neurol.*, 68(1), 1–14. <https://doi.org/10.1097/NEN.0b013e3181919a48>.Neuropathology
- Nigmatullina, Y., Hellyer, P. J., Nachev, P., Sharp, D. J., & Seemungal, BM. (2015). The neuroanatomical correlates of training-related perceptuo-reflex uncoupling in dancers. *Cerebral Cortex*, 25(2), 554–562. <https://doi.org/10.1093/cercor/bht266>
- Nigro, S., Indovina, I., Riccelli, R., Chiarella, G., Petrolo, C., Lacquaniti, F., Staab, J. P., & Passamonti, L. (2019). Reduced cortical folding in multi-modal vestibular regions in persistent postural perceptual dizziness. *Brain Imaging and Behavior*, 13(3), 798–809. <https://doi.org/10.1007/s11682-018-9900-6>
- Niogi, S. N., Mukherjee, P., Ghajar, J., Johnson, C., Kolster, R. A., Sarkar, R., Lee, H., Meeker, M., Zimmerman, R. D., Manley, G. T., & McCandliss, B. D. (2008). Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: A 3T diffusion tensor imaging study of mild traumatic brain injury. *American Journal of Neuroradiology*, 29(5), 967–973. <https://doi.org/10.3174/ajnr.A0970>
- O'Brien, H. L. (2001). Visual Mechanisms of Spatial Disorientation in Alzheimer's Disease. *Cerebral Cortex*, 11(11), 1083–1092. <https://doi.org/10.1093/cercor/11.11.1083>
- O'Keefe, J., & Nadel, L. (1978). *The Hippocampus as a Cognitive Map*. <https://doi.org/10.1097/00005053-198003000-00018>
- Okada, T., Grunfeld, E., Shallo-Hoffmann, J., & Bronstein, A. M. (1999). Vestibular perception of angular velocity in normal subjects and in patients with congenital nystagmus. *Brain*, 122(7), 1293–1303. <https://doi.org/10.1093/brain/122.7.1293>
- Olson, I. R., Page, K., Moore, K. S., Chatterjee, A., & Verfaellie, M. (2006). Working memory for conjunctions relies on the medial temporal lobe. *Journal of Neuroscience*, 26(17), 4596–4601. <https://doi.org/10.1523/JNEUROSCI.1923-05.2006>
- Padova, D., Tilak Ratnanather, J., Xue, Q. L., Resnick, S. M., & Agrawal, Y. (2020). Linking vestibular function and sub-cortical grey matter volume changes in a longitudinal study of aging adults. *MedRxiv*, c, 2020.11.17.20233684. <https://doi.org/10.1101/2020.11.17.20233684>
- Pai, M. C., & Jacobs, W. J. (2004). Topographical disorientation in community-residing patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry*, 19(3), 250–255.

<https://doi.org/10.1002/gps.1081>

- Paillard, T., & Noé, F. (2020). Does monopodal postural balance differ between the dominant leg and the non-dominant leg? A review. *Human Movement Science*, 74. <https://doi.org/10.1016/j.humov.2020.102686>
- Parizkova, M., Lerch, O., Moffat, S. D., Andel, R., Mazancova, A. F., Nedelska, Z., Vyhnaelek, M., Hort, J., & Laczó, J. (2018). The effect of Alzheimer's disease on spatial navigation strategies. *Neurobiology of Aging*, 64, 107–115. <https://doi.org/10.1016/j.neurobiolaging.2017.12.019>
- Passini, R., Rainville, C., Marchand, N., & Joanne, Y. (1995). Wayfinding in dementia of the Alzheimer type: Planning abilities. *Journal of Clinical and Experimental Neuropsychology*, 17(6), 820–832.
- Perlberg, V., Puybasset, L., Tollard, E., Lehericy, S., Benali, H., & Galanaud, D. (2009). Relation between brain lesion location and clinical outcome in patients with severe traumatic brain injury: A diffusion tensor imaging study using voxel-based approaches. *Human Brain Mapping*, 30(12), 3924–3933. <https://doi.org/10.1002/hbm.20817>
- Perttinen, N. M., Öhman, H., Strandberg, T. E., Kautiainen, H., Raivio, M., Laakkonen, M. L., Savikko, N., Tilvis, R. S., & Pitkälä, K. H. (2017). How Do Community-Dwelling Persons with Alzheimer Disease Fall? Results from the FINALEX Study. *Dementia and Geriatric Cognitive Disorders Extra*, 7(2), 195–203. <https://doi.org/10.1159/000477394>
- Peterson, M. D. (2010). A case-oriented approach exploring the relationship between visual and vestibular disturbances and problems of higher-level mobility in persons with traumatic brain injury. *Journal of Head Trauma Rehabilitation*, 25(3), 193–205. <https://doi.org/10.1097/HTR.0b013e3181dc82fa>
- Petzschner, F. H., & Glasauer, S. (2011). Iterative Bayesian estimation as an explanation for range and regression effects: A study on human path integration. *Journal of Neuroscience*, 31(47), 17220–17229. <https://doi.org/10.1523/JNEUROSCI.2028-11.2011>
- Pfefferbaum, A., Sullivan, E. V., Hedehus, M., Lim, K. O., Adalsteinsson, E., & Moseley, M. (2000). Age-related decline in brain white matter anisotropy measured with spatially corrected echo-planar diffusion tensor imaging. *Magnetic Resonance in Medicine*, 44(2), 259–268. [https://doi.org/10.1002/1522-2594\(200008\)44:2<259::AID-MRM13>3.0.CO;2-6](https://doi.org/10.1002/1522-2594(200008)44:2<259::AID-MRM13>3.0.CO;2-6)
- Philbeck, J. W., Behrmann, M., Biega, T., & Levy, L. (2006). Asymmetrical perception of body rotation after unilateral injury to human vestibular cortex. *Neuropsychologia*, 44(10), 1878–1890. <https://doi.org/10.1016/j.neuropsychologia.2006.02.004>
- Piaget, J., & Inhelder, B. (1948). *La représentation de l'espace chez l'enfant*. Paris: P.U.F. [translated from French by F.J. Landgon and J.L. Lunzer (1956). *The child's conception of space*. London: Routledge and Kegan Paul.].
- Piker, E. G., Jacobson, G. P., Burkard, R. F., McCaslin, D. L., & Hood, L. J. (2013). Effects of Age on the Tuning of the cVEMP and oVEMP. *Ear Hear.*, 34(6). <https://doi.org/10.1097/AUD.0b013e31828fc9f2>
- Pollock, A. S., Durward, B. R., Rowe, P. J., & Paul, J. P. (2000). What is balance? *Clinical Rehabilitation*, 14(4), 402–406. <https://doi.org/10.1191/0269215500cr342oa>
- Potegal, M. (1972). The caudate nucleus egocentric localization system. *Acta Neurobiologiae Experimentalis*, 32(2), 479–494.
- Powell, L. E., & Myers, A. M. (1995). The Activities-specific Balance Confidence (ABC) Scale. *The Journals of Gerontology: Series A*, 50A(1), M28–M34. <https://doi.org/10.1093/gerona/50A.1.M28>
- Previc, F. H. (2013). Vestibular loss as a contributor to Alzheimer's disease. *Medical Hypotheses*, 80(4), 360–367. <https://doi.org/10.1016/j.mehy.2012.12.023>
- Previc, F. H., Krueger, W. W., Ross, R. A., Roman, M. A., & Siegel, G. (2014). The relationship between vestibular function and topographical memory in older adults. *Frontiers in Integrative Neuroscience*, 8(JUNE), 1–8. <https://doi.org/10.3389/fnint.2014.00046>
- Purves, D., Augustine, G. J., Fitzpatrick, D., Hall, W. C., LaMantia, A.-S., Mooney, R. D., Platt, M. L., &

- White, L. E. (2017). *Neuroscience (Sixth Edition, Unit II. Sensation and Sensory Processing, 14. Vestibular System)* (and L. E. W. Edited by Dale Purves, George J. Augustine, David Fitzpatrick, William C. Hall, Anthony-Samuel LaMantia, Richard D. Mooney, Michael L. Platt (Ed.)). Sinauer Associates (Oxford University Press).
- Raphan, T., Matsuo, V., & Cohen, B. (1979). Velocity storage in the vestibulo-ocular reflex arc (VOR). *Experimental Brain Research*, 35(2), 229–248. <https://doi.org/10.1007/BF00236613>
- Reagh, Z. M., & Yassa, M. A. (2014). Object and spatial mnemonic interference differentially engage lateral and medial entorhinal cortex in humans. *Proceedings of the National Academy of Sciences of the United States of America*, 111(40), E4264–E4273. <https://doi.org/10.1073/pnas.1411250111>
- Ritchie, K., Carrière, I., Howett, D., Su, L., Hornberger, M., O'Brien, J. T., Ritchie, C. W., & Chan, D. (2018). Allocentric and egocentric spatial processing in middle-aged adults at high risk of late-onset Alzheimer's disease: The PREVENT dementia study. *Journal of Alzheimer's Disease*, 65(3), 885–896. <https://doi.org/10.3233/JAD-180432>
- Roy, J. E., & Cullen, K. E. (1998). A neural correlate for vestibulo-ocular reflex suppression during voluntary eye-head gaze shifts. *Nature Neuroscience*, 1(5), 404–410. <https://doi.org/10.1038/1619>
- Roy, J. E., & Cullen, K. E. (2001). Selective processing of vestibular reafference during self-generated head motion. *Journal of Neuroscience*, 21(6), 2131–2142. <https://doi.org/10.1523/jneurosci.21-06-02131.2001>
- Rutgers, D. R., Fillard, P., Paradot, G., Tadié, M., Lasjaunias, P., & Ducreux, D. (2008). Diffusion tensor imaging characteristics of the corpus callosum in mild, moderate, and severe traumatic brain injury. *American Journal of Neuroradiology*, 29(9), 1730–1735. <https://doi.org/10.3174/ajnr.A1213>
- Sadeghi, S. G., Chacron, M. J., Taylor, M. C., & Cullen, K. E. (2007). Neural variability, detection thresholds, and information transmission in the vestibular system. *Journal of Neuroscience*, 27(4), 771–781. <https://doi.org/10.1523/JNEUROSCI.4690-06.2007>
- Sapolsky, R. M. (2000). Glucocorticoids and Hippocampal Atrophy in Neuropsychiatric Disorders. *Arch Gen Psychiatry*, 57(10), 925–935. <https://doi.org/doi:10.1001/archpsyc.57.10.925>
- Schaer, M., Cuadra, M. B., Schmansky, N., Fischl, B., Thiran, J. P., & Eliez, S. (2012). How to measure cortical folding from mr images: A step-by-step tutorial to compute local gyrification index. *Journal of Visualized Experiments*, 59, 1–8. <https://doi.org/10.3791/3417>
- Schlack, A., Hoffmann, K. P., & Bremmer, F. (2002). Interaction of linear vestibular and visual stimulation in the macaque ventral intraparietal area (VIP). *European Journal of Neuroscience*, 16(10), 1877–1886. <https://doi.org/10.1046/j.1460-9568.2002.02251.x>
- Seemungal, BM. (2006). *The mechanisms and loci of human vestibular perception*, PhD thesis
- Seemungal, BM. (2014). The cognitive neurology of the vestibular system. *Current Opinion in Neurology*, 27(1), 125–132. <https://doi.org/10.1097/WCO.0000000000000060>
- Seemungal, BM., Glasauer, S., Gresty, M. A., & Bronstein, A. M. (2007). Vestibular perception and navigation in the congenitally blind. *Journal of Neurophysiology*, 97(6), 4341–4356. <https://doi.org/10.1152/jn.01321.2006>
- Seemungal, BM., Gunaratne, I. A., Fleming, I. O., Gresty, M. A., & Bronstein, A. M. (2004). Perceptual and nystagmic thresholds of vestibular function in yaw. *Journal of Vestibular Research: Equilibrium and Orientation*, 14(6), 461–466.
- Seemungal, BM., Rizzo, V., Gresty, M. A., Rothwell, J. C., & Bronstein, A. M. (2008). Posterior parietal rTMS disrupts human Path Integration during a vestibular navigation task. *Neuroscience Letters*, 437(2), 88–92. <https://doi.org/10.1016/j.neulet.2008.03.067>
- Seemungal, BM., Rizzo, V., Gresty, M. A., Rothwell, J. C., & Bronstein, A. M. (2009). Perceptual encoding of self-motion duration in human posterior parietal cortex. *Annals of the New York Academy of Sciences*, 1164, 236–238. <https://doi.org/10.1111/j.1749-6632.2009.03772.x>

- Semenov, Y. R., Bigelow, R. T., Xue, Q. L., Lac, S. Du, & Agrawal, Y. (2015). Association between Vestibular and Cognitive Function in U.S. Adults: Data from the National Health and Nutrition Examination Survey. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, 71(2), 243–250. <https://doi.org/10.1093/gerona/glv069>
- Sharp, D. J., Scott, G., & Leech, R. (2014). Network dysfunction after traumatic brain injury. *Nature Reviews Neurology*, 10(3), 156–166. <https://doi.org/10.1038/nrneurol.2014.15>
- Shrager, Y., Kirwan, C. B., & Squire, L. R. (2008). Neural basis of the cognitive map: Path integration does not require hippocampus or entorhinal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, 105(33), 12034–12038. <https://doi.org/10.1073/pnas.0805414105>
- Sidaros, A., Engberg, A. W., Sidaros, K., Liptrot, M. G., Herning, M., Petersen, P., Paulson, O. B., Jernigan, T. L., & Rostrup, E. (2008). Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: A longitudinal study. *Brain*, 131(2), 559–572. <https://doi.org/10.1093/brain/awm294>
- Skelton, R. W. (1998). Modelling recovery of cognitive function after traumatic brain injury: Spatial navigation in the Morris water maze after complete or partial transections of the perforant path in rats. *Behavioural Brain Research*, 96(1–2), 13–35. [https://doi.org/10.1016/S0166-4328\(97\)00199-X](https://doi.org/10.1016/S0166-4328(97)00199-X)
- Skelton, R. W., Ross, S. P., Nerad, L., & Livingstone, S. A. (2005). Human spatial navigation deficits after traumatic brain injury shown in the arena maze, a virtual Morris water maze. *Brain Injury*, 20(2), 189–203. <https://doi.org/10.1080/02699050500456410>
- Smith, J. L., Ahluwalia, V., Gore, R. K., & Allen, J. W. (2023). Eagle-449: A volumetric, whole-brain compilation of brain atlases for vestibular functional MRI research. *Scientific Data*, 10(1), 1–13. <https://doi.org/10.1038/s41597-023-01938-1>
- Smith, L., Wilkinson, D., Bodani, M., Bicknell, R., & Surethiran, S. S. (2019). Short-term memory impairment in vestibular patients can arise independently of psychiatric impairment, fatigue, and sleeplessness. *Journal of Neuropsychology*, 13(3), 417–431. <https://doi.org/10.1111/jnp.12157>
- Smith, PF. (1997). Vestibular – Hippocampal Interactions. *Hippocampus*, 7, 465–471.
- Smith, PF. (2013). Vestibular dysfunction and Alzheimer’s disease. *Medical Hypotheses*, 81(6), 1169–1170. <https://doi.org/10.1016/j.mehy.2013.09.034>
- Smith, PF. (2017). The vestibular system and cognition. *Current Opinion in Neurology*, 30(1), 84–89. <https://doi.org/10.1097/WCO.0000000000000403>
- Smith, PF. (2018). Vestibular Functions and Parkinson’s Disease. *Frontiers in Neurology*, 9(December), 1–13. <https://doi.org/10.3389/fneur.2018.01085>
- Smith, PF. (2019). The Growing Evidence for the Importance of the Otoliths in Spatial Memory. *Frontiers in Neural Circuits*, 13(October), 66. <https://doi.org/10.3389/fncir.2019.00066>
- Smith, PF. (2022). Hearing loss versus vestibular loss as contributors to cognitive dysfunction. *Journal of Neurology*, 269(1), 87–99. <https://doi.org/10.1007/s00415-020-10343-2>
- Smith, PF., & Darlington, C. L. (2013). Personality changes in patients with vestibular dysfunction. *Frontiers in Human Neuroscience*, 7(OCT), 1–7. <https://doi.org/10.3389/fnhum.2013.00678>
- Smith, PF., Darlington, C. L., & Zheng, Y. (2010). Move It or Lose It – Is Stimulation of the Vestibular System Necessary for Normal Spatial Memory ? *Hippocampus*, 20, 36–43. <https://doi.org/10.1002/hipo.20588>
- Smith, PF., & Zheng, Y. (2013). From ear to uncertainty: Vestibular contributions to cognitive function. *Frontiers in Integrative Neuroscience*, 7(NOV), 1–13. <https://doi.org/10.3389/fnint.2013.00084>
- Smith, R., Chepishcheva, M., Cronin, T., & Seemungal, BM. (2019). Diagnostic Approaches Techniques in Concussion/Mild Traumatic Brain Injury: Where are we? In *Neurosensory disorders in Mild Traumatic Brain Injury*.

- Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, 17(3), 143–155. <https://doi.org/10.1002/hbm.10062>
- Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., Watkins, K. E., Ciccarelli, O., Cader, M. Z., Matthews, P. M., & Behrens, T. E. J. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage*, 31(4), 1487–1505. <https://doi.org/10.1016/j.neuroimage.2006.02.024>
- Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, 23(SUPPL. 1), 208–219. <https://doi.org/10.1016/j.neuroimage.2004.07.051>
- Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage*, 44(1), 83–98. <https://doi.org/10.1016/j.neuroimage.2008.03.061>
- Soares, J. M., Marques, P., Alves, V., & Sousa, N. (2013). A hitchhiker’s guide to diffusion tensor imaging. *Frontiers in Neuroscience*, 7(7 MAR), 1–14. <https://doi.org/10.3389/fnins.2013.00031>
- Spiers, H. J., & Gilbert, S. J. (2015). Solving the detour problem in navigation: A model of prefrontal and hippocampal interactions. *Frontiers in Human Neuroscience*, 9(MAR), 1–15. <https://doi.org/10.3389/fnhum.2015.00125>
- Stackman, R. W., Clark, A. S., & Taube, J. S. (2002). Hippocampal spatial representations require vestibular input. *Hippocampus*, 12(3), 291–303. <https://doi.org/10.1002/hipo.1112>
- Stackman, R. W., & Taube, J. S. (1997). Firing properties of head direction cells in the rat anterior thalamic nucleus: Dependence on vestibular input. *Journal of Neuroscience*, 17(11), 4349–4358. <https://doi.org/10.1523/jneurosci.17-11-04349.1997>
- Stangl, M., Achtzehn, J., Huber, K., Dietrich, C., Tempelmann, C., & Wolbers, T. (2018). Compromised Grid-Cell-like Representations in Old Age as a Key Mechanism to Explain Age-Related Navigational Deficits. *Current Biology*, 28(7), 1108–1115.e6. <https://doi.org/10.1016/j.cub.2018.02.038>
- Stangl, M., Kanitscheider, I., Riemer, M., Fiete, I., & Wolbers, T. (2020). Sources of path integration error in young and aging humans. *Nature Communications*, 11(1). <https://doi.org/10.1038/s41467-020-15805-9>
- Stein, J. F. (1989). Representation of Egocentric Space in the Posterior Parietal Cortex. *Quarterly Journal of Experimental Physiology*, 74(5), 583–606. <https://doi.org/10.1113/expphysiol.1989.sp003314>
- Surgent, O. J., Dadalko, O. I., Pickett, K. A., & Travers, B. G. (2019). Balance and the brain: A review of structural brain correlates of postural balance and balance training in humans. *Gait and Posture*, 71, 245–252. <https://doi.org/10.1016/j.gaitpost.2019.05.011>
- Takahashi, K., Gu, Y., May, P. J., Newlands, S. D., DeAngelis, G. C., & Angelaki, D. E. (2007). Multimodal coding of three-dimensional rotation and translation in area MSTd: Comparison of visual and vestibular selectivity. *Journal of Neuroscience*, 27(36), 9742–9756. <https://doi.org/10.1523/JNEUROSCI.0817-07.2007>
- Taube, J. S. (2007). The head direction signal: Origins and sensory-motor integration. *Annual Review of Neuroscience*, 30, 181–207. <https://doi.org/10.1146/annurev.neuro.29.051605.112854>
- Teel, E. F., Ray, W. J., Geronimo, A. M., & Slobounov, S. M. (2014). Residual alterations of brain electrical activity in clinically asymptomatic concussed individuals: An EEG study. *Clinical Neurophysiology*, 125(4), 703–707. <https://doi.org/10.1016/j.clinph.2013.08.027>
- Tetewsky, S. J., & Duffy, C. J. (1999). Visual loss and getting lost in Alzheimer’s disease. *Neurology*, 52(5), 958–958. <https://doi.org/10.1212/WNL.52.5.958>
- Tomaiuolo, F., Carlesimo, G. A., Di Paola, M., Petrides, M., Fera, F., Bonanni, R., Formisano, R., Pasqualetti,

- P., & Caltagirone, C. (2004). Gross morphology and morphometric sequelae in the hippocampus, fornix, and corpus callosum of patients with severe non-missile traumatic brain injury without macroscopically detectable lesions: A T1 weighted MRI study. *Journal of Neurology, Neurosurgery and Psychiatry*, 75(9), 1314–1322. <https://doi.org/10.1136/jnnp.2003.017046>
- Tombaugh, T. N. (2004). Trail Making Test A and B: Normative data stratified by age and education. *Archives of Clinical Neuropsychology*, 19(2), 203–214. [https://doi.org/10.1016/S0887-6177\(03\)00039-8](https://doi.org/10.1016/S0887-6177(03)00039-8)
- Treble, A., Hasan, K. M., Iftikhar, A., Stuebing, K. K., Kramer, L. A., Cox, C. S., Swank, P. R., & Ewing-Cobbs, L. (2013). Working memory and corpus callosum microstructural integrity after pediatric traumatic brain injury: A diffusion tensor tractography study. *Journal of Neurotrauma*, 30(19), 1609–1619. <https://doi.org/10.1089/neu.2013.2934>
- Tu, S., Wong, S., Hodges, J. R., Irish, M., Piguet, O., & Hornberger, M. (2015). Lost in spatial translation - A novel tool to objectively assess spatial disorientation in Alzheimer's disease and frontotemporal dementia. *Cortex*, 67, 83–94. <https://doi.org/10.1016/j.cortex.2015.03.016>
- Tyrrell, R. A., & Owens, D. A. (1988). A rapid technique to assess the resting states of the eyes and other threshold phenomena: The Modified Binary Search (MOBS). *Behavior Research Methods, Instruments, & Computers*, 20(2), 137–141. <https://doi.org/10.3758/BF03203817>
- Umbach, G., Kantak, P., Jacobs, J., Kahana, M., Pfeiffer, B. E., Sperling, M., & Lega, B. (2020). Time cells in the human hippocampus and entorhinal cortex support episodic memory. *Proceedings of the National Academy of Sciences of the United States of America*, 117(45), 28463–28474. <https://doi.org/10.1073/pnas.2013250117>
- Vann, S. D., Aggleton, J. P., & Maguire, E. A. (2009). What does the retrosplenial cortex do? *Nature Reviews Neuroscience*, 10(11), 792–802. <https://doi.org/10.1038/nrn2733>
- Venkatasubramanian, P. N., Keni, P., Gastfield, R., Li, L., Aksenov, D., Sherman, S. A., Bailes, J., Sindelar, B., Finan, J. D., Lee, J., Bailes, J. E., & Wyrwicz, A. M. (2020). Diffusion Tensor Imaging Detects Acute and Subacute Changes in Corpus Callosum in Blast-Induced Traumatic Brain Injury. *ASN Neuro*, 12, 1–13. <https://doi.org/10.1177/1759091420922929>
- Ventre-Dominey, J. (2014). Vestibular function in the temporal and parietal cortex: Distinct velocity and inertial processing pathways. *Frontiers in Integrative Neuroscience*, 8(JUL), 1–13. <https://doi.org/10.3389/fnint.2014.00053>
- Vlček, K., & Laczó, J. (2014). Neural correlates of spatial navigation changes in mild cognitive impairment and Alzheimer's disease. *Frontiers in Behavioral Neuroscience*, 8(MAR), 1–6. <https://doi.org/10.3389/fnbeh.2014.00089>
- Wei, E. X., Oh, E. S., Harun, A., Ehrenburg, M., & Agrawal, Y. (2017). Saccular Impairment in Alzheimer's Disease is Associated with Driving Difficulty. *Dementia and Geriatric Cognitive Disorders*, 44(5–6), 294–302. <https://doi.org/10.1159/000485123>
- Wei, E. X., Oh, E. S., Harun, A., Ehrenburg, M., & Agrawal, Y. (2018). Vestibular loss predicts poorer spatial cognition in patients with Alzheimer's disease. *Journal of Alzheimer's Disease*, 61(3), 995–1003. <https://doi.org/10.3233/JAD-170751>
- Weniger, G., Ruhleder, M., Lange, C., Wolf, S., & Irle, E. (2011). Egocentric and allocentric memory as assessed by virtual reality in individuals with amnesic mild cognitive impairment. *Neuropsychologia*, 49(3), 518–527. <https://doi.org/10.1016/j.neuropsychologia.2010.12.031>
- Werner, C., & Engelhard, K. (2007). Pathophysiology of traumatic brain injury. *British Journal of Anaesthesia*, 99(1), 4–9. <https://doi.org/10.1093/bja/aem131>
- Whitwell, J. L. (2009). Voxel-based morphometry: An automated technique for assessing structural changes in the brain. *Journal of Neuroscience*, 29(31), 9661–9664. <https://doi.org/10.1523/JNEUROSCI.2160-09.2009>
- Wiener, J. M., Berthoz, A., & Wolbers, T. (2011). Dissociable cognitive mechanisms underlying human path

- integration. *Experimental Brain Research*, 208(1), 61–71. <https://doi.org/10.1007/s00221-010-2460-7>
- Wiener, J. M., Büchner, S. J., & Hölscher, C. (2009). Taxonomy of human wayfinding tasks: A knowledge-based approach. *Spatial Cognition and Computation*, 9(2), 152–165. <https://doi.org/10.1080/13875860902906496>
- Wijesinghe, R., Protti, D. A., & Camp, A. J. (2015). Vestibular Interactions in the Thalamus. *Frontiers in Neural Circuits*, 9(December), 1–8. <https://doi.org/10.3389/fncir.2015.00079>
- Wilkniss, S. M., Korol, D. L., Gold, P. E., Jones, M. G., & Manning, C. A. (1997). Age-related differences in an ecologically based study of route learning. *Psychology and Aging*, 12(2), 372–375. <https://doi.org/10.1037/0882-7974.12.2.372>
- Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *NeuroImage*, 92, 381–397. <https://doi.org/10.1016/j.neuroimage.2014.01.060>
- Winter, D. A. (1995). Human balance and posture standing and walking control during. *Gait & Posture*, 3(December), 193–214.
- Wolbers, T., & Wiener, J. M. (2014). Challenges for identifying the neural mechanisms that support spatial navigation: The impact of spatial scale. *Frontiers in Human Neuroscience*, 8(AUG), 1–12. <https://doi.org/10.3389/fnhum.2014.00571>
- Wood, R. A., Moodley, K. K., Lever, C., Minati, L., & Chan, D. (2016). Allocentric spatial memory testing predicts conversion from mild cognitive impairment to dementia: An initial proof-of-concept study. *Frontiers in Neurology*, 7(DEC). <https://doi.org/10.3389/fneur.2016.00215>
- Woolrich, M. W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., Beckmann, C., Jenkinson, M., & Smith, S. M. (2009). Bayesian analysis of neuroimaging data in FSL. *NeuroImage*, 45(1 Suppl), S173–S186. <https://doi.org/10.1016/j.neuroimage.2008.10.055>
- Wright, I. C., McGuire, P. K., Poline, J. B., Travers, J. M., Murray, R. M., Frith, C. D., Frackowiak, R. S. J., & Friston, K. J. (1995). A voxel-based method for the statistical analysis of gray and white matter density applied to schizophrenia. In *NeuroImage* (Vol. 2, Issue 4, pp. 244–252). <https://doi.org/10.1006/nimg.1995.1032>
- Xie, Y., Bigelow, R. T., Frankenthaler, S. F., Studenski, S. A., Moffat, S. D., & Agrawal, Y. (2017). Vestibular loss in older adults is associated with impaired spatial navigation: Data from the triangle completion task. *Frontiers in Neurology*, 8(APR), 1–9. <https://doi.org/10.3389/fneur.2017.00173>
- Yakusheva, T. A., Shaikh, A. G., Green, A. M., Blazquez, P. M., Dickman, J. D., & Angelaki, D. E. E. (2007). Purkinje Cells in Posterior Cerebellar Vermis Encode Motion in an Inertial Reference Frame. *Neuron*, 54(6), 973–985. <https://doi.org/10.1016/j.neuron.2007.06.003>
- Yakushin, S. B., Raphan, T., & Cohen, B. (2017). Coding of velocity storage in the vestibular nuclei. *Frontiers in Neurology*, 8(AUG), 1–19. <https://doi.org/10.3389/fneur.2017.00386>
- Yesantharao, L. V, Rosenberg, P., Oh, E., Leoutsakos, J., Munro, C. A., & Agrawal, Y. (2022). Vestibular therapy to reduce falls in people with Alzheimer’s disease : study protocol for a pilot randomized controlled trial. *Pilot and Feasibility Studies*, 1–14. <https://doi.org/10.1186/s40814-022-01133-w>
- Yoder, R. M., & Taube, J. S. (2009). Head Direction Cell Activity in Mice : Robust Directional Signal Depends on Intact Otolith Organs. *The Journal of Neuroscience*, 29(4), 1061–1076. <https://doi.org/10.1523/JNEUROSCI.1679-08.2009>
- Yoder, R. M., & Taube, J. S. (2014). The vestibular contribution to the head direction signal and navigation. *Frontiers in Integrative Neuroscience*, 8(APR), 1–13. <https://doi.org/10.3389/fnint.2014.00032>
- Zu Eulenburg, P., Caspers, S., Roski, C., & Eickhoff, S. B. (2012). Meta-analytical definition and functional connectivity of the human vestibular cortex. *NeuroImage*, 60(1), 162–169. <https://doi.org/10.1016/j.neuroimage.2011.12.032>