

The cortical mechanisms underlying human spatial navigation: *from afferent processing to motor efference*

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A mis padres, por esto y por todo

The content within the thesis constitutes my own work. Where the work of others is described or mentioned, appropriate reference to the author(s) has been made.

Abstract

The research described in this thesis examined the cortical mechanisms underlying human spatial navigation, both from afferent and efferent perspectives, using healthy individuals and patients with focal cortical lesions. Specifically, the role of the posterior parietal cortex in the neural integration of vestibular signals for self-location perception was examined in a series of behavioural experiments (*Chapter 2*) assessing position, motion, and timing perception during angular rotations in the dark. Hippocampal cells have been associated with spatial navigation involving allocentric (map-based) co-ordinates. A combination of landmark-based orientation and vestibular path integration paradigm was used to evaluate the role of the right hippocampus in vestibular working memory related to allo-, and ego-centric navigation (*Chapter 3*). A new hypothesis relating to theta oscillation synchronisation for binding spatial (and non-spatial) conjunctions is proposed. Vestibular-guided self-motion relies upon visual calibration, for sighted individuals. Blind individuals, however, are said to possess a ‘supersense’ as a result of cross-modal plasticity. Blind versus sighted performance was compared using a vestibular-guided auditory localisation task in footballers (*Chapter 4*), and both in turn compared to sighted non-footballers. This enables a fair assessment of the relative contribution of practice versus innate ‘supersense’ for spatial performance.

Gait is a necessary component of spatial navigation in humans, and the ability to adapt locomotor behaviour to a change in the environment is essential for everyday activity. Using the ‘broken escalator’ paradigm, the role of the primary motor cortex and premotor regions for gait adaptation was assessed in healthy participants, using non-invasive transcranial direct current stimulation (tDCS; *Chapter 5*). This technique was then applied in combination with physical therapy to patients with Parkinson’s disease (*Chapter 6*) and patients with small vessel disease (*Chapter 7*) – a common cause of gait dysfunction in the elderly – to improve gait and balance function. The complementary study in a single patient with Parkinson’s disease combining tDCS with tango dancing examined whether non-invasive brain stimulation could preferentially augment the effects of this form of physical therapy in a clinically-relevant manner (*Appendix*).

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"...the natives kept a true course towards a particular spot, whilst passing for a long distance through hummocky ice, with incessant changes of direction, and with no guide in the heavens or on the frozen sea... he, an experienced surveyor, and using a compass, failed to do that which these savages easily effected. Yet no one will suppose that they possessed any special sense which is quite absent in us. We must bear in mind that neither a compass, nor the North Star, nor any other such sign, suffices to guide a man to a particular spot through an intricate country, or through hummocky ice, when many deviations from a straight course are inevitable, unless the deviations are allowed for, or a sort of "dead reckoning" is kept. All men are able to do this in a greater or less degree ... though probably in an unconscious manner. This is effected chiefly, no doubt, by eyesight, but partly, perhaps, by the sense of muscular movement, in the same manner as a man with his eyes blinded can proceed (and some men much better than others) for a short distance in a nearly straight line, or turn at right angles, or back again. The manner in which the sense of direction is sometimes suddenly disarranged in very old and feeble persons, and the feeling of strong distress which, as I know, has been experienced by persons when they have suddenly found out that they have been proceeding in a wholly unexpected and wrong direction, leads to the suspicion that some part of the brain is specialised for the function of direction. Whether animals may not possess the faculty of keeping a dead reckoning of their course in a much more perfect degree than can man; or whether this faculty may not come into play on the commencement of a journey when an animal is shut up in a basket, I will not attempt to discuss, as I have not sufficient data.

CHARLES DARWIN, 1873

Darwin, C. R. 1873. Origin of certain instincts. *Nature. A Weekly Illustrated Journal of Science* 7 (3 April): 417-418.

C_{hapter} 1

Introduction

Afferent (from the Latin af- = ad- : to + ferre: to bear, carry) inputs carry information from our peripheral sensory organs to the brain, where these signals are processed into percepts, and enter our conscious awareness. Efferent (ex = away) inputs carry motor information from the brain towards peripheral nerve that innervate muscles and enable movement to occur. Whilst the study of afferent pathways increases our understanding of how the nervous system encodes and processes information, that then enables us to construct a perception of the self, they have been less amenable to modulation, from a clinical translational viewpoint, than efferent pathways. This thesis therefore aims to approach the cortical mechanisms underlying spatial navigation in humans from both afferent processing mechanisms (i.e. how the brain processes vestibular and visual signals to give us a sense of where we are in space) and efferent (i.e. locomotor performance) perspectives, to understand how the nervous system integrates sensory information pertaining to our movement within the environment, and attempt to influence this movement using cortical stimulation techniques applied to efferent pathways. Thus, in Part I of this thesis I will describe a series of experiments exploring the integration of sensory afferents at cortical level, and in Part II, experiments using non-invasive cortical stimulation to modulate gait in healthy subjects, and patients with defined

neurological gait disorders. The thesis attempts to encompass a holistic approach to spatial navigation in humans, from afferent processing, to motor efference.

1.1 Spatial Navigation

How we find our way in space lies at the heart of human and animal existence, and has exercised the minds of scientists and the lay public for millennia. The fundamental question “where am I?” appears trivial but lies at the heart of the self. From a neurobiological perspective, our ability to self-locate is intricate and complex. Over fifty years ago, Tolman’s discovery (1) that rats have cognitive spatial maps of the layout of their environments triggered a torrent of investigation in this field. It was not until the discovery of place cells several decades later that a physiological foundation was established for the study of navigation. Place cells are pyramidal cells in the rat hippocampus with location-specific activity (2), and increase their firing rates when the animal traverses specific regions of its surroundings to provide a context-dependent map of the spatial environment. A wealth of studies in rodents (3-6) and birds (7, 8) has built a growing framework for understanding spatial navigation. Studies have also recently begun to elucidate the neural representation of allocentric (world-centred) spatial locations in the hippocampus (9, 10) and posterior parietal cortex (11) of monkeys. Despite a convergence of findings across species and methodologies, an understanding of human navigation remains elusive. Human spatial navigation requires a synergistic interaction between afferent sensory signals detecting our location in space, and efferent motor pathways that propel us through the environment. This work tackles some of the key anonymities in the field of spatial navigation relating to everyday life experiences, from the perspectives of cortical processing of afferent signals, through to execution of motor commands that enable us to locomote through our environment.

1.2 Afferent integrators for spatial navigation– path integration versus landmarks route navigation

As Charles Darwin observed in his seminal work over 100 years ago (12), animals are able to unassumingly return to a starting point, such as a nest, in the absence of vision, even when taking a circuitous outwards journey, suggesting that they use cues to infer distance and direction in order to estimate their position. This process was later termed path integration (also termed dead reckoning or Wegintegration) to capture the mathematical concept of continuous integration of motion cues over a given route. Experimental manipulation of inertial cues confirmed that at least one of these idiothetic (multimodal sensory information from the processing of self-movement) cues is vestibular in origin (13-16). Other signals include proprioception (carrying information about the position of a joint and limb), and optic flow (from the visual system indicating how the visual world is moving across the retina). Motor efference copy (a copy of the signals of movements executed originating from the motor system that predict the motor and sensory outcomes of the movement), although not traditionally thought of as an afferent signal, also contributes to path integration and thus spatial navigation. Together, these afferent sources of information signal the direction, duration and nature of movement from the animal's perspective (egocentric).

The hippocampal formation is considered to be important for early encoding, consolidation and retrieval of memory (17). A growing evidence base from animal and human studies suggests that the hippocampus may also have a role in spatial memory (18, 19). O'Keefe and Nadel (3) have argued that such a role involves sensory information processing related to a map-based (allocentric) navigation. This has been termed the "cognitive map theory" and consists of a memory system providing information about an animal's position in space, relative to its environment, and the presence of specific objects in given locations. Allocentric

navigation is in essence a geometric triangulation process, relying primarily on perceptual sensory afferents (20, 21). The cognitive map theory, however, does not explain how the spatial metric, necessary for distance and angle estimates, arises given their dependence on movement of the body (22), which is an essential part of (egocentric) path integration. As opposed to allocentric navigation, path integration exploration uses a temporal integration of idiothetic cues only (23, 24). One theory suggests that such a metric arises from the rhythmicity of walking (25). This does not, of course, adequately explain the perception of rotational self-motion, which is a key aspect of navigation in any environment.

Whilst egocentric navigation is route or body-centered and appears to be primarily dependent on parietal cortices and striatum (3, 26-29), allocentric navigation is world-centered, independent to the observer, and dependent mainly on the hippocampus (28, 30). In humans, there appears to be functional lateralisation of the medial temporal lobe with the right hippocampus predominantly associated with spatial navigation and topographical memory (31), whereas the context-dependent episodic memory is more dependent on the left medial temporal lobe (32, 33). The study of spatial navigation is relevant to dementia, given spatial deficits observed in cognitively impaired patients (34, 35). Indeed, the spatial disorientation commonly observed in patients with Alzheimer's disease early on in the condition may reflect focal right hippocampal damage. Moreover, it is recognised that 'getting lost' is a common sequelae of certain cortical stroke syndromes, particularly involving parietal cortices. The neural basis of spatial navigation is yet to be fully elucidated, particularly in the real-space environment.

Finally, a complementary hypothesis to the cognitive map theory attempts to accommodate the non-spatial processing ascribed to the hippocampus (36-38). For example, when odours and spatial information were jointly presented to rats, subsets of stimuli respond selectively to

the quality of the odorant, irrespective of the rat's position in the environment (39). Indeed, animals with a lesioned hippocampus are unable to memorise the relation between these spatial and nonspatial stimuli. Thus, the relational hypothesis (40, 41) argues that one group of hippocampal neurons code for spatial cues, others for distances between them, and yet other groups for overlapping combinations of cues (37). A spatial map could consist of a large collection of overlapping cue conjunctions, with the conjunctions providing a framework for navigating among the cues.

The vestibular system in path integration

Located in the inner ear, the vestibular system consists of two components: three roughly orthogonal semicircular canals and the otolith organs (the saccule and utricle) (Figure 1.1).

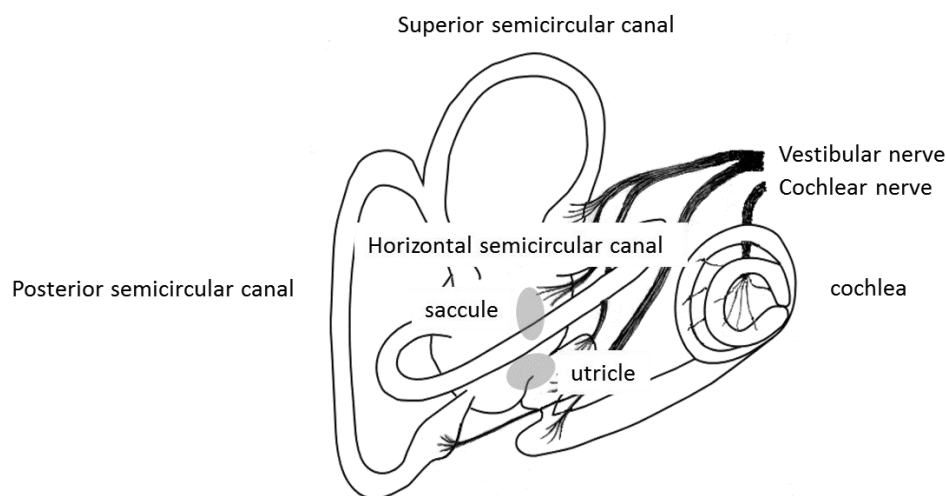


Figure 1.1 The anatomy of the vestibular apparatus. Three orthogonally orientated semicircular canals (superior, posterior, and horizontal) detect angular head acceleration as endolymphatic fluid moves within the canal and causes a deflection of the cupula. The saccule and utricle (otolith organs) detect linear head acceleration and tilt. Head acceleration signals travel to the brainstem vestibular nuclei via the vestibular nerve, and undergo a process of integration to generate a velocity signal for further cortical processing.

The semicircular canals are oriented at approximately 90° to each other, to sense angular accelerations in any direction, whilst the otolith organs sense linear accelerations, including tilt, in all planes.

Vestibular information is conveyed from the semicircular canals and otolith organs via the vestibular (eighth cranial) nerve, which project into the brainstem vestibular nuclei and the cerebellum (42). As our head translates and rotates in space, the semicircular canals and otolith organs function as inertia sensors and are extremely sensitive in detecting motion accelerations, which allows us to explore and understand the enormous range of physical motions experienced in everyday life (43).

Vestibular afferents reach the brainstem via the vestibular nerve, and undergo a process of acceleration-to-velocity integration (brainstem neural integrator) and then proceed as head-velocity signals to various cortical regions for further processing (44). For oculomotor function, to hold the eyes in eccentric gaze, the ocular motor neurons must process both eye velocity and eye position signals. A pulse of innervations from burst neurons in the paramedian pontine reticular formation (PPRF) project to ocular motor neurons giving a velocity to command that causes a phasic contraction of extraocular muscles. The ability to hold the eyes in an eccentric position in the orbit requires a mathematical integration of this velocity signal into a position signal that takes place at the neural integrator (45). When the integrator has a low time constant (i.e. is 'leaky'), the eyes will drift back toward the primary position as a result of the elastic forces on the eye, leading to corrective saccades in order to keep the eyes in eccentric gaze (so-called gaze-evoked nystagmus). The neuroanatomical substrate of the integrator is thought to involve a neural network connecting the nucleus prepositus hypoglossi and medial vestibular nucleus (horizontal conjugate movements), the interstitial nucleus of Cajal (torsional and vertical eye movements) with the

vestibulocerebellum (flocculus and nodulus). Similarly, to accurately sense *where* we are in space, the velocity signal from the brainstem must then be converted into positional information. It has been shown that perceived displacement is derived from the same signal that determines the velocity perception by an essentially ideal integration over time (46). This velocity-to-position integration is explained using the following mathematical model:

$$S = \int_0^T \mathbf{v} \cdot \delta t = \bar{\mathbf{v}} \cdot T$$

where S = angular displacement of rotation; $\mathbf{v}$ = instantaneous angular velocity; T = duration of rotation and $\bar{\mathbf{v}}$ = average angular velocity. The process of deriving and upgrading angular displacements from vestibular head velocity signals is one aspect of path integration (47). Given the complex nature of the process and its ecological significance for survival across species, one might expect the involvement of a widespread cortical network for the perceptual computation of self-location. The brain's answer to "where am I?" as we navigate through space likely requires constant updating of self-motion perception ("am I moving?"), the velocity perception ("how fast am I moving?"), the duration of said motion ("how long have I been moving for?") and the ability to integrate the velocity signals over time (a perceptual neural integrator). Although it is not yet clear whether these various processes occur within a single cortical locus, multiple separate loci, or are part of a widespread vestibular network, emerging evidence suggest the latter may be the case. Studies have shown that velocity signals are conveyed to the thalamus first and then distributed to various cortical areas (48, 49), suggesting that temporal integration of the velocity signal to derive a position signal involves cortical processing. Many studies have been performed in primates and in humans to investigate the cortical localisation of the vestibular processing (50). The areas implicated in perception of body rotations have been largely localised to temporal and

parietal cortex, in particular temporoparietal junction and contiguous posterior superior temporal gyrus (16, 50). Recently the posterior parietal cortex (PPC) has been shown to play a vital role in the process of path integration (11, 16), although the neurophysiological mechanisms underpinning this role are not clear. A population of cells located in PPC, specifically in area 7a, showed modulation of gain fields after whole-body rotations in primates (11). In addition, using the disrupting effect of repetitive transcranial magnetic stimulation (rTMS) applied over the PPC in humans, it was shown that PPC is specifically involved in path integration and motion duration but not in velocity encoding (16, 51). This suggests that there exists a cortical segregation for the processing of vestibular angular velocity and motion duration, which may reflect the need to separate information processing based on the specific functional role it will serve. This is particularly salient given that various vestibular and somatic afferents combine as early as the vestibular nuclei.

Central vestibular processing involves an early convergence of semicircular canal/otolith, visual/vestibular, and proprioceptive/vestibular afferents to maintain gaze and postural control. The fact that central vestibular processing is so strongly multimodal (43) explains why vestibular stimulation does not result in a distinct and separate conscious perception, with the range of the such percepts arguing against the existence of a single primary vestibular cortical locus. Even at the brainstem level of the vestibular nuclei, extensive processing of vestibular information and integration with other sensory information, such as visual, proprioceptive and somatosensory signals, has already taken place (52, 53).

So, where and how these vestibular afferents are processed is not yet known. However, it is known that the processing of vestibular afferents subserves a variety of everyday functions, ranging from reflexes to the highest levels of perception and consciousness. Given the potential role of the posterior parietal cortex in vestibular signal processing (16), the first

series of experiments explore vestibular-guided spatial navigation in patients with focal lesions of the parietal cortex. Meanwhile, as acquisition of vestibular memory has been linked to the hippocampus (54-56), further experiments involving whole-body angular rotations were carried out in a patient with focal hippocampal damage.

1.3 Motor efference: human gait and spatial navigation

Human gait

Walking constitutes an everyday function that appears so simple, but is in reality the result of intricate and widespread neural activity. Early work investigating the neural control of gait emanates from experiments in cats and rodents (57-60). Quadrupedal walking involves, at the spinal level, a central pattern generator (CPG) that generates a basic locomotor rhythm (61-63). Peripheral proprioceptive afferents and top-down supraspinal signals converge on the CPG to modulate the rhythmic activity based on motivational and environmental mandates. Neurons in the mesencephalic locomotor region (MLR) induce walking when electrically or chemically stimulated, suggesting its role in locomotor initiation and stepping pattern regulation (64, 65). In cats, the motor cortex plays a crucial role in locomotor adaptation (66) to the environmental context (e.g. walking along a narrow ladder, (67)).

Every part of the motor system is relevant to human gait, from peripheral nerves and muscles, through to the spinal cord, brainstem, and subcortical and cortical structures. Human gait relies perhaps more heavily on cortical and subcortical structures than other animals. For example, although rhythmic stepping movements can be elicited in patients with complete spinal cord injury when placed on a treadmill with appropriate afferent input (68), spontaneous rhythmic activity in the legs is rare (69, 70). The debilitating impact of strokes affecting primary motor and/or sensory regions on walking is further evidence to the critical

role of the motor cortex for human gait. Although traditionally considered an automatic ‘low-order’ process, it is increasingly recognised that human gait is under ‘higher-order’ conscious control, susceptible to attentional and cognitive influences (71, 72). Specifically, patients with ‘high-order’ gait disturbances exhibit difficulty initiating gait (start hesitation), shuffling steps, freezing of gait, non-fluent stepping, unsteady, insecure walking, and often develop a fear of falling (73). In addition, impairment of postural and righting reactions leads to falls during postural adjustments, such as turning or bending over (74). Adapting to perturbations, both as a result of postural changes or externally-induced, is an essential aspect real-world navigation, and constitutes a process of motor adaptation and learning (75).

Locomotor learning

Motor synergies can be defined as a set of two or more co-ordinated elements, such as joints or muscles, and are considered to be the building blocks of movement for vertebrates (76). Walking requires continuous adaptation of motor synergies in a context-specific manner, to negotiate different surfaces (a change from wooden to carpeted floor), obstacles (an uneven pavement slab) and respond to unexpected perturbations (a fellow commuter bumping into you). Gait adaptation relies upon a process of motor learning. Simplistically, motor learning can be divided into two overlapping categories; motor adaptation, which describes the modulation of previously-learned motor skills or the acquisition of new motor skills, which often takes longer to achieve (77). An important component of motor task learning (or procedural motor learning) is the acquisition of a motor skill without consciously thinking about it (78). The expression of a learnt motor skill may however be variously voluntary or involuntary (79, 80). Gait adaptation to varying terrain is essential to maintain balance in everyday life, and requires the selection of the appropriate motor strategy. The neural substrates for this type of learning are thought to be the supplementary motor area (SMA)

(81, 82), prefrontal cortex (83), and parietal cortex (83, 84). Whilst the contralateral primary motor cortex acts as the effector area (85), the SMA, particularly but not exclusively the left, has also been shown to play an important role in bilateral motor control (86, 87).

Gait modulation for neurological disease

Locomotor disturbance is a common neurological problem. Parkinson's disease (PD) is a common cause of gait and postural instability. Although it is defined pathologically by the loss of dopaminergic neurons in the substantia nigra, much of the long-term disability relates to symptoms that do not respond to levodopa (88), and is therefore therapeutically challenging. Gait disturbance in PD presents with asymmetrically reduced or absent arm swing, a stooped posture, difficulties turning, and short shuffling steps (festination). Many patients experience paroxysmal attacks of "freezing of gait", typically triggered by turning, crossing narrow spaces, or trying to initiate gait (hesitation), but also occur spontaneously during straight walking (89). Typically, dual tasking (e.g. walking whilst carrying a tray, performing mental arithmetic, or simply talking) increases gait disturbance in these patients (72, 90). In PD, an overactivity of inhibitory efferents from basal ganglia to the thalamus results in suppression on thalamocortical projections, with reduced activity in premotor and primary motor cortical regions (91-93). The motor cortex may thus be an important therapeutic neurostimulatory target in PD patients with gait disturbance (81).

Thus, from a cortical perspective, human locomotion relies upon a distributed neural network including SMA, primary motor, premotor areas and, importantly, white matter connections thereof (94). Not surprisingly, changes in the cerebral white matter, associated with vascular risk factors and frequently detected on imaging in the elderly (95), are associated with gait and balance dysfunction (96, 97). Clinically, these patients have a low gait velocity due to reduced stride length, long double support time and broad based gait (98). Small vessel

disease (SVD) is an increasing cause of falls in our ageing population (95) for which, critically, there is currently no treatment. The relevance of the primary motor and premotor cortices in the control of gait in relation to SVD has been demonstrated using fMRI (99) and cerebral perfusion techniques (98, 100). It is well recognised that the primary motor cortex is involved in the automatic execution of lower limb learned motor plans (82), while loops of the prefrontal cortex regulate and plan complex actions relevant to gait (101). Gait dysfunction in SVD is likely to involve disruption of cortico-subcortical locomotor circuits (102, 103). Therefore, exploiting healthy cortical fibres in these patients using non-invasive techniques may also be an attractive therapeutic strategy.

1.4. Aim and outline of the thesis

The principal aim of this work is to examine the cortical mechanisms that underlie spatial navigation in humans from both the afferent (input) processing and motor efferent (output) perspectives, using healthy subjects and patients with focal cortical lesions.

Chapters 2-4 focus on afferent processing pathways, whereas *Chapters 5-7* deal with efferent locomotor pathways. The study described in *Chapter 2* explores the neuro-anatomical locus, and the underlying mechanism, of everyday spatial orientation, in healthy subjects and patients with focal cortical lesions. *Chapter 3* tackles the role of the right hippocampus in vestibular memory of whole body rotations. The study aims to differentiate the neural mechanism underpinning allocentric and egocentric navigation, and explores the role of the hippocampus in binding spatial and non-spatial cues. In *Chapter 4* a comparison between auditory localisation performance in blind and sighted footballers is undertaken, using vestibular cues of self-motion, to examine the role (and absence) of vision in spatial navigation. *Chapter 5* assesses the role of the primary motor cortex in locomotor adaptation. The goal is to investigate whether non-invasive brain stimulation techniques could be used to

modulate locomotor adaptation in healthy subjects. In *Chapters 6 & 7* non-invasive brain stimulation is used in patients with Parkinson's disease and small vessel disease (leukoaraiosis), respectively, in an attempt to improve gait and balance function. Finally, *Chapter 8* provides a summary of the main findings, and outlines the scope for future research.

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Part I: Afferent processing

C_{hapter} 2

An internal clock for human spatial navigation

2.1 Introduction

The question ‘where am I?’ has for millennia exercised the human mind. Use of visual landmarks, be they a particular rock formation on a coastline or a constellation of stars has been used to guide travelers over long distances but navigation without landmarks is only possible with accurate chronometers. Surprisingly, theoretical considerations suggest that the brain may also require an internal clock for successful spatial orientation in the dark even over short angular distances. This is because humans can only update their angular position following locomotor turns using the inertial signals of motion provided by the vestibular organs (1). Since the vestibular signal provides head motion information, the derivation of head (and hence whole-body) position would require a process analogous to a temporal integration of this vestibular velocity signal, a process which is called path integration (2). The origin of the path integrator signal is unknown, however outputs from subcortical neural integrators could be used, e.g. the brainstem neural integrator which enables the eye to be held in a steady head-eccentric position following a head movement (4) (i.e. a vestibular-ocular related eye position signal). One prediction though would be that such low-order integrators would not require an explicit timing signal to enable velocity-to position integration. In contrast if the perceptual outputs of path integration in humans engaged high order integrators, e.g. involving the cerebral cortex, one could predict that deficits in interval timing mechanisms may correlate with spatial deficits in the path integration process. There is no evidence however, that humans or any other species, utilize an internal clock for path integration.

The fact that there is no evidence to suggest that timing signals are used in human path integration could support the notion that the neuro-anatomical locus of human path

integration resides in low-order subcortical integrators or even in human analogues of HD (head direction) and PC (place cell) systems. Animal HD cells are found in the Papez circuit and represent an animal's current heading relative to visual landmarks (5) whilst PCs in the medial temporal cortex represent an animal's two-dimensional location in an environment (6). Both HD and PC spatial representations are updated in the dark by vestibular cues, behaviour compatible with a neuronal system subserving path integration. Whilst path integration experiments with patients with lesions of the Papez circuit have not been performed, patients with lesions in the hippocampus and entorhinal cortex show no deficit in path integration suggesting that these regions do not mediate human path integration (7). Another potential candidate region would be parietal cortex (8) where vestibular position signals have been isolated. Indeed we have previously shown impaired spatial performance in an angular homing task when repetitive transcranial magnetic stimulation (rTMS) was applied during the passive outbound phase, to the P3 and P4 parietal regions (according to the international 10-20 electroencephalographic system). A potential confound of this study however is that the rTMS could have disrupted planning of the homing trajectory rather than disrupting path integration *per se* (9). Thus despite much investigation, the neuro-anatomical substrate of human path integration is unknown.

Hence in order to ascertain the neuro-anatomical locus underlying human path integration, and whether human path integration may utilize a time-based mechanism, we assessed perceived self-location (**POSITION** experiment; Figure 2.1A), motion duration (**TIME** experiment; Figure 2.1B) and velocity (specifically angular velocity - **MOTION** experiment; Figure 2.1C) in a vestibular guided (passive whole-body rotation) task in the dark in 14 right hemisphere stroke patients whose cumulative lesion distribution involved a large extent of the right cerebral cortex and 14 age-matched controls. We confirmed the dependence of these tasks upon vestibular functioning by testing a patient with complete peripheral vestibular

failure and no brain lesion. Right hemisphere damage can often result in spatial neglect, a syndrome associated with reduced awareness of contralesional space (10). As it is unclear whether neglect *per se* is related to disrupted self-location perception, we tested for the presence of neglect (**NEGLECT BATTERY** – see Methods).

2. 2 Materials and Methods

Participants

We tested 14 patients with focal right hemispheric cortical strokes. Behavioural tests and clinical assessments were performed between 3 and 12 days of symptom onset (see Table 2.1 for actual timing of testing with respect to stroke onset for all patients). All patients underwent clinical and psychometric assessments of neglect including star cancellation, copying of drawings (27), and line bisection (18 cm lines), immediately before taking part in the experiment. Fourteen age-matched controls with no history of neurological or peripheral vestibular disease were also tested. Two patients (a man of 45yrs and a woman of 73yrs) with absent vestibular function also performed all behavioural tasks. A full neurological and neuro-otological examination was performed on all subjects.

Neuroimaging

Brain lesions in stroke patients were imaged by MRI or CT (two patients - S11 and S13) and plotted using MRIcro software (<http://www.cabiatl.com/mricro/mricro/index.html>) using a graphics tablet (WACOM). A T1-weighted template consisting of 12 axial slices was used to demarcate the lesions for all patients. Lesion overlap and subtraction were carried out in MRIcro.

Group	Initials	Sex	Age	Scan	Aetiology	Lesion location	TTS (days)	LHH	EXT	SC (R,L)	Line bisection	Regression slope		SYMMETRY GAIN (POSITION expt)
												R	L	
Stroke														
S1	MP	F	71	MRI	Infarct	Temporo-parietal	10	No	Yes	26,27	0.9	0.8	0.19	0.24
S2	DW	M	60	MRI	Infarct	Fronto-parietal	4	No	No	27,27	-0.1	0.9	0.78	0.87
S3	WP	M	70	MRI	Infarct	Temporo-parietal	8	Yes	Yes	0,5	10.0	0.87	0.78	0.90
S4	SB	F	50	MRI	Infarct	Thalamo-striatal	5	No	No	27,27	-0.2	0.74	0.7	0.96
S5	PB	M	48	MRI	Infarct	Parietal	4	No	No	20,27	2.4	0.87	0.21	0.24
S6	DR	F	72	MRI	Infarct	Thalamo-striatal	12	Yes	No	26,27	2.5	1	1	1.00
S7	DL	M	68	MRI	Infarct	Thalamic	7	No	No	27,27	0.5	0.79	0.84	1.06
S8	MH	F	71	MRI	Haemorrhage	Parietal	3	No	No	26,26	-0.8	0.76	0.7	0.92
S9	PL	M	64	MRI		Parietal	5	No	No	27,27	0.1	0.84	0.81	0.96
S10	JF	F	53	MRI	Infarct	Lentiform	6	No	No	26,26	-1.0	0.85	0.89	1.05
S11	CK	M	80	CT	Infarct	Parieto-occipital	3	Yes	No	16,26	6.8	0.68	0.78	1.15
S12	BW	M	48	MRI	Infarct	Parieto-insular	4	No	No	25,27	1.2	0.79	0.89	1.13
S13	PE	M	68	CT	Infarct	Parieto-occipital	5	No	No	12,26	8.4	0.69	0.68	0.99
S14	DB	F	71	MRI	Infarct	Parietal	3	No	No	27,27	0.2	0.74	0.35	0.47
Control														
C1	AS	F	61	N/A	N/A	N/A	N/A	No	No	N/A	N/A	0.87	0.78	0.90
C2	RM	M	66	N/A	N/A	N/A	N/A	No	No	N/A	N/A	1.01	0.78	0.77
C3	DL	M	55	N/A	N/A	N/A	N/A	No	No	N/A	N/A	0.73	0.86	1.18
C4	JL	F	62	N/A	N/A	N/A	N/A	No	No	N/A	N/A	0.89	0.84	0.94
C5	BG	M	72	N/A	N/A	N/A	N/A	No	No	N/A	N/A	0.87	0.92	1.06
C6	DB	M	64	N/A	N/A	N/A	N/A	No	No	N/A	N/A	0.92	0.87	0.96
C7	EV	F	60	N/A	N/A	N/A	N/A	No	No	N/A	N/A	0.78	0.84	1.08
C8	JW	F	62	N/A	N/A	N/A	N/A	No	No	N/A	N/A	0.95	0.86	0.91
C9	JM	M	68	N/A	N/A	N/A	N/A	No	No	N/A	N/A	0.97	0.84	0.87
C10	MG	M	65	N/A	N/A	N/A	N/A	No	No	N/A	N/A	0.89	0.93	1.04
C11	ML	F	64	N/A	N/A	N/A	N/A	No	No	N/A	N/A	0.86	0.96	1.12
C12	PL	M	66	N/A	N/A	N/A	N/A	No	No	N/A	N/A	0.90	0.73	0.81
C13	OT	F	60	N/A	N/A	N/A	N/A	No	No	N/A	N/A	0.87	0.84	0.97
C14	PC	F	67	N/A	N/A	N/A	N/A	No	No	N/A	N/A	1.0	0.89	0.89
Avestibular														
A1	JT	M	42	N/A	N/A	N/A	N/A	No	No	N/A	N/A			
A2	PS	F	76	N/A	N/A	N/A	N/A	No	No	N/A	N/A			

Table 2.1 Patient demographics, lesion location and summary of performance in the POSITION experiment and NEGLECT battery. TTS= time to stroke; LHH= left homonymous hemianopia; EXT= extinction; SC= star cancellation; N/A= not applicable; Symmetry gain refers to the performance gain for the POSITION experiment (L/R); Avestibular= complete peripheral vestibular failure.

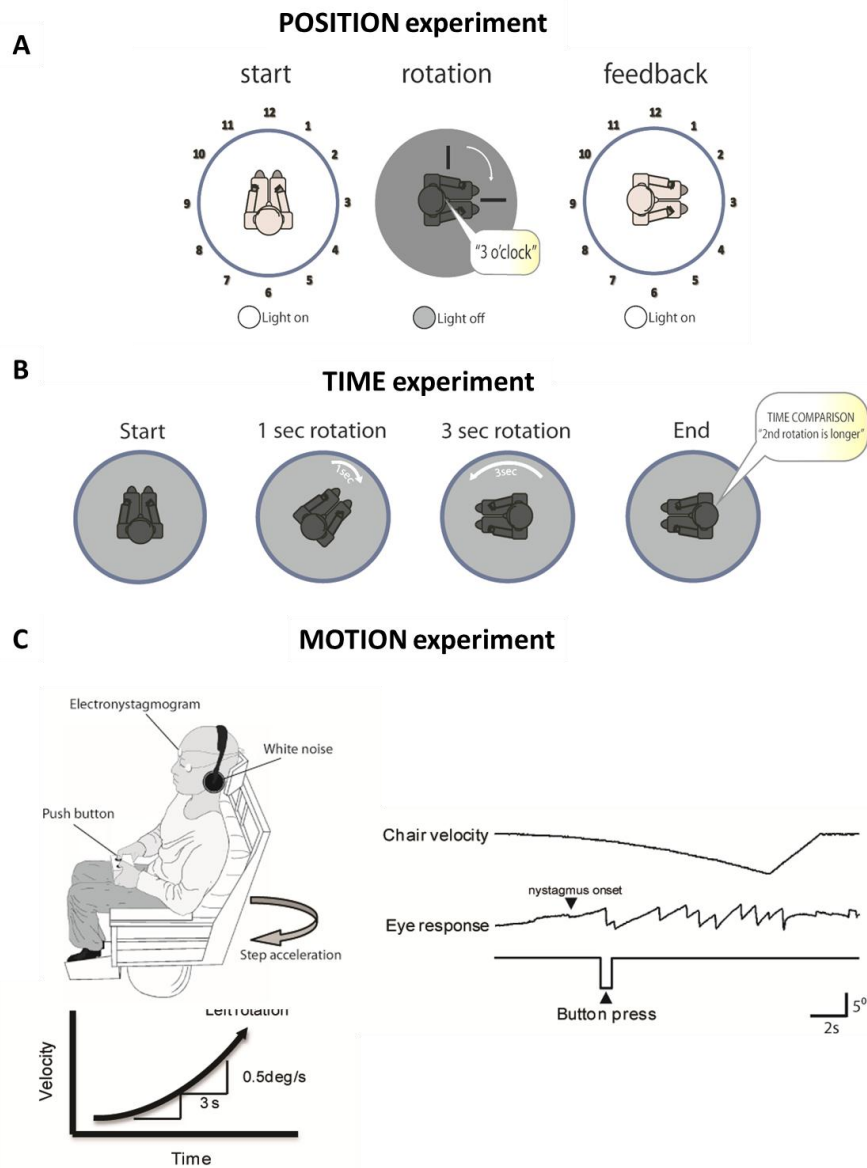


Figure 2.1. Methods (A) Participants sat in a motorised rotating chair, surrounded by a curtain with the numbers of clock facing the participant. The chair rotated from the *start* 12 o'clock position to another location in the dark, and subjects then indicated their clock face position. (B) Participants were seated in a rotating chair in the dark (*START*), and rotated in one direction for a given length of time ('1s rotation'). They were then rotated in the opposite direction ('3s rotation') and were asked to call out which of the two rotations was the longer "1st" or "2nd". If unsure, they were asked to guess. They were then rotated back to the start (*END*). (C), Participants began seated in the motorised rotating chair in the dark. The chair was rotated with step accelerations of $0.5^\circ/\text{s}^2$ every 3 seconds, up to a maximum acceleration of $3.5^\circ/\text{s}^2$. Participants were asked to indicate their perception of motion using a button press as soon as they felt they were moving. If unsure, they were asked not to press any button. Ocular motor responses were recorded using electro-oculography. Time differences between the two rotations used were 0, 0.25, 0.5, 0.75, 1, 2, and 3 seconds. Angular velocities of $60^\circ/\text{s}$ and $90^\circ/\text{s}$ were used in random order.

POSITION experiment

Subjects were seated in a motorised Barany chair and surrounded by a black curtain suspended from a fixed drum above the chair (Figure 2.1A). Numbers from 1 to 12 (angular size 14.8°) were attached to the inside of the curtain, equally spaced by 30° , representing a clock face. The start position was with the subject facing 12 o'clock. White noise was given via headphones and the subjects then rotated in the dark to directly face a number on the curtain. Whilst still in the dark they were asked to say what number they believed they were facing. Visual feedback was then provided by briefly turning the lights on. The lights were switched off and the subject rotated back to the start (12 o'clock). The lights were briefly switched on to provide confirmation to subjects that they were back at the start position (12 o'clock), and the task repeated (72 repetitions in total). Subjects were rotated to the left or the right, through angles of 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330 and 360° in randomised order with peak angular velocities of $60^\circ/\text{s}$ or $90^\circ/\text{s}$ such that all rotations were within the optimal range for vestibular stimulation (28). To ensure a standard response across subjects, prior to the formal experiment, subjects performed 10 'practice' trials.

TIME experiment

Subjects were seated in a motorised rotating chair in the dark, with white noise played through headphones. In this task, subjects were specifically asked to concentrate on the duration of self-rotations. To ensure that patients were clear that the task required a temporal discrimination and not self-location perception, we removed the clock numbers from the visual surround. Specifically subjects were given two discrete angular rotations of varying duration, and asked to indicate which of the two rotations was the longer in duration – 1st or 2nd (Figure 2.1B). Angular velocities of $60^\circ/\text{s}$ and $90^\circ/\text{s}$ were used, with durations of either 1, 1.5, 1.75, 2, 2.5, 3 or 4 seconds to produce relative time differences between rotations of 0,

0.5, 0.75, 1, 2, or 3 seconds. The time task was shortened for the lesion patient group to ensure maintenance of vigilance by testing time differences of 0 and +/- 3 seconds.

MOTION experiment

Perceptual responses were recorded to measure the threshold of horizontal canal-mediated motion perception. We used a modified version of the technique described by Seemungal et al. (29) as in Cutfield et al. (30). Subjects sat on a motorised chair that rotated in the yaw (horizontal) plane, with white noise played through headphones (Figure 2.1C). The chair was rotated to either the left or the right in the dark with an initial step acceleration of $0.5^\circ/\text{s}^2$, and subsequent increments of $0.5^\circ/\text{s}^2$ every 3 seconds until either the subject correctly indicated their motion direction via push button or the maximum allowed acceleration of $3.5^\circ/\text{s}^2$ was breached. Only patients with peripheral vestibular failure failed to indicate self-motion before the $3.5^\circ/\text{s}^2$ limit. Four motion thresholds were obtained for each direction. Simultaneous ocular motor responses were recorded using electro-oculography. The lights were turned *off* just prior to each rotation to cue subjects to the imminent chair motion, and switched *on* 20 seconds after each rotation to signal the end of the trial. This allowed sufficient time for nystagmus to disappear.

2.3 Data Analysis

DC coupled horizontal electro-oculography, filtered at 30Hz, was performed to record ocular motor responses to angular acceleration during the motion task only. There was no spontaneous nystagmus in the light or dark, and no vestibular ocular motor asymmetries detectable in any patient. A chair tachometer was used to record chair velocity for all tasks. Angular displacement was obtained by integrating the velocity signal from the chair tachometer. All signals were recorded at a sampling rate of 250 Hz for off-line analysis. For

the position task, regression slopes between right and left rotations were compared using a two-tailed *t*-test, and correlation coefficients were compared using Fisher's *r*-to-*z* transformation. *z* values were obtained using the formula $z_r = (1/2)[\log_e(1+r) - \log_e(1-r)]$ where *r* is the regression co-efficient. A line was fitted through the data set using the method of least squares. A *z*-test was performed to calculate the *p* value. Psychometric probability curves were plotted to display the time perception data using Sigmaplot (Systat, version 11). A Chi-square test was performed to compare probability responses for zero second differences (the point at which responses cross the *y* axis) in the time task. For the motion task, onset of nystagmus was calculated as the point at which the slow phase velocity leaves baseline and does not return. Velocity and acceleration values were extracted from the chair tachometer and the ocular motor and perceptual threshold responses were analysed as the time to button press and nystagmus onset (Figure 2.1C). For passive physiological range head angular accelerations (28) of circ. 3 seconds or less, semi-circular canal cupula deflection, and in turn subjective estimation of the angle of displacement, depends upon both the absolute angular acceleration and the duration of the acceleration (31). Thus a low angular acceleration will be perceived if applied for long enough (Mulder's law (31)). To account for this time and acceleration dependence, the subjective acceleration threshold was calculated by multiplying angular acceleration (α) by time (τ), whereby α is the whole-body angular acceleration at time of button press and τ was the time taken for subjects to press the button for that given acceleration. Since the stimulus comprised a staircase of incremental accelerations (Figure 2.1C), we derived a cumulative measure of $\alpha\tau$ (Mulder's coefficient) for the acceleration range used. Statistical analysis was performed on the cumulative $\alpha\tau$, using a one-way ANOVA, as acceleration thresholds are not continuous data. A post-hoc comparison of motion detection thresholds between patients with lesions involving the posterior insular

(n=4), all other stroke patients, and controls, was performed using a repeated measures ANOVA.

2.4 Results

Cortical lesions for all patients are delineated in Figure 2.2. Patients' spatial performances were assessed via linear regression (response vs. stimulus angle – see Figure 2.3 for individual regressions). Table 2.1 (far right) shows each subject's **POSITION** experiment performance analysed via a 'symmetry gain' that is a measure of symmetry between rightward vs. leftward regression slopes. We performed t-tests between leftward and rightward responses for subjects' respective regression r^2 (following a Fisher's r-to-Z transformation) and slopes. Only three patients (S1, S5 and S14) showed a significant difference between right and left rotations for both r^2 and slopes ($P < 0.0001$; Figure 2.3 indicated by **) with all three subjects showing worse *leftward* performance. Hence we performed a lesion overlap analysis, dividing patients into normal spatial performance (Figure 2.5A) versus abnormal spatial performance (Figure 2.5B). The lesion overlap for patients with poor spatial performance (Figure 2.5B) included the right posterior insular cortex, considered to be a core region of the vestibular cortex (11) as well as the right angular gyrus in the temporoparietal junction (TPJ). A lesion subtraction analysis i.e. lesion overlap of poor performing patients minus lesion overlap of well performing patients, (Figure 2.5C) showed a resulting region of interest involving the right TPJ focused in the angular gyrus, but now without insular cortex. We surmise that an intact right angular gyrus is required for accurate self-localisation for contralaterally directed whole-body rotations.

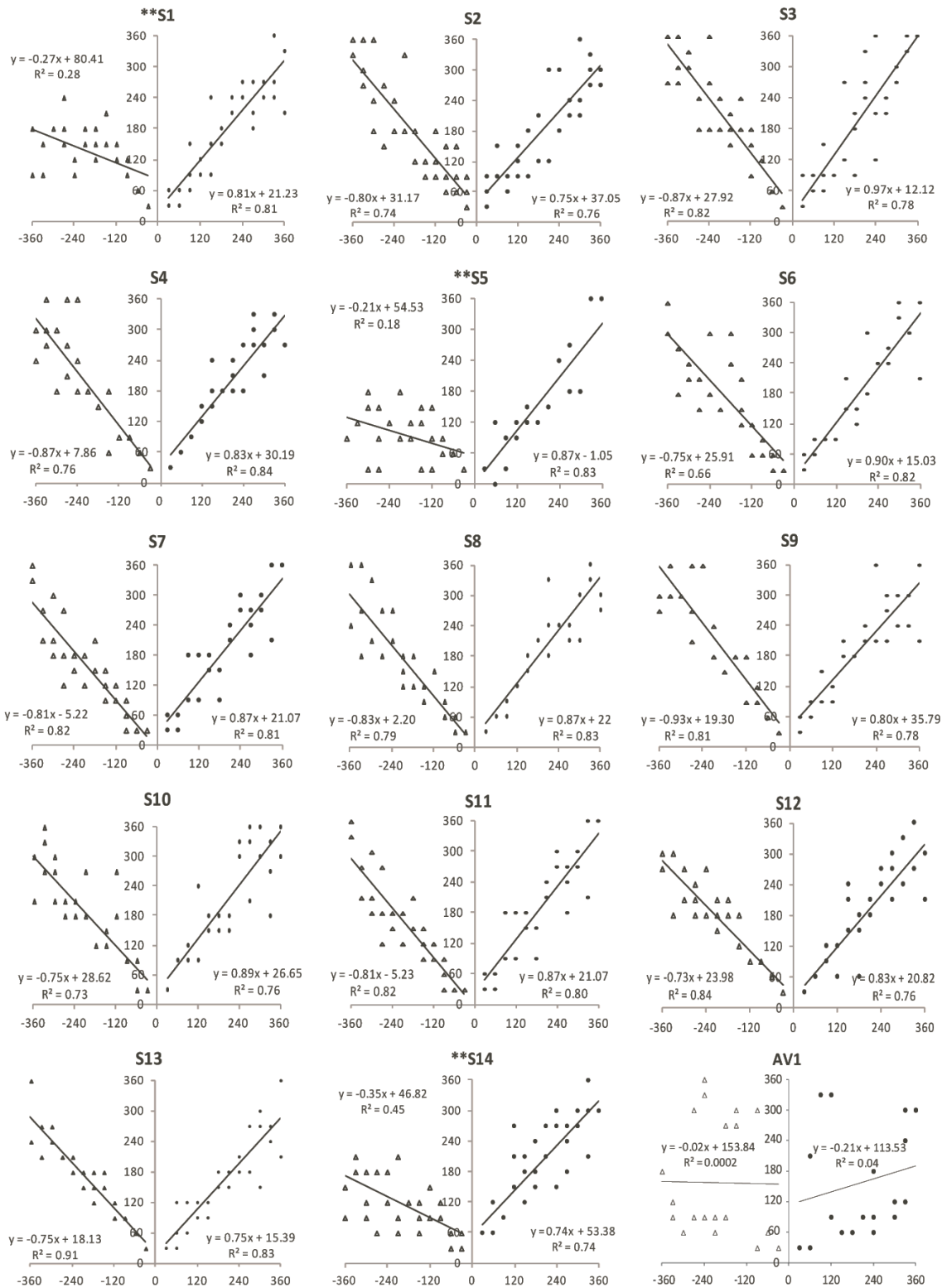


Figure 2.3 Individual patient data. Individual performance in the POSITION experiment for all stroke (S1-S14) and avestibular (AV1) patients.

A parsimonious explanation for the spatial deficit seen in right angular gyrus lesion patients could be that these patients did not adequately perceive their passive rotations, in which case a deficit in the **MOTION** experiment could explain their spatial performance. We obtained subjects' motion perception thresholds (**MOTION** experiment; Figure 2.1B) by rotating subjects in the dark, initially at low acceleration and then at progressively higher accelerations until the subjects correctly indicated their direction of motion. All patients irrespective of lesion location, showed normal motion thresholds compared to healthy age-matched controls for both ocular motor and perceptual measures (**MOTION** experiment, Figure 2.1C and Table 2.2).

Since all subjects' motion perception measures were normal, and since in theory, perceived position is derived by a process analogous to a temporal integration of the vestibular velocity signal, could a deficit in perceived time explain the impaired spatial performance of patients S1, S5, and S14? Remarkably, the three TPJ (angular gyrus) lesion patients were the only patients to display a clear bias in motion duration perception for comparison rotations of equal duration, i.e. when right rotation duration minus left rotation duration was zero (Figure 2.1C; $P_{\text{Right} > \text{Left}} = 0.82$; χ^2 ; $P < 0.05$), in a manner that could potentially explain their spatial deficit (Figure 2.3). Specifically, these patients (S1, S5, S14) displayed hypometric spatial estimates of motion for leftward rotations congruent with their report of a perceived shortened motion duration for leftward compared to rightward rotations (Figure 2.4 *top*). We also assessed subjects' comparison of motion durations between rotations of the same direction (right vs. right, and left vs. left) and found that performance was uniform across all subjects, with preserved detection of 3s differences between rotations, and chance-level functioning for equal-duration rotations. Finally, the order of presentation did not bias subjects' responses since for equal duration rotations, the probability of a subject saying that

the “1st rotation was longer than the 2nd rotation” was not significantly different (one-way ANOVA with factors group and response; $p=0.58$).

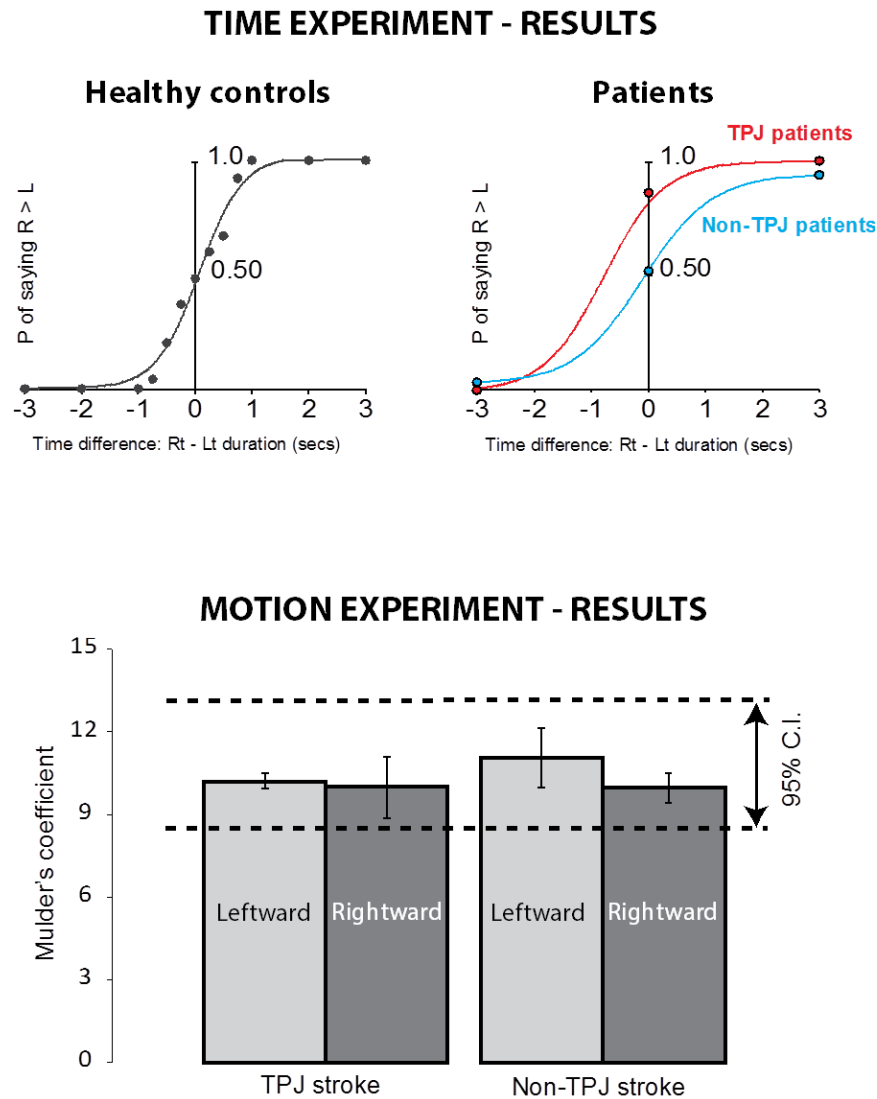


Figure 2.4 *Top*: TIME EXPERIMENT results. Subjects were required to compare the durations of two consecutive rotations (see Fig. S1E). Shown are the probabilities of subjects saying that the rightward rotation was of longer duration than the leftward for controls (black), TPJ (red) and ‘non-TPJ’ lesion patients (blue). *Bottom*: MOTION EXPERIMENT results. Angular velocity thresholds (Mulder’s coefficients) for ‘TPJ’ stroke patients, and ‘Non-TPJ’ patients.

	Right						Left					
	Acceleration (deg/s ²)		Velocity (deg/s)		Duration (s)		Acceleration (deg/s ²)		Velocity (deg/s)		Duration (s)	
	Perceptual	Eyes	Perceptual	Eyes	Perceptual	Eyes	Perceptual	Eyes	Perceptual	Eyes	Perceptual	Eyes
S1	1.2 (0.29)	1.0 (0.5)	6.7 (0.57)	1.5 (0.21)	7.3 (0.74)	3.7 (0.68)	1.0 (0.5)	1.3 (0.29)	7.2 (0.66)	3.4 (0.54)	7.6 (1.6)	4.8 (0.43)
S5	1.3 (0.29)	1.0 (0.5)	7.3 (0.76)	1.9 (0.43)	7.7 (0.54)	3.2 (0.34)	1.5 (0)	1.3 (0.29)	8.5 (0.50)	6.7 (0.23)	8.13(0.44)	5.5 (0.31)
S14	1.4 (0.31)	1.3 (0.43)	7.7 (0.51)	6.0 (1.2)	8.1 (1.1)	5.0 (0.8)	1.6 (0.44)	1.3 (0.29)	7.4 (0.55)	6.2 (1.6)	6.4 (1.9)	4.6 (0.5)
Stroke (n=11)	1.7 (0.71)	1.51 (0.76)	9.5 (1.3)	6.6 (1.1)	9.6 (3.0)	5.6 (1.8)	1.7 (0.74)	1.6 (0.82)	9.2 (1.4)	7.1 (2.2)	9.1 (3.2)	6.2 (2.9)
Controls (n=14)	1.8 (1.6)	1.7 (1.3)	11.2 (1.6)	6.9 (1.7)	10.0 (3.1)	5.4 (2.1)	1.8 (1.1)	1.6 (0.99)	10.0 (1.7)	4.5 (2.7)	9.9 (3.3)	6.1 (2.6)
Avestibular (n=2)	>3.5	>3.5	>80	>80	>30	>30	>3.5	>3.5	>80	>80	>30	>30

Note: Test sensitivity and specificity was as follows:

Healthy (n=14), false -Ve rate = 3.6%, false +Ve rate = 6.3%, giving a specificity of 98.2% and sensitivity of 97.4%.

Stroke (n=14), false -Ve rate = 3.6%, false +Ve rate = 4.8%, giving a specificity of 98.2% and sensitivity of 94.1%.

Table 2.2 Performance for the MOTION experiment

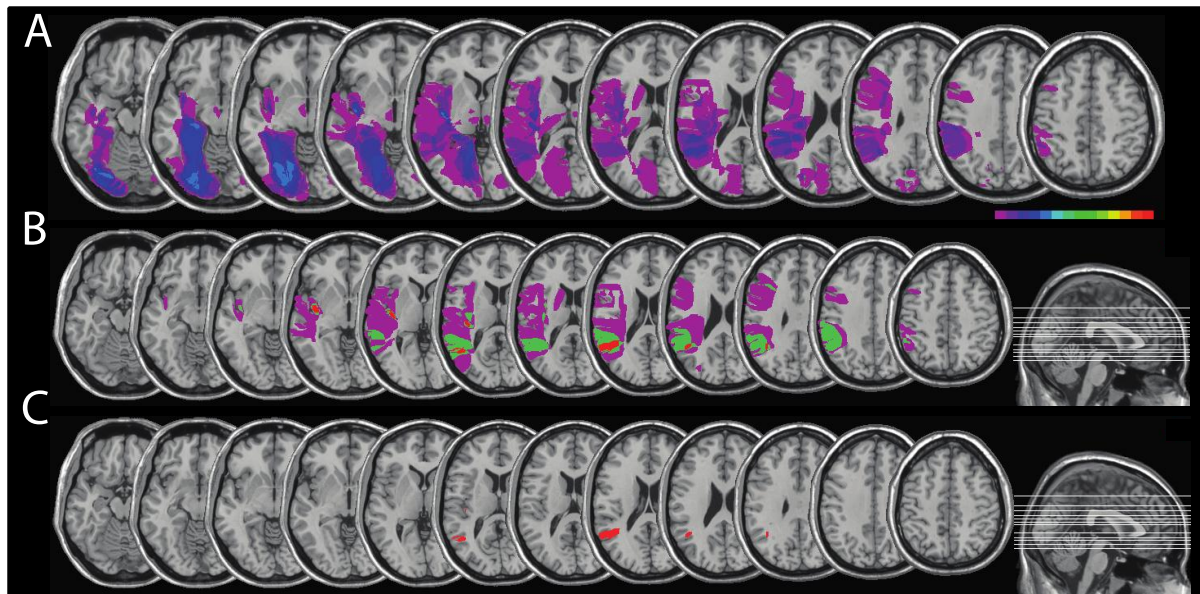


Figure 2.5 MRI lesion analysis. (A) Lesion overlap for the eleven stroke patients displaying *normal* performance in the POSITION experiment. Colour key on the bottom right indicates the number of patients with damage in that particular cortical region. (B) Lesion overlap for the three patients S1, S5 and S14 with *abnormal* performance in the POSITION experiment. Areas in purple are damaged in only one patient (S5), areas in green show damage common to two patients (S1 and S5), and the areas in red are damaged in all three patients (S1, S5, and S14). (C) Finally, the lesion overlap region common to all three patients (S1, S5, and S14) but not lesioned in the other eleven stroke patients. The MNI coordinates for this region shown in red are 41, -52, 24 (angular gyrus) extending inferiorly to 44, -59, 13 (middle temporal lobe).

A potential confound for our data was that of hemi-spatial neglect. Neglect typically accompanies right-hemisphere damage, often in the TPJ (12, 13), and is characterized by an inability to report, respond or orient to novel or meaningful stimuli presented on the contralesional side (14). Importantly, we found that visuospatial neglect could not explain our findings since the observed abnormalities in space perception were dissociated from the occurrence of spatial neglect (Figure 2.6 and Table 2.1). Additionally, all patients had normal behavioural responses to inertial chair rotations (**MOTION** experiment; Table 2.2 and Figure 2.4 *bottom*) indicating preserved attention to angular motion bilaterally. Note that the **MOTION** task required subjects' to indicate (via button press, see Materials and methods) as

soon as they confidently perceived themselves to be rotating in a particular direction; i.e. there is a time element to this task. That we did not find an asymmetry in **MOTION** responses indicates that a problem with the instantaneous encoding and decoding of motion perception *per se* could not explain the observed spatial impairments. In addition, neglect has been shown to disrupt the mental number line – a “metaphor for the representation of numbers in the brain” (15) potentially explaining the spatial bias observed in the position experiment in the angular gyrus lesion patients. Mental number line deficits manifest bias, but not increased variability, which is incongruent with the observed bias *and* increased variability in the angular gyrus lesion patients’ spatial performance (Figure 2.3).

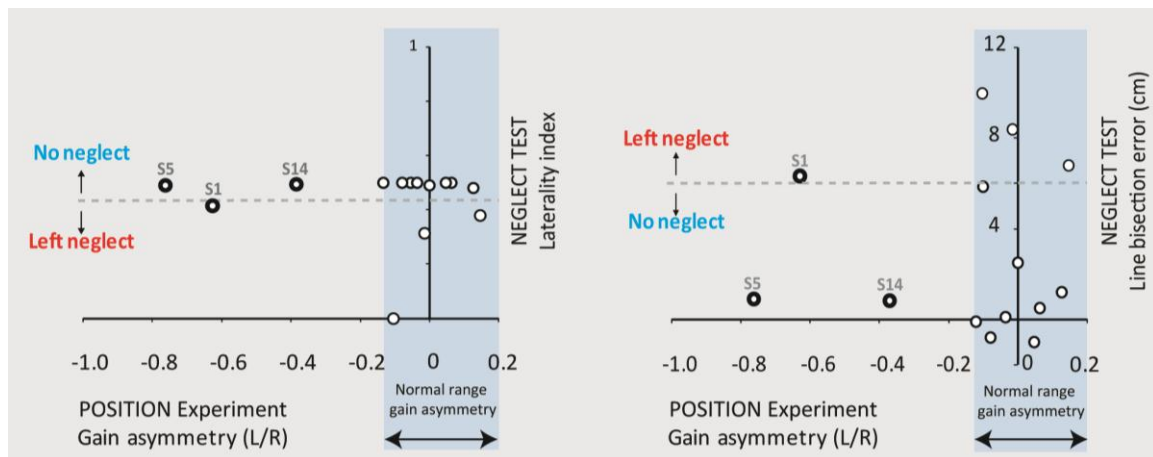


Figure 2.6 Correlation between spatial orientation and neglect. Star cancellation task (*Left*). Laterality index is calculated as the total number of stars observed in the left hemispace divided by the total number of stars. Values below 0.43 signify the presence of left neglect. Gain asymmetry was obtained from the individual regression slopes for the POSITION experiment shown in Figure 2.3 and calculated by dividing the leftward regression slope by the rightward regression slope. Negative values denote a leftward spatial deficit. The gain asymmetries for the three patients with a POSITION experiment spatial deficit are labelled in grey. The range of gain asymmetry for the healthy control group is shaded in blue. Line bisection task (*Right*). Line bisection error is calculated as the deviation (in cm) from the midpoint of an 18cm horizontal line. A deviation ≥ 6 cm signifies neglect.

Although our patient data provides compelling evidence that perceived angular position is causally dependent upon an accurate percept of motion duration, another explanation is that the two measures of self motion regarding space and time are not causally linked but that

their neuro-anatomical substrates are juxtaposed in cortical location. A causal link would seem the more likely explanation since the observed co-lateralization of the deficit in time and space makes a casual association less probable. Indeed, this data supports previous data (Seemungal, thesis 2004) that assessed the effect of distorting internal estimates of self-orientation on perceived motion duration. When visual feedback was perturbed so that the visually-indicated distance was greater or lesser than the actual travelled distance, then subjects indicated that they had travelled for a greater or lesser duration respectively. Our results indicate that self-location perception relies upon time perception, a hitherto not described function of interval timing mechanisms (16).

2.5 Discussion

Our results are consistent with an internal model whereby path integration is derived via an explicit temporal integration of vestibular head velocity signals, and the patient lesion results indicate that this neural temporal integration is mediated by the angular gyrus. Interestingly, the concept of an internal model mediating vestibular perception in the TPJ cortex is hinted at in two related studies. Firstly Indovina et al. (17) found increased TPJ activation (via fMRI) when subjects viewed objects falling under g versus negative g implying an internal model of acceleration due to gravity (g). Secondly, perturbing TPJ function via TMS impaired subjects' timing of interception in response to a moving visual target, but only when the target was moving in a direction consistent with g (18).

Current consensus includes the posterior insular cortex as a core vestibular region in humans (19). We did not find an insular locus in patients with a spatial deficit, but considered whether an insular lesion could preferentially affect self motion perception. Four patients (S1, S3, S5,

and S12) with posterior insular involvement however, showed normal angular motion thresholds as compared to patients whose lesions spared the posterior insular, or indeed to healthy controls (repeated measures ANOVA_{lesion-side} $F(1,26) = 1.69$, $p = 0.25$). Our data thus show that unilateral lesions of the posterior insular cortex do not disrupt angular motion perception. Indeed clinical data (20) supports a more superficial cortical location for vestibular processing than the deep insular region, initially identified in primates (21). Indeed, the lack of any effect on vestibular motion processing despite the across-group swath of lesioned cortex suggests that motion perceptual responses are elaborated by a distributed cortical network and hence damage in one hemisphere may be compensated for by the intact hemisphere. The dichotomy in motion versus spatial perceptual function following cortical damage may also indicate that vestibular-derived percepts of position and motion are distinct entities mediated by separate neuro-anatomical substrates, a concept supported by previous data in healthy subjects (9, 22).

Recent data from Out of Body Experiences (OBEs) evoked by electrocortical stimulation or epileptic seizures at the TPJ (23-25) has been used to suggest that the TPJ mediates 'everyday' spatial orientation perception. Our task is quite far removed from OBE-type sensations but our data do support the notion that updating ones perceived self-location does require the angular gyrus in the TPJ but specifically via a process of path integration. Since the TPJ is involved in many different types of processes (26) including those totally unrelated to self-location perception, the co-localisation of two functions to the TPJ do not imply a causal relationship of the two functions. However, the co-localisation of a path integrator function and a function that mediates sensations of body location are clearly complementary. Thus our findings suggest that the current model of self-location perception being the result of a multi-modal visual and somatosensory integration is incomplete (23), since our data show that

internal estimates of time must also be integrated into the multi-modal derivation of a percept of self-location.

In summary, we have shown that lesions involving the right angular gyrus in the TPJ impair the spatial updating of self-location perception and estimates of motion duration, following contralateral whole body rotations under vestibular guidance. We thus conclude that the angular gyrus in the TPJ acts as a cortical temporal integrator to support the updating of self-location perception during whole-body motion.

2.6 References

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Selected Case Histories:

Patient S1

MP is a 67 year old lady with a background history of hypertension and hypercholesterolaemia. She presented following an acute visual disturbance whilst at home with her grandson. Whilst trying to make a tea, she was unable to locate the teabags, normally on the left hand side of the cupboard. Although she recalls being “sure that they must have been there” she was unable to see them. The grandson found the teabags, which were in front of the patient. A few minutes later, he noticed that the patient was slurring her speech, and that the left hand seemed to drag by her side. Suspecting a stroke, he called the ambulance and the patient was admitted to hospital. A CT scan confirmed the presence of a right middle cerebral artery territory stroke, confirmed later as an acute infarct on diffusion-weighted magnetic resonance images (MRI) affecting the posterior parietal lobe, the insula and temporoparietal junction.

Two days later, the patient was found wandering the corridors of the hospital on the ground floor. The occupational therapist who found the patient commented that the patient was surprised “she had been gone so long” and had “lost track of time”.

Patient S5

PB is a right-handed 48 year old Police officer with a history of hypertension. He described sudden onset weakness in the left arm, with sensory loss. His speech was only mildly affected and he had gone to sleep that night, and represented the following morning with worsening speech and loss of power in the left side of the body. He described a sensation of

disorientation that morning, and a feeling of “dizziness” which he likened to “lightheadedness” rather than spinning-type vertigo.

The MRI scan confirmed a right hemispheric middle cerebral artery territory stroke involving the parietal lobe.

C_{hapter} 3

The right hippocampus in spatial navigation processing

3.1 Introduction

The hippocampal formation is widely agreed to be important for processing early encoding, consolidation and retrieval of memory (1). Moreover, considerable evidence obtained from animal and human studies highlights a hippocampal role in spatial memory functions (2-4). Three types of neurons related to spatial behaviour have been found within the medial temporal lobe. Firstly, place cells primarily encode information about the animal's location within an environment and exhibit their peak discharge when the animal occupies that cell's particular "place field" (5, 6). Secondly, head direction (HD) cells encode the animal's directional heading in the horizontal plane, with each cell discharging to a particular "preferred firing direction", independent of the animal's location (7). HD cells have also been identified in other brain areas within the classic Papez circuit (8), the anterior thalamic nucleus in particular (9). Thirdly, grid cells located upstream of place cells in the entorhinal cortex, exhibit a grid-like structure of place fields that repeat at regular intervals along the environment. These three cell types together form an allocentric (world-centred) representation of the animal's location and orientation within its environment, which is also referred to as a "cognitive map" (10).

Place cells are driven by self-motion signals via a process termed 'path integration', whereby proprioceptive, vestibular, and motor efference copy signals from intended movements, incrementally update the actual position relative to the starting position during navigation. In fact, idiothetic cues of vestibular and proprioceptive origin are sufficient to encode space in an egocentric reference frame. Thus, landmark recognition relies upon remembered scenes in familiar environments, whereas path integration is independent of visual surroundings. Marr proposed a seminal computational model of hippocampal function (11), later extended and clarified (12-14), in which a given event, represented as a pattern of activity in a population

of neurons, is temporarily stored in the hippocampus. Subsequent retrieval of the whole representation can occur from an incomplete cue through ‘pattern completion’ by activating sufficient cells that originally responded in the storage of the full event. It follows that reinstatement of the full representation of a given event can occur in disparate neocortical areas. This model predicts that the initial encoding of multi-modal afferent information occurs in the hippocampus, where cortical afferents can come together.

Considerable neuroanatomical and neurophysiological evidence suggest that one such afferent source of information to hippocampal processing of spatial information is vestibular (15). Vestibular signals may reach the hippocampus via 2 different routes. The prevailing route involves projections from vestibular nuclei to the parietal cortex via the thalamus, which then project back to the hippocampus via the perirhinal and entorhinal cortices (16, 17). Via this route, the position signal derived from the posterior parietal cortex (see Chapter 2) reaches the hippocampus and provides an egocentric (head-centred) representation of animal’s position after movement. A more direct route involving the HD cell system has also been proposed, from the vestibular nuclei through the anterior thalamic nuclei, the mammillary bodies and the postsubiculum to the hippocampus (18).

Support for the role of vestibular afferents in hippocampal-based navigation stems from a variety of sources: **1)** Hippocampal place cells and HD cells in the anterior thalamic nuclei were shown to change the location at which they discharged as a result of whole-body movement in the absence of visual or proprioceptive input (19, 20); **2)** Hippocampal slow (type I theta) wave was significantly enhanced during whole-body rotations in the dark (21); **3)** “disorienting” vestibular stimulation disrupted the control of the firing patterns of place and HD cells by external cues (i.e. landmarks cues in the environment) (22). **4)** Temporal inactivation of the peripheral vestibular system results in disruption of location-specific firing

in hippocampal place cells and direction-specific discharge of HD cells in hippocampal formation (23); **5)** A human MRI study showed that modulation of peripheral vestibular activity by caloric stimulation caused activation of the hippocampal formation (24); **6)** Patients with bilateral vestibular loss develop selective atrophy of the hippocampus and exhibit significant spatial memory and navigation deficits (25). Taking animal and human studies together, there is now considerable evidence for the role of vestibular system in updating the firing patterns of HD and place cells during self-motion. This constitutes a change in allocentric representation of body position during movement. Therefore, it appears that vestibular information has a role in updating both egocentric and allocentric representations of body position in hippocampus to increase the accuracy of spatial navigation.

Whilst the contribution of vestibular signals to hippocampal spatial information processing is clear, the importance of the integrity of the hippocampus for the correct interpretation and memory of vestibular information is debatable. A study by Wiest et al. (26) showed that humans with unilateral hippocampal lesions showed deficits in performing a whole-body rotation return task, which suggested errors in vestibular memory. In contrast, Shrager et al (27) showed that patients with hippocampal lesions, when blindfolded, were able to perform well in a walking task that involved up to two turns and their performance was only impaired after a delay of over 1 min.

We hypothesised that medial temporal structures are important for the rendition of world-based spatial cognition whereas posterior parietal cortex is important in egocentric vestibular-derived motion perception (see Chapter 2 of this thesis). We predicted normal egocentric navigation performance, and impaired allocentric performance in patients with hippocampal lesions. Additionally, we hypothesised that cortical lesion patients with impairments in

vestibular working memory may demonstrate decrements in spatial performance over time. We assessed the vestibular working memory of whole body rotations in a 65-year-old female patient with a well-defined and characterised right hippocampal ischaemic lesion, and 8 age-matched healthy controls, and consider whether visuospatial working memory performance relates to visuo-spatial memory span constraints.

3.2 Materials and Methods

Subjects

We assessed the vestibular memory of whole-body rotations in a 65 year old lady with a focal lesion of the right hippocampus. The case history of this patient has been previously published (28). Clinical and neuropsychological details as described in this publication are reproduced at the end of this chapter. The patient was not taking any medication at the time of testing. Eight healthy aged-matched subjects served as controls (see Table 3.1 for demographic details). All subjects were free of neurological, ophthalmological, or psychiatric illnesses, other than the defining hippocampal disease of the patient. All subjects had a corrected visual acuity of $> 20/40$ and MMSE $> 24/30$. There was no history of a vestibular disorder in any participant, and all subjects had a normal neurological and neuro-otological assessment, including electronystagmography.

Egocentric task (SELF)

Subjects were observed at all times via infrared video camera. They sat on a vibration-free rotating chair (Contravez; torque 120 Nm) in the dark with white-noise sound masking via earphones. The chair could be rotated by external computer control (stimulus) or the subject could actively rotate himself by manipulating a directionally congruent joystick (Figure 3.1B) attached to the chair that provided a velocity demand to the servo-motor (response).

SUBJECT	HANDEDNESS	GENDER	AGE
EF	R	F	65
C1	R	M	61
C2	R	M	68
C3	R	M	64
C4	R	F	65
C5	L	F	66
C6	R	F	54
C7	R	F	60
C8	R	M	66

Table 3.1 Patient and control subject demographics

Subjects were passively rotated to a discrete angular position (left or right 15–360° from the origin) and instructed to return actively to the start position as accurately as possible, using the joystick to move themselves in the opposite direction to the stimulus movement. Time delays of 1, 4 or 8 seconds followed the passive outbound rotation, marked by a ‘beep’, after which subjects were instructed to rotate themselves actively to the origin. Time delays, rotation direction, and stimulus angle were randomised for all subjects. Subjects were asked to reproduce the displacement rather than the velocity or duration of the chair movement.

The highly responsive nature of the chair to joystick deflection required an initial period of free practice during which only subject-driven chair rotations were made (≈ 15 min; without visual, auditory cues or other indication of performance).

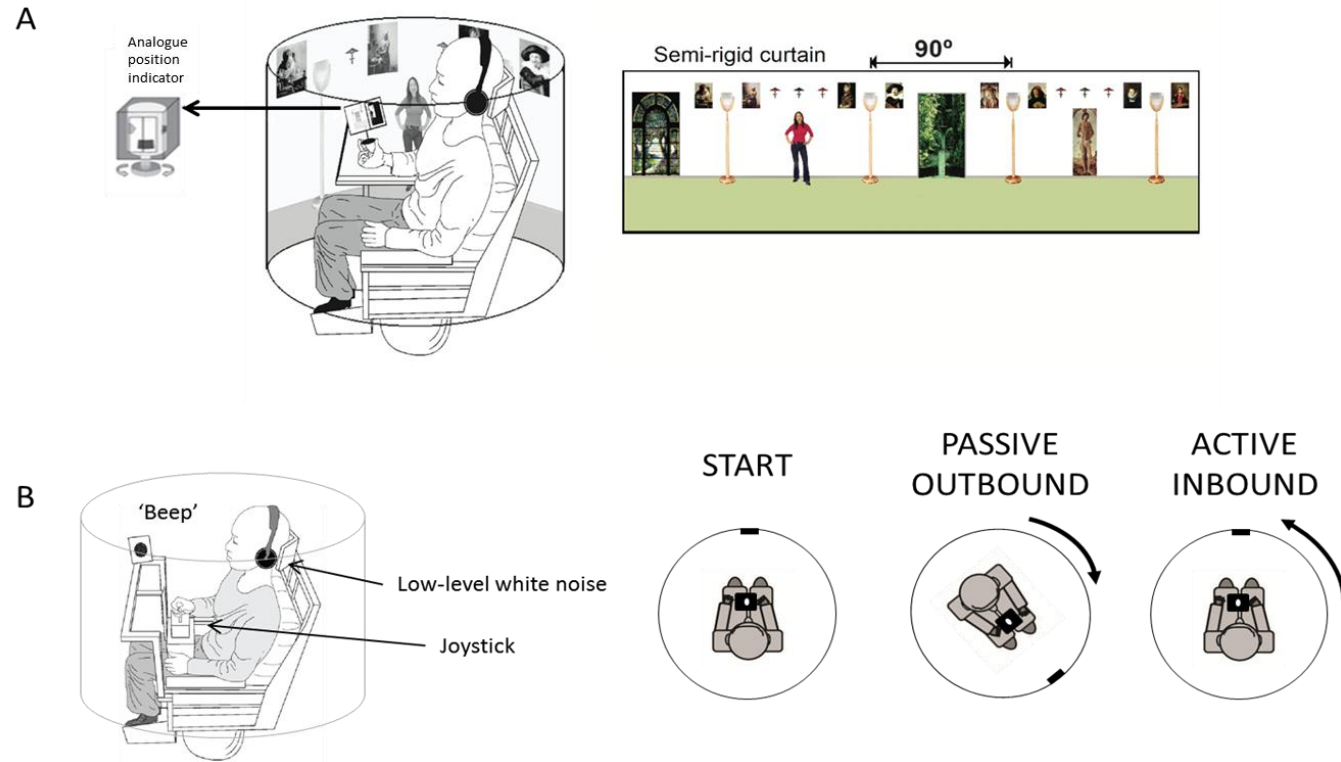


Figure 3.1 Materials and methods. (A) Allocentric navigation task (WORLD). Subjects sat in a motorised rotating chair surrounded by a curtain suspended on a fixed drum. Images on the curtain, representing pieces of art, people, or household objects, were separated by 15 degrees. A manual position indicator ('analogue position indicator') that consisted of a scale version of the visual surround was mounted on the chair. Following a period of orientation, subjects were rotated in the dark through a given angle, and asked to indicate their perceived position relative to the visual surround. (B) In the egocentric navigation task (SELF), subjects were passively rotated through a given angle in the dark, without a visual surround. They were asked to reproduce their displacement using a chair-mounted joystick, a 'return to start' task.

Allocentric navigation task (WORLD)

Subjects sat in the motorised rotating chair, which was surrounded by a large (diameter 152.4cm), semi-rigid, motorized curtain with distinct images at 15° intervals. Mounted on the chair was an analogue manual position indicator that consisted of a scale version of the large visual surround and pasted on an 8cm diameter cylinder. This was enclosed in an opaque housing with a window facing the subject. The indicator's interior was illuminated by a low intensity LED so that the subject viewed a quadrant of the visual scene, without illuminating the visual surround. By means of a dial, the 8cm drum of the 'position indicator' could be rotated (note subject's right hand turning analogue position indicator dial in Figure 3.1A) and hence subjects could indicate their perceived straight ahead with respect to the large curtain (the latter only visible with the main light on) by aligning the appropriate image on the position indicator with a central vertical crosshair in the viewing window. An on-axis potentiometer connected to the 'position indicator's' spindle recorded subjects' indicated position. Subjects started in the light (signified by white background inside curtain in Figure 3.1B), by facing the start-finish position (START). The lights were extinguished (grey background inside curtain) and subjects rotated in the dark. Subjects were instructed to indicate their perceived angular position (using the manual position indicator) at the end of the rotation and whilst still in the dark. The lights were then turned on to provide visual landmark feedback of the subject's position relative to the curtain. The subject was then rotated back to the start in the dark for the start of the next trial. Subjects always returned to the START after every OUTBOUND - INBOUND rotation pair, and the lights switched on to ensure subjects were fully orientated before the next trial. Subjects were asked to return the indicator to the start position at the beginning of each new trial.

As for the SELF task, time delays of 1, 4 or 8 seconds were introduced between the outbound chair rotation and subject's indicator response. Time delays, rotation direction, and stimulus angle were randomised for all subjects.

Visuospatial span task (ACCRUE)

In a separate session, the WORLD task was repeated with a varying number of simplified everyday visual landmarks in the patient. In the first session, we used 2 targets (chair and telephone), in the second session 3 targets (chair, telephone, football), in the third session 4 targets (chair, telephone, football, plant) and in the fourth session 5 targets (chair, telephone, football, plant, spectacles) as shown in Figure 3.2. As for the WORLD task, the patient was instructed to indicate her perceived angular position (using the manual position indicator with the simplified images) at the end of the rotation and whilst still in the dark. Delays of 1, 4 or 8 seconds were randomly assigned between the encoding and retrieval stages of the task (see Figure 3.6). Six trials were performed for each painting for each time delay (total 108 trials).

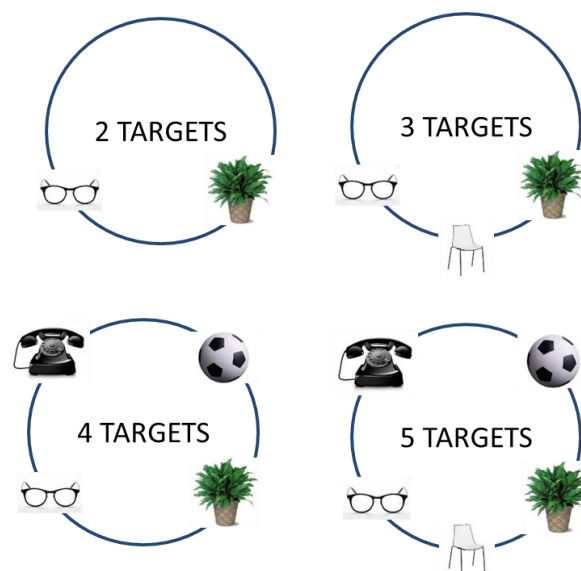


Figure 3.2 ACCRUE methods. Subjects were seated in the light in a rotating chair, surrounded by a visual scene containing everyday objects. They were then rotated in the dark to face a target. They were instructed to indicate their perceived position, relative to either 2, 3, 4, or 5 everyday targets, located at positions (clockwise) 60, 120, 180, 240, and 300 degrees.

Visual recall

The patient was shown one from a total of six renaissance paintings (Figure 3.3). She was then given all six paintings and was asked to identify which of these she had just been shown. The interval between seeing and selecting the paintings was 1, 4, 8, 30, or 60 seconds. The task was performed a total of 6 times for each painting and interval (total 108 trials).



Figure 3.3 Visual recall paradigm. Subjects were shown a target picture (encoding phase) and asked to identify this picture after a delay of either 1, 4, 8, 30, or 60 seconds from a choice of 3 pictures (middle panel). The experiment was repeated for a choice of 6 possible pictures (far right).

Audiovisual recall (BIND)

All subjects were asked to perform this task in a separate sitting at least 1 week after the chair rotation experiments. They were shown 6 renaissance paintings. Each painting was associated with a given distinctive sound of equal duration (bell, glass breaking, dog barking, bird, rain, car horn). Subjects were then randomly played one of these sounds, and asked to identify to which picture this sound belonged, from a choice of all 6 paintings. The interval between

hearing and selecting the paintings was 1, 4, or 8 seconds (Figure 3.4A&B). The task was performed a total of 6 times for each painting and interval (total = 102 trials).

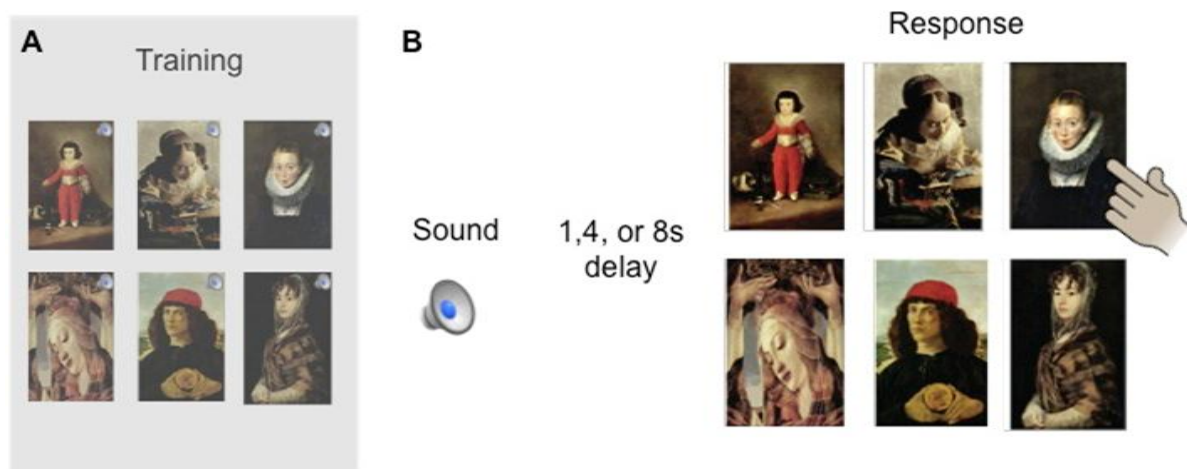


Figure 3.4 Audiovisual (BIND) task and results. (A) Subjects underwent a training period in which an image was shown together with a sound. This was performed over a period of 10-15 minutes. (B) In the experimental session, subjects were played a sound belonging to a given image. There followed a delay of 1, 4, or 8 seconds, and all 6 pictures were shown. The subject was asked to select which figure the sound played belonged to (hand).

3.3 Data analysis

For the WORLD, SELF, and VSR tasks, quantitative analysis of displacement performance was obtained by linear regression between response and stimulus displacements. Regression slopes of WORLD, SELF, and VSR tasks were compared using a two-tailed t-test, and correlation coefficients were compared using Fisher's r-to-z transformation. Z values were obtained using the formula $z_r = (1/2)[\log(1+r) - \log(1-r)]$ where r is the regression coefficient. A line was fitted through the data set using the method of least squares. A z-test was performed to calculate the p value. Absolute percentage error was calculated for each position response and compared using a one-way ANOVA. A two-tailed t test was used to compare responses between EF and controls for the visual recall and audiovisual recall tasks. Statistical analysis was carried out using SPSS (version 18).

3.4 Results

Egocentric navigation task (SELF)

Normal subjects (mean age 63 years (SD= 4.33) were highly consistent in reproducing the angular displacement as shown in Figure 3.5. The cumulative regression analysis between response (R) and stimulus displacements (S) of all data points from all normal subjects (n = 576) yielded $R = 0.78S + 14.57^\circ$ and r^2 of 0.83 ($p < 0.0001$). Separate analysis for time delays (1s, 4s and 8s) and the stimulus displacement directions (leftward or rightward), provides the values of r^2 in the range of 0.80 to 0.94 ($p < 0.0001$ for all).

Figure 3.6 shows the regression plots between response and stimulus displacements for patient EF. Patient EF performed consistently and comparatively well to normal subjects on the SELF task (Figure 3.5). SELF performance of patient EF was not significantly different from the control group for r values (Fisher's r-to-z transformation; $p > 0.05$) for their respective regressions between response and stimulus displacements.

Within-subject analysis of patient EF performance at SELF using 2×3 repeated measures ANOVA showed that the laterality (right vs. left) and time delay (1s vs. 4s vs. 8s) are not significant factors in % error displacement responses ($p > 0.05$).

SELF (Controls)

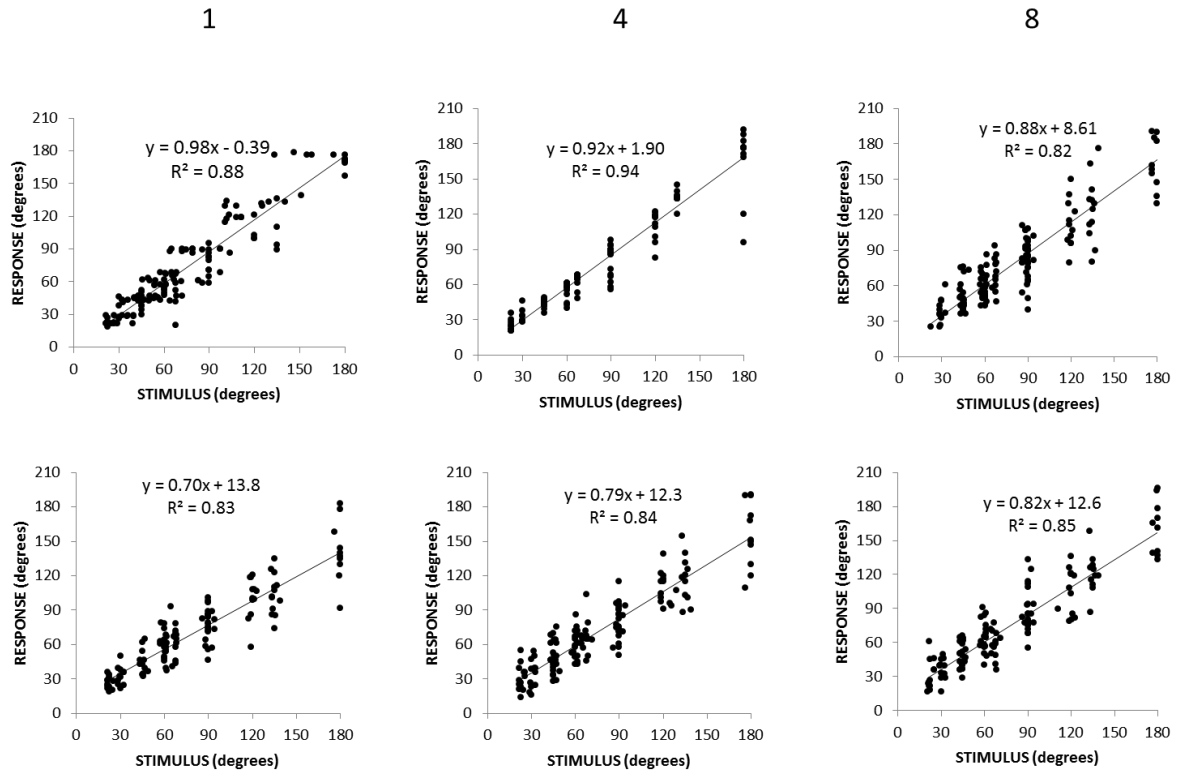


Figure 3.5 Individual responses for SELF task for the control group for 1, 4, and 8 second delays for rightward (upper panel) and leftward (lower panel) rotations. Regression slopes and coefficients appear above each plot.

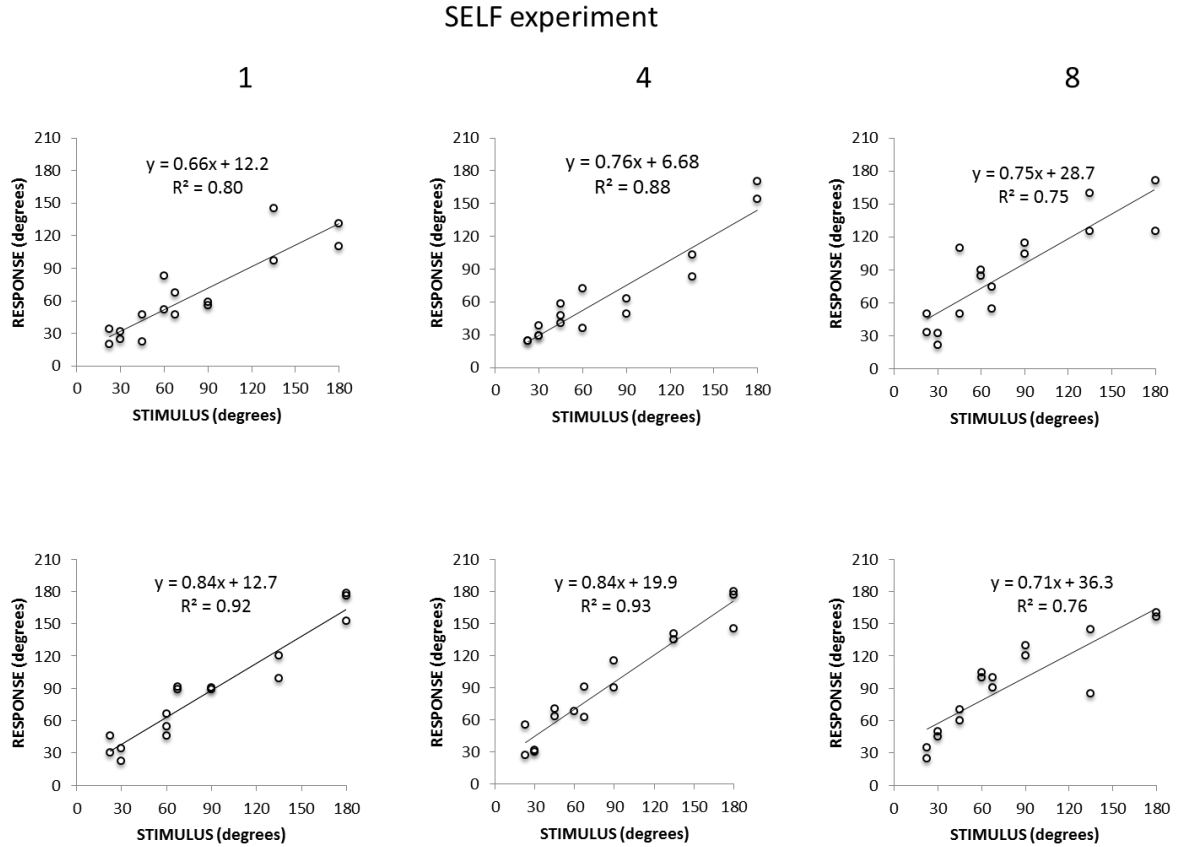


Figure 3.6 Regression plots showing performance of patient EF in the SELF task for rightward (upper panel) and leftward (lower panel) stimulus displacements at time delays of 1, 4 and 8 seconds. Regression slopes (x) and coefficients (R^2) are also shown. Each data point represents an average of three individual trials for each given stimulus displacement.

Allocentric navigation task (WORLD)

Control subjects were able to accurately update their position relative to the curtain using the analogue position indicator (Figure 3.7). A cumulative regression analysis between indicator response (R) and stimulus displacements (S) of all data points from all control subjects ($n = 575$) yielded $R = 0.85S + 6.54^0$ and r^2 of 0.80 ($p < 0.0001$). Separating the grouped data points into different experimental variables: time delays (1s, 4s and 8s) and the direction of the stimulus displacements (leftward or rightward), provides the values of r^2 in the range of

0.80 to 0.85 ($p < 0.001$ for all). Individual performances for C1-C8 were similarly consistent with r^2 ranging from 0.73 to 0.97 ($p < 0.001$ for all).

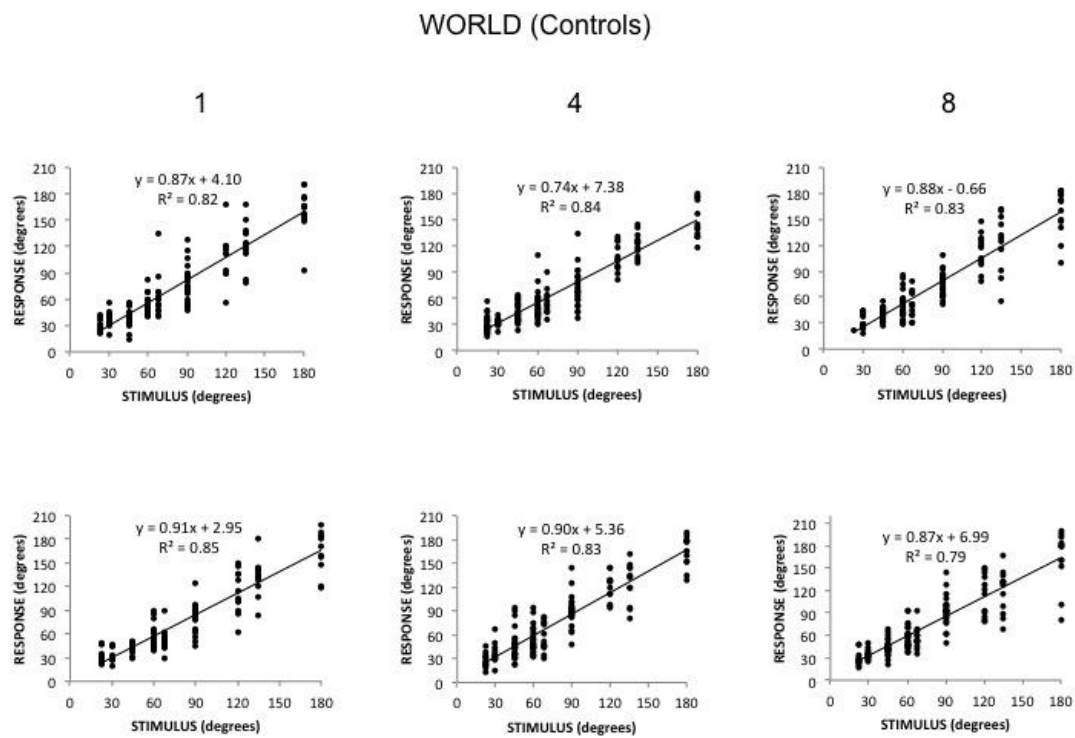


Figure 3.7 Individual responses for WORLD task for the control group for 1, 4, and 8 second delays for rightward (upper panel) and leftward (lower panel) rotations. Regression slopes and coefficients appear above each plot.

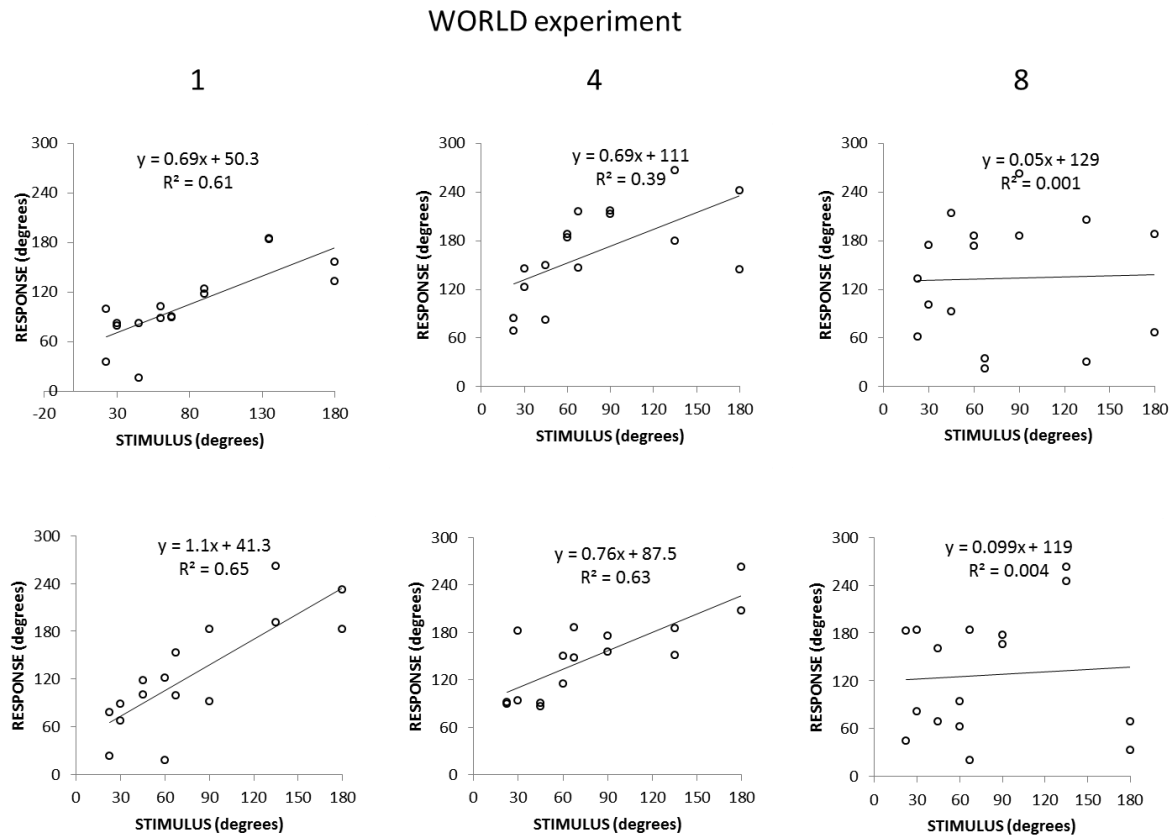


Figure 3.8 Regression plots showing performance of patient EF in the WORLD task for rightward (upper panel) and leftward (lower panel) stimulus displacements at time delays of 1, 4 and 8 seconds. Regression slopes (x) and coefficients (R^2) are also shown. Each data point represents an average of three individual trials for each given stimulus displacement.

Performance of patient EF in the allocentric navigation task was highly variable, particularly for longer delays (see dispersion of data points in Figure 3.8). Indeed, the regression plots between response and stimulus displacements for patient EF and the control group demonstrate that the patient's ability to produce consistent responses reduced over increasing time delays (Figure 3.8). When the patient was performing the task at 1s delay, the r values were not significantly different to the control group (Fisher's r -to- z transformation; $p > 0.1$). At 4s delay, r values for right and leftward displacements were significantly different to the control group (Fisher's r -to- z transformation; $p < 0.01$ for both right and left rotations). Equally, for an 8s delay r values for displacements to both directions (left and right) were

significantly smaller than controls (Fisher's r-to-z transformation; $p < 0.0001$ for both right and left rotations). This suggests that the performance of patient EF in the allocentric task becomes impaired after a time delay longer than 1 second.

Visuospatial span task (ACCRUE)

Patient EF was able to accurately indicate her perceived position relative to two, three and four visual landmarks, across all time delays (Figure 3.9). She made significant errors when asked to orientate with respect to five everyday visual landmarks, but only for an 8 second delay. Thus, we observed an overall effect of landmark ($F=8.05$, $p=0.003$) and delay ($F=18.4$, $p=0.001$), but not direction ($F=0.22$, $p=0.65$). There was a significant interaction between landmark and delay ($F=4.5$, $p=0.005$). A post hoc analysis (t-test) confirmed a significant difference between errors made for 5 landmarks at 8 seconds compared to 4s ($p=0.035$), and 1s ($p=0.01$).

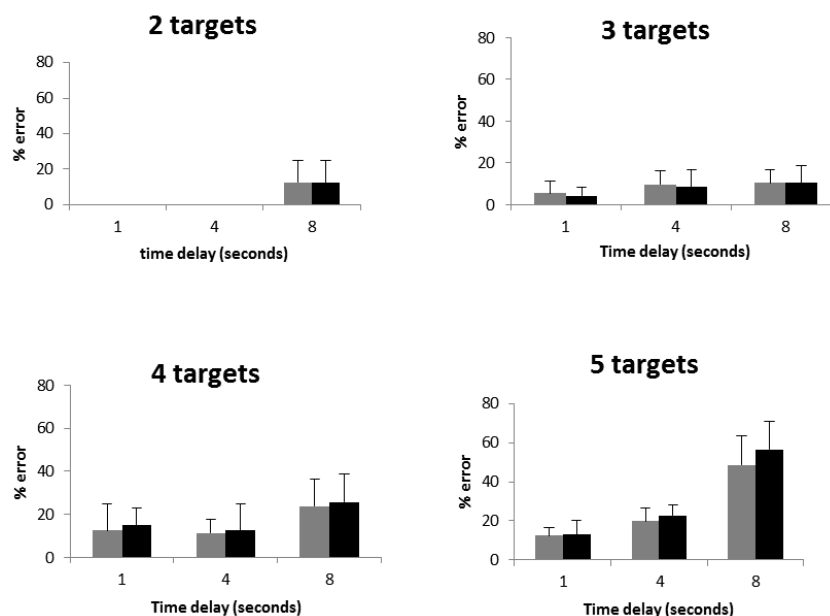


Figure 3.9 ACCRUE task results. Average percentage error for 2, 3, 4, and 5 landmarks for patient EF for right (grey) and left (black) rotations. Vertical bars represent standard errors.

Visual recall task

We found no deficits in static visual recall, across any time delays (1, 4, 8, 30, or 60 seconds; $p > 0.1$ for all) for patient EF.

Audiovisual task (BIND)

EF performed significantly worse than controls, with a total mean score of 34% (SD= 12%) correct responses, versus 89% mean correct responses (SD=15%) in aged-matched healthy controls (t-test, $p = 0.0018$, Figure 3.10).

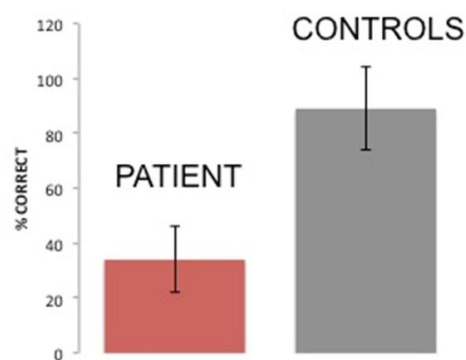


Figure 3.10 The percentage of correct responses for the BIND task.

3.5 Discussion

Our data suggest that orientation strategies using raw vestibular cues are not dependent upon right hippocampal functioning. In contrast right hippocampus is involved in the elaboration and maintenance of vestibular position signals referenced to external visual landmarks.

These findings provided the first evidence of the importance of hippocampus in retention of allocentric spatial processing after angular displacements over very brief delays i.e. the role

of hippocampus in vestibular spatial working memory. Previous studies have suggested the role of the hippocampus in supporting a flexible allocentric representation of environmental spatial relationships e.g. recognition of object locations when tested from a new viewpoint (29) and virtual spatial navigation and map drawing (30). Since the famous case of the patient HM published in 1957, the hippocampus has been implicated in forming new memories for long-term storage (1). Recent studies however, have also shown impairments in hippocampal patients' memory after brief delays in the order of seconds (31, 32). Moreover, a specific role of hippocampus in allocentric processing and storage over short timescales has also recently been shown (28, 33). Patient EF was one of the test subjects for the study conducted by Hartley et al (28), who used a topographical allocentric memory task - that tests memory for environmental spatial relationships - to show deficits in performance after a delay of only 2 seconds (28). Although the hippocampus has been implicated in specific aspects of spatial navigation (allocentric spatial processing and working memory), few studies have been conducted to explore its involvement in processing and/ or storage of vestibular information. Moreover, the studies that have been conducted so far have produced contradictory results (26, 27).

Our study shows that intact hippocampus is not required for vestibular processing to update the allocentric representation in space, since the performance of patient EF in allocentric task was not impaired after 1 second. It is, however, critical for the retention of the updated allocentric representation of the subject's current position over very brief delays since patient's performance was impaired after a delay of just 4 seconds.

Patient EF performed consistently well in the SELF task at all time delays. This suggests that the right hippocampus is not involved in storing information of vestibular-derived angular displacements, a role perhaps for the posterior parietal cortex. It was found, however, that the

average % error was higher for rightward displacement stimuli when compared to the control group. This finding, together with the observation of faster deterioration of allocentric task performance for rightward rotations, suggest that the right hippocampus might contribute to some extent to accurate vestibular processing of angular displacements of ipsilaterally directed whole-body rotations.

One explanation for a failure of allocentric navigation in hippocampal damage is a deficit in static visual recall, such that the patient may have been unable to store the visual items in memory during the training phase, before any chair rotations. Firstly, despite the curtain subtending a total of twelve visual landmarks, patient EF showed normal performance in the allocentric navigation task at 1 second, suggesting that immediate recall was not affected. Secondly, results from the visual recall task show that isolated visual recall was intact in this patient, even with delays of up to 1 minute.

The mechanism behind the vestibular working memory deficit observed in our patient appears to relate to a saturation of allocentric visual cues, given that spatial performance declined only once the limiting number of landmarks was exceeded (ACCRUE task). This is analogous to immediate serial recall tasks (e.g. digit span), but in the context of visuo-spatial memory. As for auditory verbal memory, only a restricted number of items can be simultaneously represented in visual working memory (34-36), with a cut-off limit of approximately three or four items (35, 36). It has been suggested that limited visual memory resources are shared out between items, such that the precision with which visual items are remembered will decrease with increasing numbers of items. We are unable to comment on this issue as this was not assessed in our paradigm.

The proposed roles of the PPC and hippocampus in vestibular navigation contribute to our understanding of the underlying basis of spatial disorientation in stroke patients. Patients with

lesions in the parietal cortex often get lost in familiar environments. This can be explained by deficits in path integration and by problems in updating their current position within an allocentric frame of reference. In other words, the patients find it difficult to navigate between familiar landmarks and as a result end up getting lost. In contrast, patients with hippocampal lesions and atrophy (Alzheimer's disease) have difficulty with their sense of direction when walking in unfamiliar places. For everyday navigation, these patients can rely on intact path integration between known local landmarks. In unfamiliar environments, however, this navigation strategy can no longer be employed and patients are forced to rely more on vestibular input for navigation. Since, as we have shown here, an intact hippocampus is required for vestibular spatial memory, hippocampal patients might have difficulty in remembering the path they took and become disorientated as a result. Uncalibrated vestibular cues of self-motion are maintained in working memory and transferred into a visual landmark reference frame. In the context of hippocampal damage, the ability to bind the idiothetic cues to the visual frame could result in a 'leaky' position signal, with subsequent inaccurate updating of spatial location.

Our results suggest that some functional dissociation exists between the posterior parietal cortex and the hippocampus in vestibular spatial navigation. The posterior parietal cortex is implicated in path integration (37) whereas hippocampus is critical for vestibular working memory of allocentric representation. Lesions in these regions cause impairment in spatial navigation both in familiar and unfamiliar environments, which often causes considerable distress in many stroke patients, and hinder rehabilitation. This handicap could perhaps be reduced by the use of vestibular orientated rehabilitation strategies in the future.

Human data supports the role of the hippocampus beyond spatial constraints (38). Hippocampal patients also show short-term impairments in nonspatial relational processing

(38, 39), even over short time delays (31). One speculation is that the role of the hippocampus is in binding multimodal inputs to form contextually appropriate maps. We tested this hypothesis using a nonspatial audiovisual associative task in which subjects were asked to identify an image based on its associated sound. Right hippocampal damage impaired the ability to 'bind' the visual and auditory conjunctions. Indeed, from a physiological perspective the hippocampus seems ideally suited to binding multimodal cues. Brain oscillations of different frequencies can interact in several ways (40, 41). One type of cross-frequency coupling is phase–amplitude coupling, whereby a higher frequency oscillation is modulated by the phase of a slower rhythm (40, 42–44). Phase–amplitude coupling is a feature of both working memory and decision-making (44–46). Theta rhythm is a high-amplitude, sinusoidal 4–12Hz electroencephalographic activity that has been extensively examined in the rat hippocampus (47). It has behavioural correlates that have led to inferences of its role in sensorimotor integration (48), and cognitive processing (49). Moreover, restoring theta rhythmicity recovers hippocampal function. The synchronisation and co-occurrence of theta-range activity between hippocampal and cortical/subcortical brain regions appears to be central to correct the expression of learned behaviour. In the hippocampus, theta phase modulates gamma amplitude (25–100 Hz) (50–53), an oscillatory coupling that appears to underlie learning and memory retrieval (54, 55). In rodents, spatial memory tasks increase gamma synchronisation in area CA3 of the hippocampus (56), involved in spatial memory (56–58) suggesting that the capacity of the CA3 network to generate gamma oscillations is a useful index for spatial processing ability.

One limitation of the nonspatial binding data is that the visuo-auditory cues were not presented in randomized order, such that the same sound was associated with the same particular picture in every trial. Subjects may thus have undergone a process of learning,

which may explain the almost perfect performance in healthy controls. That EF was unable to ‘learn’ such associations may have implications worthy of further exploration. Future experiments could be run in which audiovisual cues are randomized from trial to trial to eradicate learning.

Clinical implications

Our findings highlight the importance of the vestibular system for navigation and for the development of spatial memory. It is therefore reasonable to hypothesise that increased vestibular stimulation could enhance spatial memory and may potentially be used in rehabilitation of stroke patients. It has previously been shown that vestibular galvanic stimulation alleviated the symptoms of hemi-spatial neglect (59). Indeed an animal study showed that stimulation of the vestibular system by rotation improved rat’s accuracy in the water maze task (60). Therefore it will be interesting to test whether vestibular stimulation in patient EF might reduce the deficits in performance of vestibular navigation task (i.e. allocentric task).

3.6 References

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EF Case history (taken from Hartley et al., 2007)

This patient is a 58 year old female, who developed sudden onset tingling and weakness in the left arm in 1966. Subsequently, she noticed difficulty recalling events, appointments and conversations. She also began to notice a difficulty with her sense of direction particularly when walking in unfamiliar places. Neurological examination was entirely normal. Despite memory improvements at the time of publication, the patient's husband still noted a mild topographical disorientation that was more pronounced in unfamiliar environments. Two recent MRI brain scans have identified atrophy involving the right hippocampus only, with normal appearance of the fusiform and parahippocampal gyrus and the remainder of the temporal lobes.

Verbal and performance IQ were both in the average range, consistent with estimates of premorbid ability. Language, visual perception and executive functions were all unimpaired. Verbal memory was also unimpaired. However, she performed poorly on tests of visual recall and a test of visual recognition. Given the sudden onset of her symptoms and her static neuropsychological profile, a vascular (ischaemic) aetiology was suspected.

C_{hapter} 4

Cortical plasticity: enhanced spatial navigation in the blind

4.1 Introduction

The visual-deprivation literature is a murky sea of contradictions. On the one hand, anecdotal stories and evidence from both animal (1, 2) and human visually-deprived subjects (3-7) support a heightened ability in the blind in the remaining senses. On the other hand, blind individuals are exposed to extensive training in the non-visual domains which may account for an underlying superior ability (8). Current consensus purports better auditory localisation in blind compared to sighted individuals as a result of use-dependent cross-modal plasticity.

Early blind versus late blind

Given the time-dependent nature of cortical plasticity, it is not surprising that non-visual performance in the blind is related to the onset of blindness. Lessard et al. (9) showed a superior ability to localise sounds in early blind (EB) as compared to both sighted and late blind (LB) subjects. These results are supported by similar reports showing enhanced monaural hearing localisation in azimuth in EB subjects (10, 11). EB subjects are better able to discriminate pitch and melody than LB subjects, and occipital cortical thickness appears to correlate with such auditory performance (12). In addition Gougoux et al (10) showed a correlation between degree of occipital activation and performance in the blind, but not sighted. These results support the prediction that compensation through the functioning senses occurs in the blind, enabling them to form accurate spatial representations of the external world. The same group, however, previously found equivalent auditory localisation performance between early and late onset blind subjects (13), suggesting that the association between the time of onset of visual deprivation and performance remains ambiguous (see Appendix for a literature review).

Given that auditory spatial localisation can be improved in sighted individuals receiving task-specific training (14), the observed differences between sighted and blind subjects (including within group differences) in auditory localisation may be heavily dependent upon the individual's prior experience (e.g. vision) and daily routine (e.g. sportsmanship). Cross-modal plasticity and practice are, however, not mutually exclusive mechanisms to account for a blind 'supersense'. A synergistic effect of sensory deprivation and training has been proposed, but has been difficult to test experimentally (15). We aimed to specifically address this question by comparing 8 blind Paralympic footballers with 8 professional sighted footballers, matched for training and age, in a vestibular-guided auditory localisation task. The finding of comparable tactile spatial thresholds in early- and late-onset blind subjects argues against the importance of early sensory deprivation (8). We therefore hypothesised that allocentric navigation performance would be equal in both groups, given the overriding effect on training on cross-modal plasticity versus the effects of visual deprivation.

4.2 Materials and Methods

Subjects

4 male paralympian GB blind football players and 8 sighted male football players took part in the study, following written informed consent. Paralympian football recruitment was halted as a result of the upcoming Paralympic games, but will be completed after the end of the games. The study was authorized by the local ethics committee. All footballers underwent pure tone audiograms, and subjects with hearing impairments were excluded. 8 healthy age-matched male subjects served as controls. A clinical neuro-otological assessment was performed in all subjects to exclude a peripheral vestibular deficit.

Materials

Subjects sat on a vibration-free rotating chair (Contravez; torque 120 Nm) in the dark with white-noise sound masking via earphones (Figure 4.1A). The experimenter observed the subject at all times via infrared video camera. The subject could actively rotate himself by manipulating a directionally congruent joystick that provided a velocity demand to the servo-motor (response). This technique has been described previously (16). The subject was surrounded by 9 speakers distributed in a circular arc formation around the chair, each 30 degrees apart (Figure 4.1B).

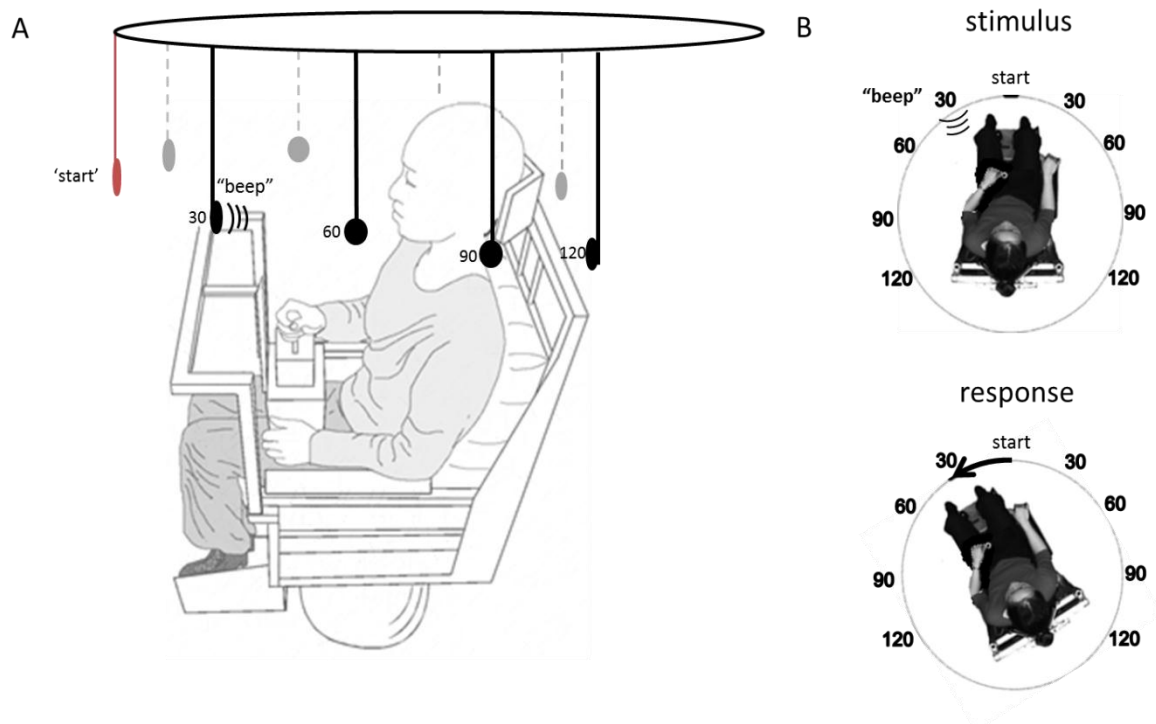


Figure 4.1 Materials and methods. (A) Subjects sat in a motorised rotating chair, surrounded by speakers suspended from a fixed drum. Speakers were separated by 30 degrees. (B) Subjects began facing the central speaker (start position) in the dark. A “beep” was then produced by one of the speakers surrounding the subject (30 degrees left from centre in this example). The subject then navigated to directly face the sound source using the chair-mounted joystick. Subjects were asked to move only after the beep had ended. Subjects were then passively rotated to the start position, and the lights were switched on to re-orientate the subject before the next trial.

Subjects were given a 15 minute period of free practice during which only subject-driven chair rotations were made (without visual, auditory cues or other indication of performance) to get accustomed to the highly responsive nature of the chair to joystick deflection. During free practice, the maximum joystick-driven angular velocity was incrementally increased from 20 to 140°/s. Subjects were encouraged to explore the new limits of the joystick-driven dynamic range, and this was monitored on infrared camera. Subjects proceeded to the practice experiment stage once they were able to confidently use the joystick at the experimental setting of peak 140°/s, which was achieved within 15 minutes in all subjects. During the practice experiments, subjects were asked to produce a smooth chair trajectory and to arrive at their chosen location in one motion (rather than small incremental movements). They were asked to use this technique consistently in the formal experimental session.

Sound localisation experiment

After practice experiments, subjects then performed formal sound localisation experiments. Subjects heard two discreet tones from the central speaker (directly facing the subject) to indicate the start of every trial. This was followed by a 1 second-duration tone from one of the 8 surrounding speakers (right 30, 60, 90, or 120°; left 30, 60, 90, 120°). Subjects were informed that the largest tone was 120°. Subjects were asked to orient themselves to directly face the tone using the chair-mounted joystick. The joystick dynamics were selected with the limitations imposed by the dynamic response range of the semi-circular canals in mind (i.e., 0.167 Hz) (17). Subjects were instructed only to move the joystick after the tone had ended. After their ‘outbound’ movement towards the sound source, subjects were returned to the centre (‘inbound’) using a position-feedback homing device, and the lights switched on to re-

orientate subjects to the start. We performed a total of 72 trials, with tones randomised for direction (left/right) and position (degrees).

Then ensued a training session, in which subjects were exposed to the central tones ('beep'- 'beep'), followed by a further beep to the right at 90° or to the left at 90°. The subject was moved under computer control at one of three velocities (45, 60, or 90°/s) to directly face the sound source of this beep. Subjects were again returned to the central (start) position three seconds later, and the lights were switched on. During the training session subjects were asked to concentrate on the sound source and the movement of the chair. Regular breaks were provided to avoid fatigue.

Finally, the sound localisation experiment was repeated following the training session, with subjects using the joystick to rotate themselves to face the sound source.

4.3 Data Analysis

We recorded the chair velocity (joystick-controlled; maximum 140°/s) of subjects' responses via a chair-mounted tachometer. The chair tachometer (velocity) output was recorded at 250 Hz and analysed off-line. We obtained a position signal (in degrees) from position-feedback encoder on the chair for each subject response. Regression slopes between right and left rotations were compared using a two-tailed *t*-test, and correlation coefficients were compared using Fisher's *r*-to-*z* transformation. *z* values were obtained using the formula $z_r = (1/2)[\log_e(1+r) - \log_e(1-r)]$ where *r* is the regression co-efficient. A line was fitted through the data set using the most parsimonious 'best-fit'. A *z*-test was performed to calculate the *p* value. Additionally, the regression slopes between groups before and after training were compared using a one-way ANOVA (group_{cont/sighted/blindFB} vs. phase_{pre/post}). The duration of the response (from initial deflection of the velocity trace from its resting zero position to its

baseline final position) was also taken as a measure of response confidence. The velocity waveforms across all responses were averaged for each individual and are represented graphically.

4.4 Results

As expected, the blind avestibular control subject performed significantly worse in this auditory localization navigation task ($rsq = 0.0013$; $p < 0.001$), confirming that this task relies upon an intact vestibular system.

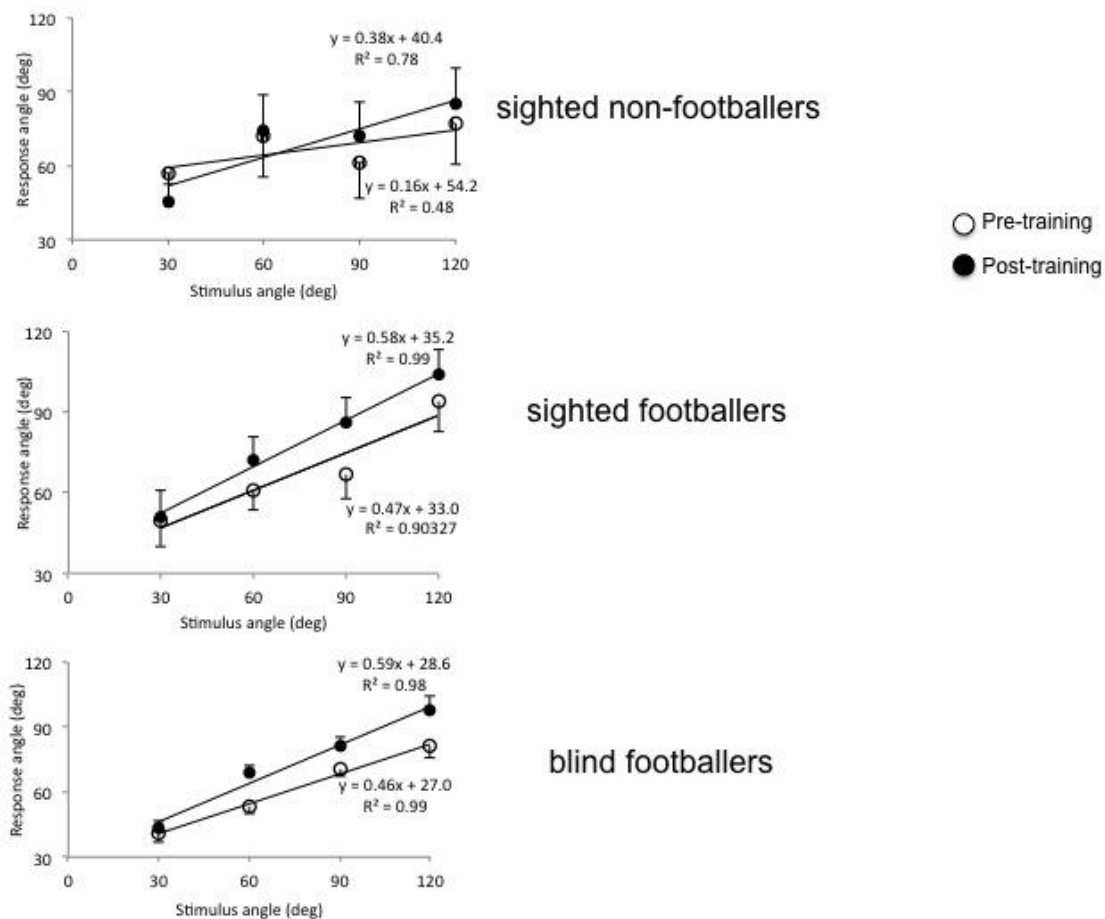


Figure 4.2. Averaged group regression plots for sighted non-footballers (top), sighted footballers (middle), and blind footballers (bottom). Vertical bars represent standard errors.

We found a significant interaction between the three groups (sighted control, sighted footballers and blind footballers) compared to control sighted non-footballers (ANOVA for regression slopes; $p=0.001$) at baseline (prior to training). Post-hoc analysis confirmed a superior performance in footballers (sighted and blind) compared to control sighted non-footballers (Turkey post-hoc test; $p=0.001$; $p=0.047$). We found no difference between sighted and blind footballers in overall sound localization performance ($p=0.075$). Sighted non-footballers made mean errors of 28.7 degrees (SD=12.2), compared to 15.11 (9.3) degrees in sighted footballers, and 16.4 (11.7) degrees in blind footballers (Figure 4.3A). Mean errors were greater in the sighted groups for larger angles than smaller angles, and vice versa for the blind group (Figure 4.3A). Sighted controls had significantly greater variability in responses (CoVar = 55.2 [SD=6.1]) compared to sighted subjects (CoVar =37.0 [6.2]) and blind (CoVar= 30.8 [3.8]) footballers and this was statistically significant (ANOVA; $p<0.001$; Figure 4.3B). Turkey's post hoc test confirmed significant differences between control and both sighted ($p=0.03$) and blind ($p<0.001$) footballers, but no significant differences between the footballer groups ($p=0.30$).

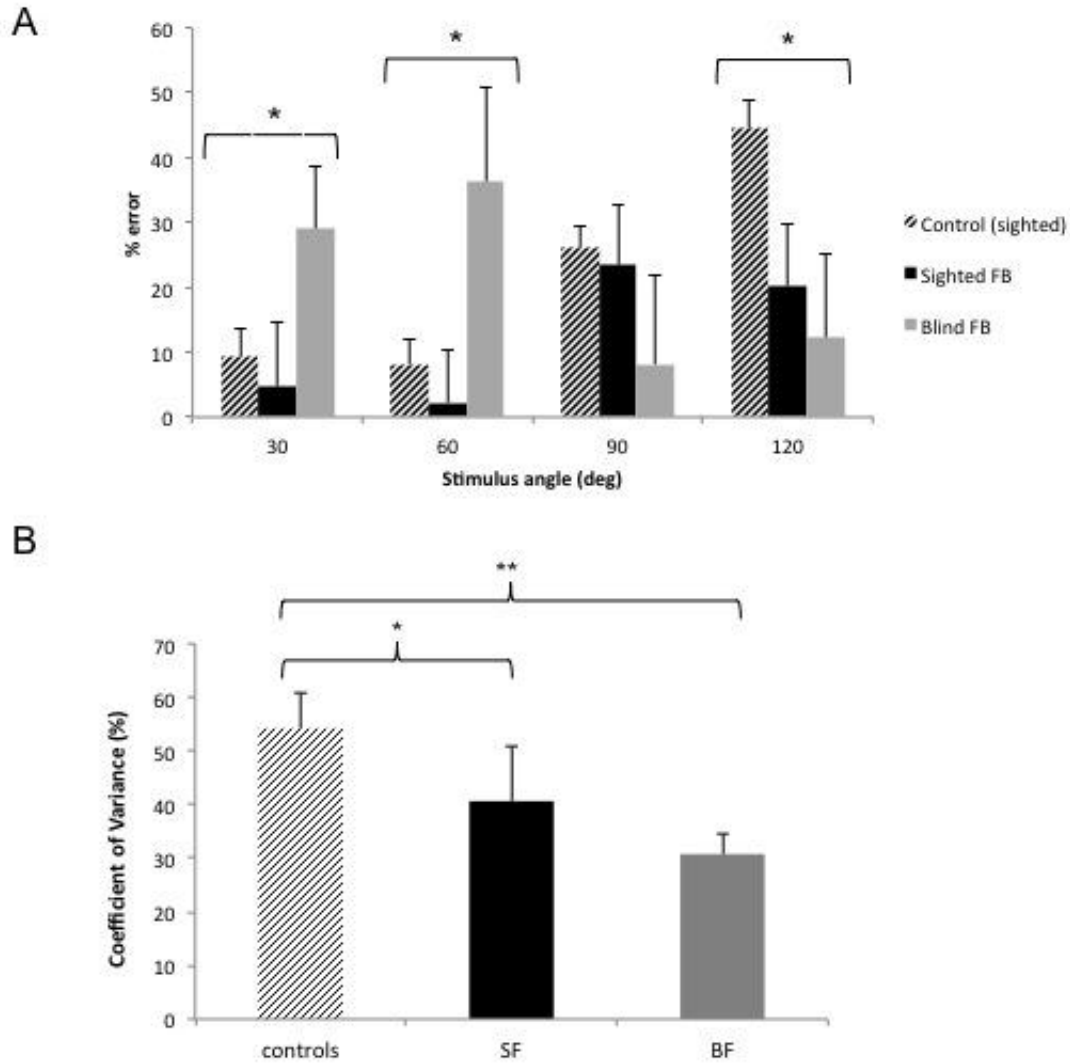


Figure 4.3 (A) pre-training absolute percentage angular errors across groups for all angles. (B) Averaged group coefficient of variance (%) for all responses. Vertical bars represent standard errors. * $p < 0.05$

Blind footballers showed a significant improvement with training (t-test between regression slopes; $p = 0.006$). We found no significant improvement with training in sighted footballers ($p = 0.29$) or controls ($p = 0.42$).

Response dynamics of the chair rotations also varied between groups (see Figure 4.4 for representative traces). Response duration was significantly shorter in blind footballers compared to sighted footballers and to controls. There was no difference between sighted

footballers and controls. Waveforms appear more uniform for the blind footballers compared to sighted footballers and sighted controls, and response duration shorter in blind footballers ($p < 0.001$ compared to controls, $p < 0.001$ compared to sighted footballers).

We did not have sufficient subjects in the blind footballer group to make meaningful comparisons between early and late blind subjects.

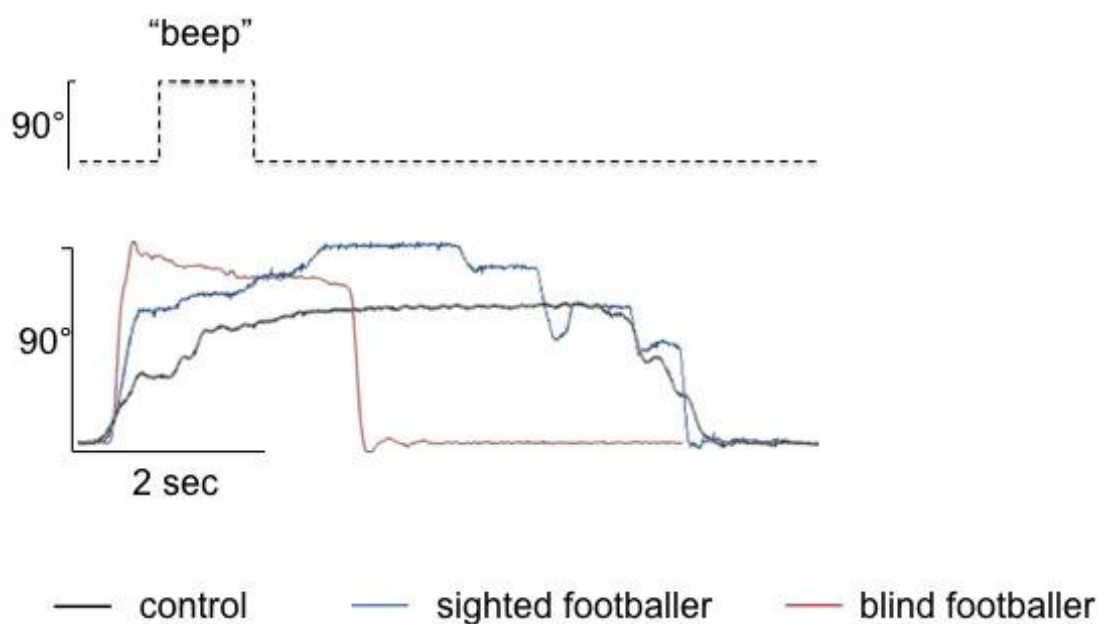


Figure 4.4 Individual representative traces showing chair displacement profiles made using the joystick to face the recalled sound source, followed by a return to the start position. The example shows a 90-degree sound location (*top*). The control subject (black) performs a smooth response over the course of approximately 3 seconds to achieve an angular displacement of 63 degrees (peak response on trace). The sighted footballer (blue) executes a response of similar duration but uses a faster velocity to reach the desired displacement, and has a more accurate response. The blind footballer (red) reaches the desired location in under 1 second with a rapid and confident response, of greater velocity (note sharper slope for red trace).

4.5 Discussion

We have shown equivalent performance in a vestibular-guided sound localisation task between sighted and blind footballers. During football practice, blind athletes are required to follow the ball (sound source) using non-visual calibration (vestibular, proprioceptive) of

auditory function. As expected given the nature of the blind football practice, we observed less variability in blind subject's motion responses than sighted athletes and sighted non-athletes.

In agreement with other studies (18) our blind subjects demonstrated better sound localisation ability in the far lateral space than sighted subjects. However, sighted subjects were actually more accurate for small angles (30-60 degrees) than blind subjects. Hence, it would also be true to say that sighted subjects' sound localisation ability, whilst apparently superior than early blind subjects in the straight ahead, also showed a more dramatic performance fall-off than the blind in the far lateral space. Why might this be? One explanation may relate to a differential connectivity between peripheral and central auditory space and visual cortices seen in primates (19, 20). A more prosaic, but no less valid explanation, is based upon everyday responses in the sighted to stimuli in peripheral visual space. For example, a peripheral auditory target greater than 20-30° from the horizontal midline will induce a sighted individual to make a combined eye-head saccade (maximum ocular range is +/- 50° from midline) towards the stimulus with fine-tuning of the response carried out under visual control (21, 22). Indeed even in echolocating bats, the primary function of passive sound localisation is to direct the eyes to the sound source (23). Hence, although auditory space undergoes constant recalibration by retino-visuomotor feedback in the sighted (7), the necessity for anything but an approximate calibration of peripheral auditory space is made redundant by retinal-slip feedback. In contrast, central auditory space, almost by default, will receive continuous high fidelity visuospatial feedback. It follows that in sighted humans, auditory localisation will be most acute frontally. Hence, in a sighted subject, an alerting auditory stimulus in the 70°-90° range (18) would always result in a large head-eye saccade towards the target. Given that auditory spatial localisation can be improved in sighted

individuals receiving special training (14), the observed differences between sighted and blind subjects (including within group differences) in auditory localisation may be heavily dependent upon the individual's prior experience (e.g. vision) and daily routine (e.g. sportsmanship).

It has been suggested that the supranormal monaural sound localisation ability of the blind may have arisen from increased use of spectral auditory information (9). Sound intensity, however, varies with distance (24). Indeed, there was no decrement in auditory localisation in azimuth in blind subjects when the sound transfer characteristics of the pinnae were changed by application of acoustic paste (11). Given that the pinnae are crucial in determining the spectral shape of incident sound, these findings would suggest that in fact, the blind subjects tested by Doucet et al. (11) were not predominantly using spectral cues in sound localisation. In fact, auditory localisation in the vertical plane as opposed to in azimuth is a much better test of spectral cue usage. Normal humans show a dramatic degradation of sound localisation in the vertical plane with the application of moulds to the pinnae (25). Healthy subjects are however able to adapt to their modified pinnae, with auditory localisation performance returning to baseline within weeks (25). Separate groups have now found that the blind are actually less good than the sighted (6, 24) in localising vertical auditory targets. Hence, the existence of superior auditory spectral performance in the blind remains unclear.

Early blind subjects seemingly show superior pitch discrimination compared to late blind (10). In this the average duration of blindness in the congenital group was 28.1yrs (range 1-36 yrs.) and late onset was 14.4yrs (range 21-40); in addition four late onset subjects were 40yrs age and over, and of these, three had relatively recent onset blindness (1-3 yrs.) hence the two groups (congenital and late blind) may not have been well matched. The correlation between performance and age of blindness onset found by Gougoux et al. (10) could thus also

have been related to number of years of exposure to no vision. The distribution of duration of blindness was clearly bimodal in the late blind versus a more normal distribution in the early blind group. When the confound of duration of blindness was removed only 0.24% of the performance data variance ($r = 0.49$) was explained by age of blindness onset. In the conclusion of this article, the authors state that “a large part of the variance (42%) could be accounted for by the age of blindness”; here the authors should have quoted 24% and not the 42% variance since a co-factor (here duration of blindness) was a major contributor to the quoted r^2 value. In fact the correlation between age of blindness onset and duration of blindness was not trivial with an r value of 0.86 ($P < 0.0001$; regression calculated from supplementary information supplied online). Such data may be confounded by duration of blindness and hence possibly by other concomitant associations (e.g. experience-dependent practice). In addition, recent data in other aspects of auditory perception has shown no differential performance ability between early and late blind subjects (13). Further studies which control for duration of blindness are thus required to answer the original question that the blind inherently possess better sound perception capabilities as a result of their blindness and not because of the effect of continuous practice.

Vestibular guided navigation

Vestibular input is required for accurate locomotion in the dark, such as the everyday task of walking to the kitchen for a glass of water at night. Sighted subjects are able to derive their location during locomotion in the dark via a process called *path integration* in which position is derived from inertial vestibular and haptic signals via mathematical integration and vector addition (26). Haptic input is sufficient to inform the path integration process for sighted subjects during translational movements in the dark; however, only vestibular input adequately updates position when subjects make walking turns (27). It has been shown that

congenitally blind subjects have impaired spatial strategies (16) compared to sighted individuals.

The disparate results reported may stem from group selection bias (most blind participants are high functioning), poor study design, or small study numbers. For example, Gougoux et al. (10) used unequal numbers of blind and sighted subjects. Additionally, performance was correlated to occipital activation for the blind group but not for the sighted group. Small control numbers, normally the non-limiting factor in subject recruitment, also make interpretation difficult. Moreover, the finding that 2 out of 5 sighted subjects had superior performance (10) is highly incongruent when compared to data showing no sighted subjects with superior auditory localisation after testing 36 (9) and 5 (11) sighted subjects. This observation casts some doubt over the variability in the control (sighted subject) auditory localisation data.

Study limitations

Recruitment of blind Paralympic footballers was prematurely terminated as a result of the forthcoming Paralympic games 2012. Subjects have agreed to return to complete the study. A further potential confound is the environmental surround where the experiment took place, which was not completely anechoic. This means that localizing sound sources could be more difficult. However, conditions were identical for all subjects, which makes the task more challenging but still allows for group comparisons. As in ordinary football games, a poor performance on this task could not be blamed on the 'pitch'!

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Part II: Motor efference

C_{hapter} 5

Modulation of locomotor learning using tDCS in healthy humans

5.1 Introduction

The “broken escalator” phenomenon describes the unusual sensation and transient imbalance experienced when walking onto a stationary escalator, as frequently occurs on the underground (subway or metro) stations. Gait adaptation to varying terrain is essential to maintain balance in everyday life and requires the selection of an appropriate motor strategy. In the experimental setting, stepping onto a stationary platform that was previously moving elicits a locomotor aftereffect (1) that attests to a process of motor adaptation. Motor adaptation refers to a motor learning process that occurs over a short time course of minutes to hours and allows effective motor control in the face of an external perturbation (2). It involves modulation of previously learned motor skills and differs from the acquisition of a new motor skill, a form of procedural motor learning, which often takes longer to achieve (3).

The expression of a learned motor skill may be variously voluntary or involuntary (4, 5). Indeed, voluntary and involuntary motor control mechanisms are relevant to the broken escalator effect since one conundrum is the inability to suppress the motor aftereffect despite full awareness that the escalator is in fact broken, which implies the selection of a previously learned motor response (1). The broken escalator aftereffect is, however, dissipated with the second trial as a result of de-adaptation, a type of error-based learning. In addition, the selection of a motor response is influenced by prior learning and the frequency of exposure to the motor context (6, 7) that is also presumably under cortical control. Perhaps the most salient rationale for invoking a cortical mechanism in the broken escalator phenomenon is that the release of the aftereffect is context-dependent, i.e., it will only occur if the subject walks on the sled that was used during the adaptation (MOVING) phase (8).

There is substantial evidence highlighting the cortical influences over locomotor control. For example, patients with grey matter frontal lobe dysfunction display difficulties initiating and sustaining locomotion (9), implying a role in locomotor initiation processes. Evidence from cats suggests that the corticospinal tract plays a crucial role in the modification and resetting of the locomotor rhythm (10, 11). In humans, it is well-recognized that the primary motor cortex is involved in the automatic execution of lower limb learned motor plans (12), whereas loops of the prefrontal cortex regulate and plan complex actions relevant to gait (13). The importance of cortical control on human gait is highlighted by the clinical higher-level gait disorders (9) and is supported by functional neuroimaging studies (14, 15). The neural correlates of motor adaptation are therefore thought to involve M1 and the premotor cortex (16, 17).

Transcranial magnetic stimulation (TMS) (18-22) and transcranial direct current stimulation (tDCS) (23) studies have highlighted the involvement of the primary motor cortex (M1) in the different stages of motor skill learning. For example, repetitive TMS (rTMS) to M1 disrupts consolidation, a strengthening of memory that occurs between practice sessions, if it is applied within 6 h (20) or 2 h (22) of initial skill acquisition. If applied before learning, subsequent consolidation can be blocked (21). Hadipour-Niktarash et al. (19) used single-pulse TMS to show that M1 is involved in retention of arm movement adaptation when TMS is applied immediately following the arm movement. When low-frequency (inhibitory) rTMS (<1 Hz) was applied over M1 after arm reaching with no force fields, but before adaptation, the acquisition of learned novel force field-induced dynamics during adaptation was not affected. However, movement errors were greater 1 day later when subjects repeated the reaching tasks with no force perturbations (21). Low-frequency rTMS applied to M1 shortly

after force-field motor adaptation, however, did not disrupt subsequent consolidation of the newly formed internal model (18). Furthermore, when TMS was delivered immediately after each reaching trial during adaptation to visuomotor rotation, subjects showed fewer de-adaptation trials to return to baseline values for target errors (19). These results suggest a possible role of M1 in motor de-adaptation of upper limb motor learning. The broken escalator paradigm therefore offers an opportunity to explore the role of M1 and premotor cortex in lower limb locomotor adaptation.

We posed two associated questions: first, can anodal tDCS over M1 and premotor cortex alter locomotor adaptation? Based on the upper limb adaptation data (21, 23), we predicted that increasing the excitability of the primary motor and premotor cortical leg areas using anodal tDCS would increase the amplitude of the forward sway and gait velocity in the first AFTER trial (aftereffect). We further hypothesized that anodal tDCS over M1 would prolong the aftereffect given the role of M1 in memory retention (24). To test our hypothesis, we applied anodal tDCS over Cz to induce prolonged excitability changes over M1 and premotor cortex bilaterally before the broken escalator paradigm. Second, are the behavioural changes associated with tDCS related to neurophysiological changes in M1 cortical excitability of the legs, and can these neurophysiological changes be predicted using a computational model? We used TMS to probe changes in cortical leg excitability before and after tDCS to M1 using different electrode montages and simulated the current flow of tDCS on the human brain via a geometrically simple (25) finite element model in these different tDCS montages. We used this model to confirm that one of these montages would induce greater current density in M1 bilaterally and would therefore preferentially increase lower limb excitability of both legs.

5.2 Materials and Methods

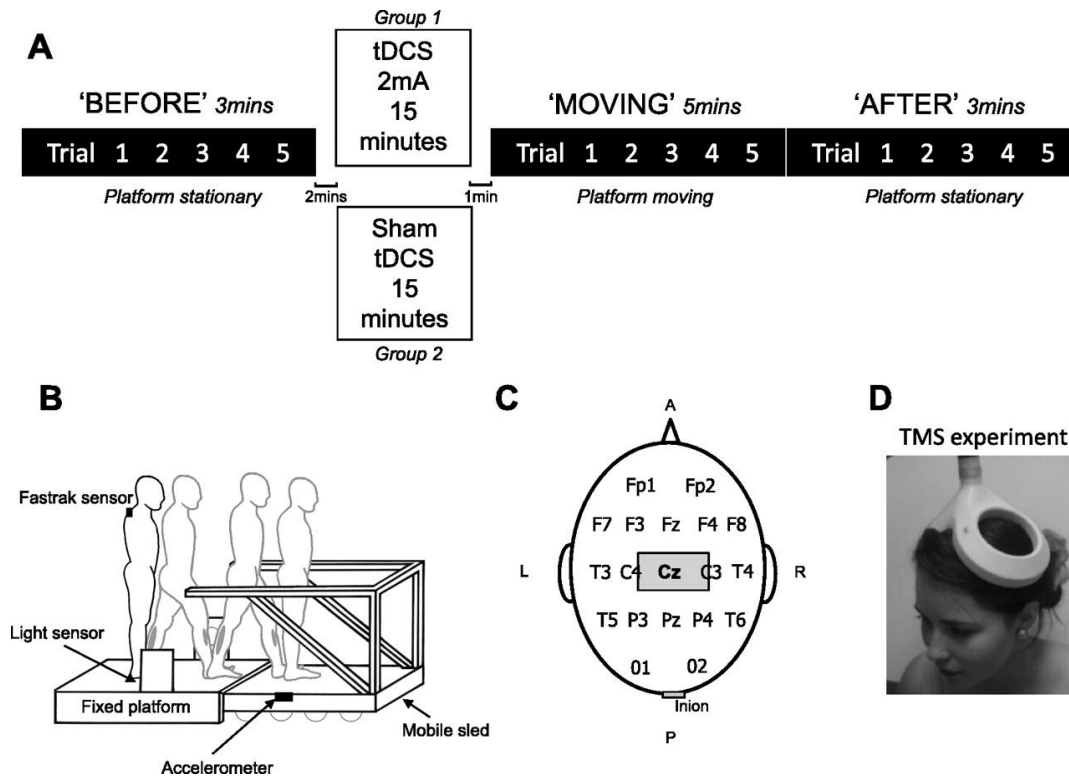


Figure 5.1: (A) experimental sequence. Subjects received either real or sham stimulation while seated in an office chair. Transcranial direct current stimulation (tDCS; or sham) lasted for 15 min exactly, but trial times shown are approximate. (B) the motorized sled is enveloped by the fixed platform but remains freely mobile. Its movement is initiated by the subject's leg via a light sensor. Ankle flexor [medial gastrocnemius (MG)] and extensor [tibialis anterior (TA)] from where electromyogram (EMG) was recorded are shaded. (C) international 10-20 EEG electrode placement. The anodal (stimulating) electrode was placed over Cz and covered a region 10–20% anterior to Cz as measured from the midpoint of the electrode. The cathode was placed over the inion. (D) transcranial magnetic stimulation (TMS) over Cz using double-cone coil. EMG activity was recorded simultaneously from the right and left TA muscles. A, anterior; P, posterior; L, left; R, right.

Thirty healthy participants, 15 females, mean age 25.5 yr. (range 17–32 yr.), and 15 males, mean age 30.1 yr. (range 22–44 yr.), took part in the study. All participants were right-handed and right-footed. The participants were allocated to 2 separate groups for testing. The “real tDCS” group (7 males and 8 females) received tDCS at 2 mA over 15 min, and “sham tDCS” group (8 males and 7 females) received sham stimulation (see Procedure, below) for 15 min.

Both groups performed 5 “BEFORE” trials, 5 MOVING trials, and 5 AFTER trials (Figure 5.1A). All participants were naïve to both the task and tDCS stimulation.

5.3 Materials

A mobile sled (1) was powered by two linear induction motors and moved with a maximum velocity of 1.4 m/s. The sled was enveloped by a fixed platform under which it could freely pass (Figure 5.1B). Movement of the sled was controlled by a computer, triggered by gait initiation via a leg-activated infrared light switch. On passing through the sensor, after a 600-ms delay, the sled would travel a distance of 3.7 m in 4.2 s; maximum velocity was reached at 1.3 s after motion initiation. Acceleration of the sled up to peak velocity was therefore 1.08 m/s². Sled velocity was recorded using a tachometer.

Subject anteroposterior trunk position was measured using a FASTRAK electromagnetic tracking device (Polhemus, Colchester, VT). The sensor was placed over the C7 vertebra, and the transmitter was attached to the sled. A second FASTRAK sensor was attached to the wall and allowed measurement of sled displacement during the moving trials. Step-timing information was given by foot contact strips overlying the shoes at the level of the metatarsophalangeal joints. A linear accelerometer attached to the sled provided independent accurate information of foot-sled contact timing (Figure 5.1B). Electromyogram (EMG) activity from the medial gastrocnemius (MG) and tibialis anterior (TA) muscles of each leg was recorded with bipolar electrodes placed 5 cm apart on the belly of the muscle. The EMG signal was band-pass filtered (10–600 Hz), recorded on a personal computer, and sampled as the other signals at 500 Hz.

5.4 Procedure

Moving platform task.

The experimental sequence (Figure 5.1A) was as follows: BEFORE (5 trials), MOVING (5 trials), and AFTER (5 trials). Subjects were asked to take their 1st step after an auditory cue (3 “beeps”), at their own pace, with the right leg forward 1st. In the BEFORE trials, the sled remained stationary. Subjects would thus land from the fixed platform onto the sled with the left leg, where they were asked to stop and adopt a quiet stance, with both legs approximately in line until recording was completed (Figure 5.2). Each trial lasted 16 s. Depending on which group they were allocated to, on completion of the BEFORE trials, subjects then received either sham stimulation or tDCS stimulation while sitting in an office chair for 15 min. Participants read a magazine and conversed with the experimenters during this period. Before continuing onto the MOVING trials, each participant was shown once how the platform would move. Subjects then performed 5 MOVING trials. The number of learning trials used was chosen on the basis that this locomotor aftereffect can be generated with few adaptation trials (45). Subjects were instructed to avoid the use of the available handrails when stepping on the moving sled unless this was absolutely necessary. When the MOVING trials were complete, all subjects received the warning, “I will now switch the motor off so the platform will not move - it will be stationary as it was in the first 5 trials,” and the motor was ostensibly turned off (subjects were able to hear and see this). All subjects then completed another set of 5 stationary (AFTER) trials.

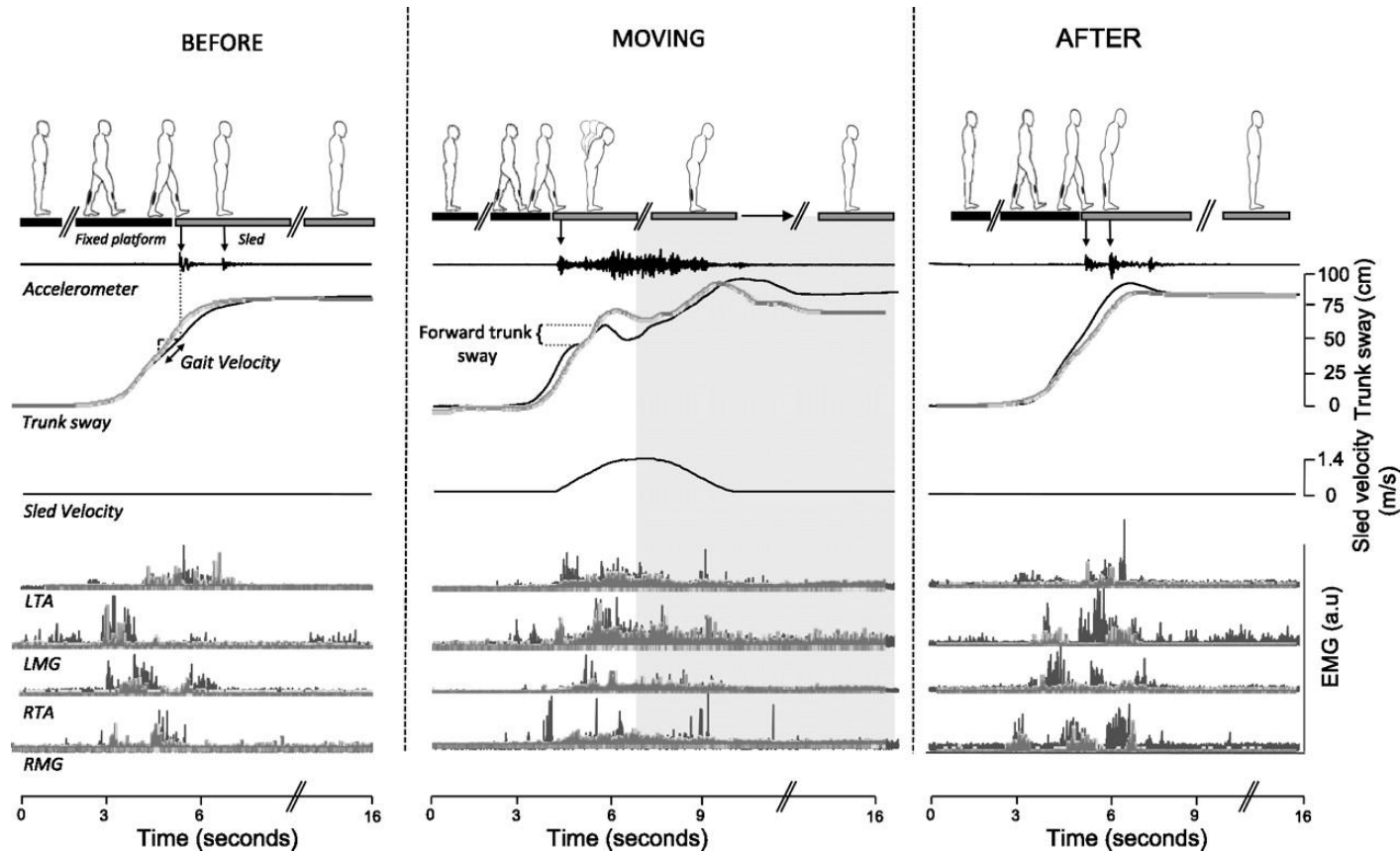


Figure 5.2: Representative data from 1 subject receiving real tDCS stimulation and 1 subject receiving sham stimulation during the experimental conditions (BEFORE trial 1, MOVING trial 1, and AFTER trial 1). Trunk sway, gait velocity, and EMG activity are shown in light grey for the subject receiving sham stimulation. Trunk sway data in AFTER trial 1 show the characteristic trunk overshoot in addition to increased EMG activity and are more marked in the real stimulation (black lines). Note that the sled velocity profile during the BEFORE and AFTER trials is 0 m/s as the sled remained stationary. The accelerometer was not calibrated as it was just used to detect accurately foot-contact timing (down-pointing arrow) and was subject to interference from the motor in the MOVING trials. a.u, Arbitrary units.

Transcranial direct current stimulation

We determined the tDCS electrode montage using evidence from MRI studies (26) and three-dimensional probabilistic anatomic correlation techniques (27) showing that the scalp topography of Cz [international 10-20 EEG system (28)] corresponds to lower limb primary motor cortex. Thus a DC stimulating rectangular saline-soaked sponge electrode (10×4 cm; surface area 40 cm²) was placed centrally across the scalp to cover a region 10–20% anterior to Cz as measured from the midline of the stimulating electrode (Figure 5.1C). The reference electrode (4×4 cm) was positioned at the inion. A 2-mA current was delivered by a battery-driven Magstim Eldith DC stimulator (neuroConn, Ilmenau, Germany) between the end of the BEFORE trials and the beginning of the MOVING trials (i.e. just before the adaptation period; Figure 5.1A). The current was initially increased by a ramp input over 10 s until reaching 2 mA (current density 0.05 mA/cm²). Stimulation duration of 15 min, as chosen, can result in an excitability change lasting up to 90 min (29). The sham stimulation is identical to the real stimulation condition except that the current drops off to zero after 30 s. Participants reported a “tingle” sensation beneath the electrodes at the beginning of the stimulation for both sham and real conditions, which typically faded away after 10–20 s in both groups. In these experiments, as documented in the literature, naïve participants are unable to distinguish between real and sham tDCS when employed in this fashion (30) and have similar perception thresholds for sham and real stimulation (31).

In the second series of experiments, described below, we investigated the changes that occur in lower limb excitability following anodal tDCS over M1 using two different electrode montages (TMS). Given that one of these montages involved placing the reference electrode over the inion, we probed whether cathodal tDCS over the inion induced changes in

cerebellar cortex excitability (Eyeblink conditioning). Finally, we modelled the current flow induced by tDCS through a schematic human head using a computational model (A topographic tDCS model) in an attempt to predict the neurophysiological changes observed in our TMS experiments and support the choice of electrode placement in the escalator experiments.

TMS.

To confirm that tDCS was indeed modulating lower limb M1 excitability, we evaluated the effect of tDCS on TMS-induced motor-evoked potentials (MEPs) in TA bilaterally in 16 additional healthy subjects, 2 of whom took part in the main broken escalator locomotor experiment. The gastrocnemius muscle (the activity of which was recorded during the moving platform task) was not tested as it is less readily accessible with TMS, owing to its smaller cortical representation. These TMS experiments were performed in a separate session, at least 2 weeks apart from the gait experiments. Magnetic stimuli were delivered to the motor cortex using a Magstim 200 stimulator connected to an angled double-cone coil (Magstim, Whitland, United Kingdom) positioned over the TA hotspot (Figure 5.1D), with the current induced in the brain flowing in a posterior-to-anterior direction. Surface EMG was recorded using disposable Ag-AgCl electrodes (Viasys; CareFusion) in a belly-tendon montage. Maximum voluntary contraction (MVC) was determined for all subjects before sampling using forced dorsiflexion against a strap over the dorsum of the foot that was connected to the visual biofeedback (of EMG). Subjects were then asked to contract tonically TA muscles bilaterally to ~20% of MVC to standardize the muscular activity within and between subjects. Active muscle recording (compared with rest) enables the use of lower TMS output intensities, which ensures higher compliance with the task when using a double-cone coil. The two muscles (right and left TA) were recorded simultaneously. TMS pulses

were delivered over the hotspot for bilateral TA, starting at 20% of maximum stimulator output (MSO) and increasing by 5% steps to 60% MSO. The hotspot was taken as the scalp location where the peak-to-peak MEP amplitudes were greater in the target muscle than amplitudes of adjacent scalp locations for a given TMS stimulus intensity. For all subjects, this site was approximately 2–3 cm anterior to the vertex. EMG signals were amplified and band-pass filtered between 20 Hz and 2 kHz, digitized at a sampling rate of 5 kHz, and relayed onto a computer using Signal 3.06 software [Cambridge Electronic Design (CED), Cambridge, United Kingdom]. Electrode placement for tDCS was identical to that used during the main broken escalator experiments. Eight subjects (3 females and 5 males; age range 22–31 yr.) received real stimulation, and 8 subjects (4 females and 4 males; age range 22–34 yr.) received sham stimulation.

MEPs were defined as peak-to-peak amplitudes of >0.1 mV. MEP peak-to-peak amplitudes were measured from unrectified single traces. Silent-period duration was measured from the end of the MEP to the restoration of background EMG activity and was then averaged for the last 10 frames (highest TMS stimulator output intensity used) for pre- and post-tDCS stimulation blocks. Recruitment curves were constructed based on MEP amplitude as a function of TMS intensity. To detect any tDCS-induced changes, we measured MEP amplitude and the length of the silent periods. Curves were fitted using the Boltzmann equation for a 3-parameter sigmoid fit where a = the upper asymptote, x = TMS intensity, x_0 = midpoint value of the curve, and b = slope:

$$f = a / \{1 + \exp [-(x - x_0) / b]\}$$

Paired t-test comparisons between pre- and post- stimulation were performed for midpoint values of the curves (x_0), maximum MEP amplitude, and silent-period duration between tDCS and sham conditions for both right and left TA muscles.

Eyeblink conditioning.

We performed a series of experiments to assess what effect, if any, cathodal stimulation over theinion could have had on cerebellar structures, given the recognized role of the cerebellum in motor learning and adaptation (24). We predicted that our electrode montage would spare cerebellar structures, as this is a suboptimal placement to stimulate the cerebellar cortex (32). Eyeblink classic conditioning (EBC) is a well-characterized experimental paradigm that is conserved across species and is dependent on the cerebellum (33). There are, to date, no studies investigating the use of tDCS to modulate EBC. EBC consists of pairing a weak conditioning stimulus (CS) with a strong unconditioning stimulus (US) repeatedly to produce conditioned responses (CRs) consisting of an eyeblink starting before the US. Patients with cerebellar disease are unable to produce CRs (34-36). EBC was performed as described in Teo et al. (37). We used a loud (~ 80 -dB) 200-Hz auditory tone as the CS, lasting 400 ms, played via binaural headphones. The CS produced an acoustic startle (α -blink) within 100 ms after the CS (Figure 5.3A). The US was an electric pulse (200- μ s pulse width at $5\times$ sensory threshold, ~ 1.0 mA) given to the supraorbital nerve 400 ms after the CS to elicit an eyeblink. Repeated pairs of CS and US at 400-ms intervals (i.e., delay eyeblink conditioning) yield CRs occurring within 200 ms before the US, which are independent of basal ganglia and cerebral function (38, 39).

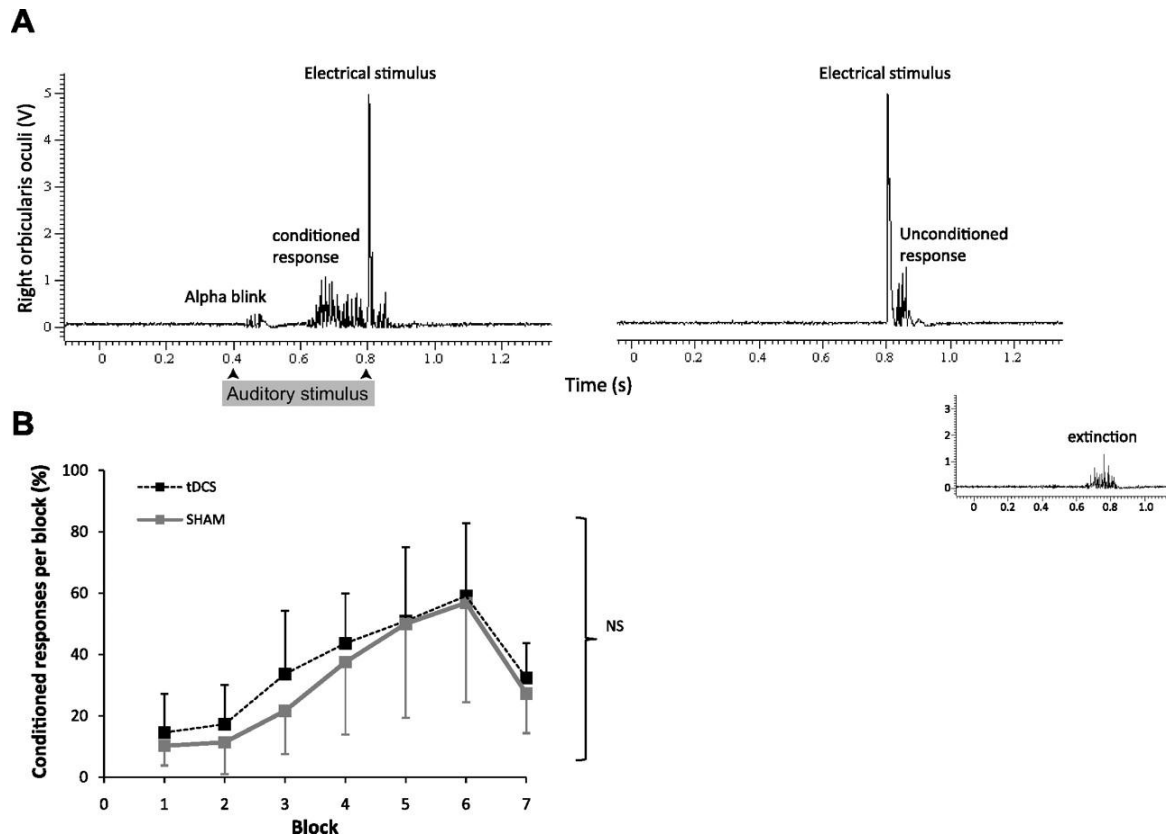


Figure 5.3. (A) representative normalized EMG recording from right orbicularis oculi in response to a 400-ms duration auditory stimulus with onset at 400 ms and electric stimulus at 800 ms. Eyeblink conditioned responses are seen before the electric stimulus. Extinction phase (inset) consisted of conditioning (auditory) stimuli alone. (B) averaged data for healthy subjects following 15 min of anodal tDCS or sham stimulation showing the presence of conditioned responses in both groups. NS, not significant.

Conditioning consisted of 6 learning blocks of 11 trials: trials 1-9 were always CS-US pairs, trial 10 was US only, and trial 11 was CS only. A 7th block consisted of 11 CS trials to measure extinction (Figure 5.3A, inset). The inter-trial interval was randomized with a range of 10–20 s to reduce habituation. A period of 400 ms before the CS was recorded to detect spontaneous blinks. The CS was applied to the left orbicularis oculi in all subjects. EMG was recorded from both orbicularis oculi muscles with the active electrode over the inferior belly and the silent electrode over the lateral canthus. EMG bursts were regarded as CRs when present 200 ms post-CS and before the US. Data analysis consisted of a 2×2 factorial repeated-measures ANOVA with within-subject factor block (blocks 1–6) and the between-

subject factor group (real tDCS and sham). The tDCS montage was identical to that used in the locomotor experiment described above (tDCS). Eight subjects (4 females) underwent 15 min of real tDCS, and 8 subjects underwent sham stimulation (4 females).

A topographic tDCS model.

The computational modelling was carried out by Dr Nada Yousif. We estimated the effect of tDCS on the human brain and compared the current density induced in M1 by two different montages using a finite element model. Such a model represents an idealized geometry of the head and calculates the electric field induced by current flow within this geometry. The geometry was defined using a previously reported four-layer sphere model (25). This model is based on four nested spheres for the scalp (7.65-cm radius), skull (7.18-cm radius), cerebrospinal fluid (CSF; 6.40-cm radius), and brain (6.15-cm radius).

Geometrically simplified models have been used to model tDCS and TMS and for source localization models in EEG and magnetoencephalography (40, 41). However, it is important to note that this model does not account for either the detailed geometry of the human head or the anisotropic electric conductivity of white matter. Therefore, the model simulations are not intended to provide an absolute value of the exact current density distribution induced by tDCS in the brain. Rather, the model allows us to compare quantitatively the relative current density induced by two different electrode montages. Specifically, we compared the current density induced in the leg area of the primary motor cortex by anodal stimulation (electrode placed at Cz) with the cathode placed on the inion, relative to anodal Cz stimulation with a supraorbital cathode (Figure 5.4), as used in the TMS experiments (see TMS).

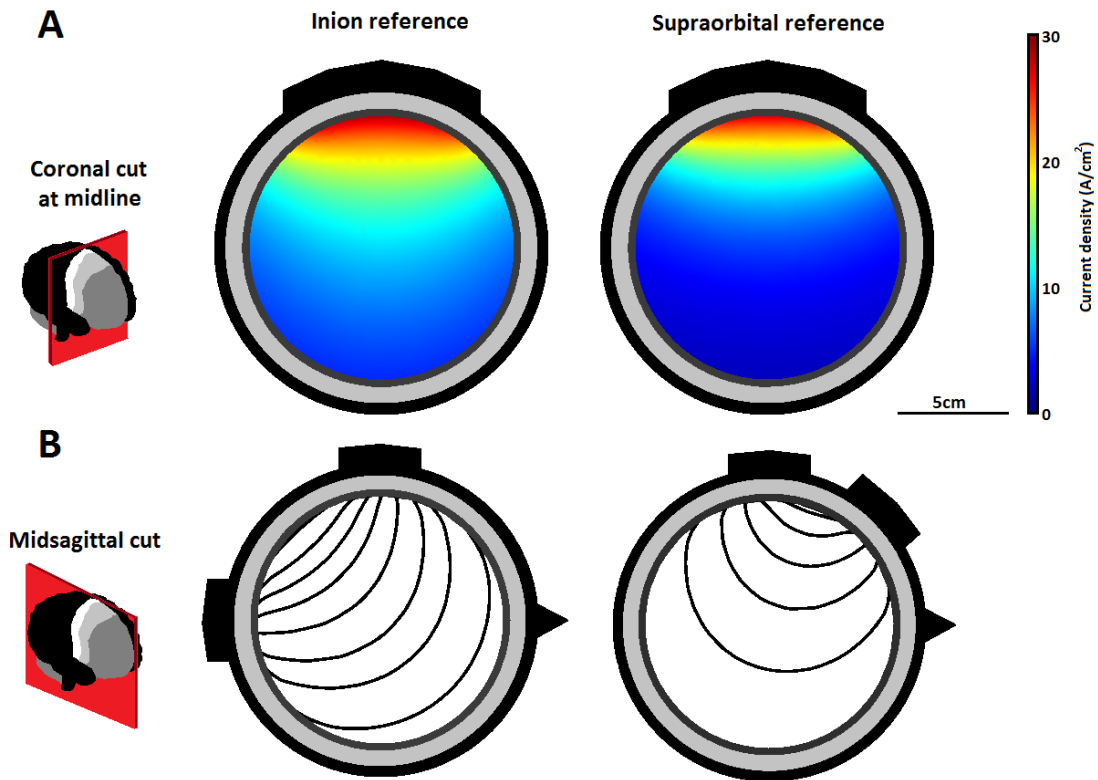


Figure 5.4. The simulation of a 4-layer finite element model allows visualization of the flow of current beneath the tDCS electrodes. (A) the coronal cut through the midline of the model shows the current density at the level of M1 in 2 electrode montages. The anode is placed bilaterally across M1 in both cases, and the reference is either on the inion (left) or on the supraorbital region (right). The distribution shows that the peak of the current density is similar in the 2 cases immediately beneath the anode (0.29 A/m² with the inion reference vs. 0.28 A/m² with the supraorbital reference). As shown previously, the current density drops rapidly with distance (40), but this decay is more gradual with the inion reference, and the current density stays above threshold (0.1 A/m²) deep into the motor region, hence supporting our choice of electrode positioning. (B) the sagittal cut highlights the direction of current flow via the field lines. When the reference is at the inion, the field lines penetrate deeper into the brain, whereas with a supraorbital reference there is more current passing superficially through the brain.

The modelling package COMSOL Multiphysics 3.3 (COMSOL, Stockholm, Sweden) was used to create a three-dimensional geometric representation of the whole head, with tDCS electrodes modelled as two cuboids on the surface of the scalp with dimensions 10×4 and 4×4 cm. The defined geometry was meshed into tetrahedral elements using the default Delaunay triangulation method in COMSOL. The electric potential distribution induced by stimulation was calculated by solving the Laplace equation:

$$\nabla \cdot \sigma \nabla V = 0$$

where V is the potential (measured in volts), σ is the constant conductivity (measured in Siemens per meter), ∇ is the gradient of the potential, and $\nabla \cdot$ is the divergence of the resulting vector field. The mean conductivity values of the brain tissue were defined based on previous biological studies with 0.45 S/m for the scalp, 0.06 S/m for the skull, 1.7 S/m for the CSF, and 0.45 S/m for the brain (42, 43). The surface of the electrode in contact with the scalp was set to the desired stimulating current in milliamperes using Neumann boundary conditions.

5.5 Data Analysis

Pre- and post foot-sled contact epochs were derived from the sled accelerometer (Figure 5.2) and corroborated with the foot contact strip data. Trunk position along the anteroposterior axis was provided by the FASTRAK (Figure 5.2). For trials where the sled was kept stationary (BEFORE and AFTER), trunk sway was measured as the maximum forward deviation or “overshoot” of the trunk, relative to the mean final resting stance position in the last 3 s of the trial (Figure 5.2). Because of the complex oscillations of the trunk during the MOVING trials, trunk sway was measured as the maximum backward-forward (peak-to-peak) displacement of the trunk before sled deceleration (44). The FASTRAK position sensor was also used to calculate walking velocity, defined as the mean linear trunk velocity in a 0.5-s time window before foot-sled contact (Figure 5.2). The EMG signals were rectified and integrated over a 500-ms time window after foot-sled contact. For graphic display, EMG values were normalized with respect to mean BEFORE (trials 3-5) values. Within-subject comparisons were made using a two-way repeated-measures ANOVA. Bonferroni multiple

comparisons were performed for post hoc analysis of each trial. To assess the presence of the aftereffect, a mean BEFORE value for trials 3-5 for each subject was taken for comparison against AFTER trial 1; a significant ($P < 0.05$) larger value in the AFTER trials indicated the presence of an aftereffect. To assess the duration or persistence of the aftereffect, AFTER trial 2 was also compared with the mean value of the BEFORE trials (3-5) using a two-way repeated-measure ANOVA. When interactions were found, each AFTER trial was investigated individually. Between-group comparisons (tDCS vs. sham) were carried out using two-way repeated-measures ANOVA. Statistical analysis was done using SPSS 16.0.

5.6 Results

The results from the main broken escalator experiments are reported first and the results of the neurophysiological and computational experiments later.

Linear trunk displacement and gait velocity were similar across all subjects in the BEFORE trials, and trunk velocity increased appropriately in the MOVING trials in all subjects. Trunk sway in the MOVING condition was highly variable between individuals, ranging between 11.4 and 40.4 cm in trial 1. Trunk sway reduced considerably in the subsequent MOVING trials as subjects familiarized themselves with sled motion and reached a plateau gait velocity by the second MOVING trial. In the AFTER trials, we found an increase in the magnitude of trunk sway and gait velocity in subjects receiving real tDCS stimulation and a persistence of the aftereffect into the second AFTER trial (Figure 5.5). In the sham stimulation group, the aftereffect was only present in the AFTER trial 1.

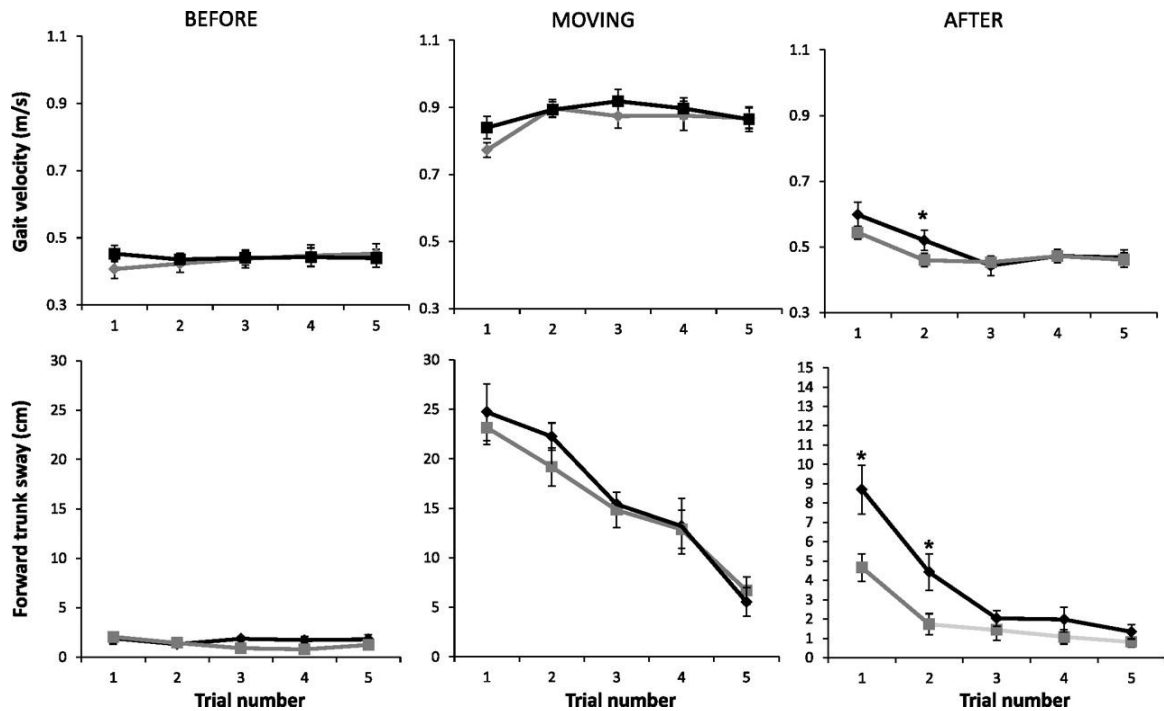


Figure 5.5. Mean ($\pm$ SE) group data for real (black) and sham (gray) tDCS during conditions BEFORE, MOVING, and AFTER for gait velocity (top) and trunk sway (bottom). The horizontal axis shows the trial number (1-5). Note the presence of the aftereffect in AFTER trial 1 in both groups and to a lesser extent in AFTER trial 2 in the real tDCS stimulation group. The aftereffect is seen as an increase in trunk displacement and gait velocity compared with baseline trials. Note the change in y-axis scaling for trunk forward sway in the AFTER trials for graphic representation. * $P < 0.05$.

BEFORE

Gait velocity was not significantly different within individuals for real tDCS ($P = 0.58$) or sham ($P = 0.93$). There was also no difference in trunk displacement within individuals ($P = 0.57$ for real stimulation and $P = 0.20$ for sham). Gait velocity was not significantly different between groups ($P = 0.1$) in the BEFORE trials (mean velocity 0.42 m/s).

MOVING

To negotiate the accelerating sled, gait velocity before foot-sled contact in the moving trials is expected to increase, and there is a forward trunk displacement to shift the centre of mass anteriorly (1). As in previous studies (1, 45), these changes were observed for all subjects (Figure 5.5 for grouped data; individual data not shown). However, no difference was seen in

gait velocity ($P = 0.55$ for real and $P = 0.72$ for sham) or trunk displacement ($P = 0.83$ real and $P = 0.93$ sham) during MOVING trial 1 within individuals. Gait velocity during MOVING trial 1 was not significantly different between stimulation groups ($P = 0.67$). There was no significant difference in the rate of reduction in trunk sway between the two groups. Subjects receiving real tDCS had a faster gait velocity in MOVING trial than those in the sham group, although this did not reach significance (0.77 m/s for sham, 0.84 m/s for real; $P = 0.14$). Gait velocity in the first MOVING trial did not correlate with the magnitude of the aftereffect ($r = 0.36$, $P = 0.19$ for real tDCS; and $r = 0.41$, $P = 0.23$ for sham).

AFTER Trial 1

AFTER trial 1 was compared with the mean of the BEFORE trials (3-5) to determine the presence of an aftereffect. There was a significant increase in gait velocity in both the real ($P < 0.001$) and sham ($P < 0.001$) groups. There was also evidence of a trunk sway aftereffect with a significant increase in forward trunk displacement in AFTER trial 1 compared with mean BEFORE values ($P < 0.001$ for real stimulation and $P < 0.001$ for sham).

We found a statistically significant difference between tDCS and sham in the size of the locomotor aftereffect and its duration (Figure 5.5) as measured by the trunk displacement. The mean forward trunk displacement in AFTER trial 1 was 8.55 cm ($SE = 1.25$) for real tDCS and 4.66 cm ($SE = 0.7$) for sham stimulation ($P = 0.04$). This represents an 83% increase in forward displacement of the trunk in the tDCS group over the sham group. A similar trend was seen in gait velocity [0.6 m/s (tDCS), 0.54 m/s (sham)], although this did not reach significance ($P = 0.15$). There was no correlation between gait velocity during the moving trials and the magnitude of the aftereffect (as measured by both gait velocity and trunk overshoot). The effect of DC stimulation on trunk displacement was apparent even

when subjects that did not have an aftereffect were excluded from the analysis (unpaired t-test, $n = 13$ for sham, $n = 14$ for tDCS; $P < 0.05$).

AFTER Trial 2

In the real tDCS group, trunk displacement was also greater in AFTER trial 2 compared with BEFORE trials ($P = 0.0013$). Unlike in the real stimulation group, no aftereffect was observed beyond AFTER trial 1 in the sham group, with AFTER trial 2 being no different from the mean of the BEFORE trials ($P = 0.13$). For both trunk displacement and gait velocity, a locomotor aftereffect was present in AFTER trial 2 in the tDCS group ($P = 0.001$ and $P = 0.001$, respectively; Figure 5.5) but not in the sham group ($P = 0.25$).

AFTER Trials 3, 4, and 5

Trunk displacement in AFTER trials 3, 4, and 5 was not different within individuals ($P = 0.2$ for tDCS and $P = 0.12$ for sham stimulation). Gait velocity in AFTER trials 3-5 was also not different within individuals ($P = 0.24$ tDCS and $P = 0.36$ for sham). There was no significant difference in gait velocity between AFTER trials 3, 4, or 5 and the mean of the BEFORE trials 3-5 in the real stimulation group ($P = 0.28$) or in the sham stimulation group ($P = 0.22$). There was no significant difference in gait velocity between AFTER trials 2, 3, 4, or 5 and the mean of the BEFORE trials in the real tDCS group ($P = 0.19$) or sham group ($P = 0.19$). Gait velocity in AFTER trials 3-5 was not different between groups ($P = 0.75$).

EMG Data

A comparison of rectified and integrated EMG activity (BEFORE vs. AFTER) for the left MG muscle in the real and sham groups is shown in Figure 6. As in previous studies, we have focused on the left MG as the left leg is the first leg to contact the sled and therefore has to

absorb the brunt of the initial impact for reducing the forward momentum. As described in previous studies using this paradigm (1, 8), EMG activity increases in the MG muscles (particularly the left) just after foot-sled contact. Thus the EMG data also showed the presence of an aftereffect (Figure 5.6).

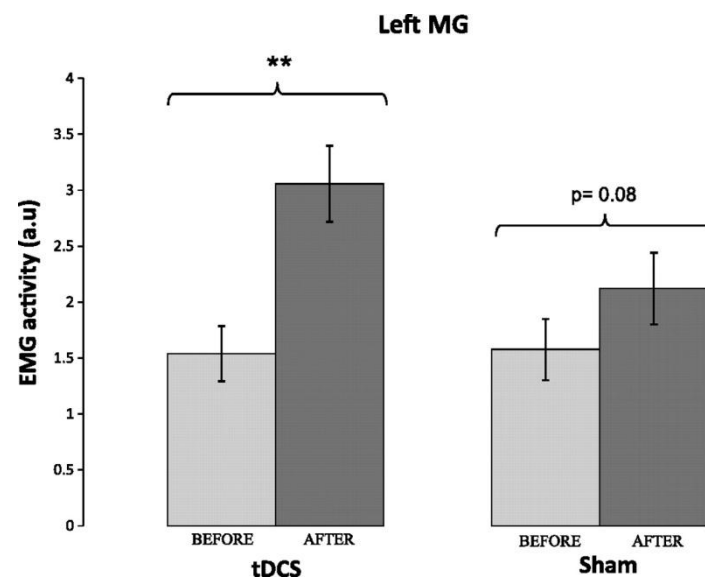


Figure 5.6. EMG activity in the left MG muscles (mean of the BEFORE trials 3-5 vs. AFTER trial 1) for real and sham tDCS groups. EMG activity was greater in the 1st AFTER trial compared with BEFORE trials, consistent with the presence of an aftereffect. Vertical bars represent standard errors. ** $P < 0.001$.

In the tDCS group, significant increases were observed in the left and right MG muscle activity in AFTER trial 1 compared with BEFORE values ($P < 0.001$ for left MG and $P = 0.03$ for right MG). EMG activity from the right MG in AFTER trial 1 was also greater than BEFORE values in the sham group ($P = 0.018$). A similar trend was seen for the left MG in the sham group but did not reach significance ($P = 0.075$). No significant difference was seen in TA muscles.

Additional Experiments

TMS.

A repeated-measures ANOVA revealed no difference in background EMG activity (at 20% of MVC) across subjects, right and left TA, nor between groups (mean EMG activity 1.29 mV for real tDCS, 1.53 mV for sham; $P = 0.26$). Averaged data are shown in Figure 5.7A (inion cathode) and Figure 5.7B (supraorbital cathode). We found a significant increase in MEP amplitudes in right ($P < 0.001$) and left TA muscles ($P < 0.001$) following 15 min of 2-mA anodal tDCS using an inion reference electrode (as used in the broken escalator experiment) but not for sham stimulation ($P = 0.93$ for the left TA and $P = 0.43$ for the right TA). Concordantly, silent-period durations increased with real stimulation (real tDCS: $P = 0.019$ for right TA and $P = 0.012$ for left TA) but not with sham ($P = 0.76$ right TA and $P = 0.95$ left TA). Using a supraorbital reference (cathode) electrode did not significantly change MEP amplitude with real tDCS ($P = 0.19$ for right TA and $P = 0.45$ for left TA) nor with sham stimulation ($P = 0.74$ for right TA and $P = 0.29$ for left TA). There was no overall effect of tDCS using this second montage on silent-period durations in the last 10 frames ($P > 0.1$). These data provide further evidence that tDCS placement over Cz is able to modulate cortical excitability in leg areas bilaterally. In addition, it supports the simulation results of our computational model, which predicted the neurophysiological effects of tDCS.

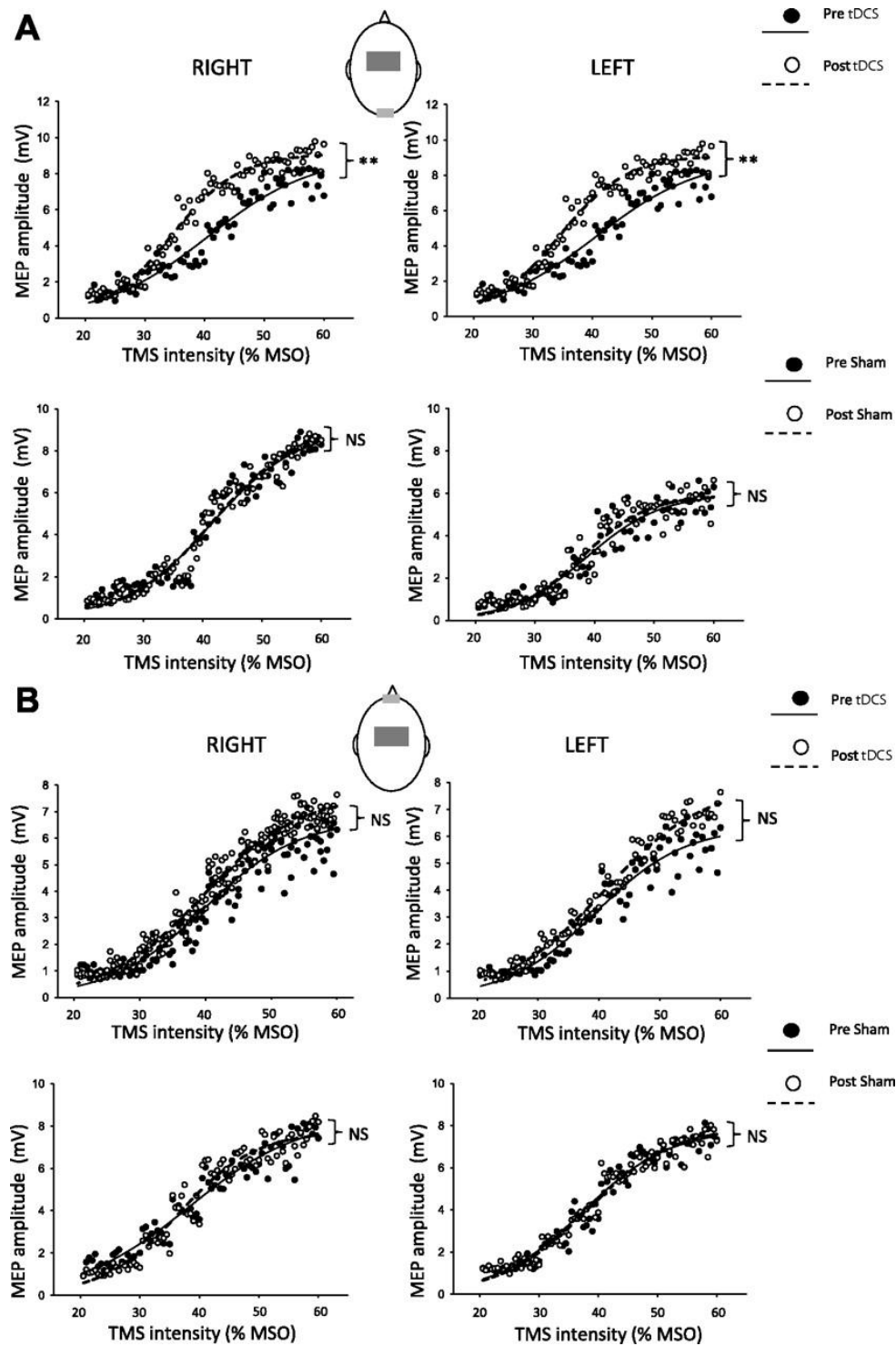


Figure 5.7. Averaged group data showing TMS-induced motor-evoked potential (MEP) amplitudes in right and left TA before and after tDCS or sham. (A) reference electrode placed at the inion. Top: MEP amplitudes pre- (black spots) and post- (white spots) real tDCS. Bottom: MEP amplitudes pre- and post sham stimulation. MSO, maximum stimulator output. (B) supraorbital reference (cathode) electrode. Top: MEP amplitudes pre- (black spots) and post- (white spots) real tDCS. Bottom: MEP amplitudes pre- (black spots) and post- (white spots) sham stimulation. Sigmoid curves were fitted using MATLAB (The MathWorks, Natick, MA). r^2 Values ranged from 0.93 to 0.99. Muscle excitability was increased following 15 min of tDCS but not following sham but only when a reference electrode was placed at the inion.

Eyeblink conditioning.

Cathodal effects over the cerebellum would be expected to impair conditioned eyeblink responses. All subjects ($n = 8$) in the real tDCS and 7 subjects ($n = 8$) in the sham group acquired the CR. Comparison of CRs per block revealed no differences between real and sham groups [ANOVA; tDCS/block, $F(1,14) = 0.54$, $P = 0.74$] with normal CRs in both groups (Figure 5.3B). There was a significant effect of block [$F(1,14) = 8.78$, $P = 0.002$] with increasing CRs across blocks but no effect of group [$F(1,14) = 0.32$, $P = 0.58$]. Latencies of CRs and α -blinks were not statistically significant between groups. Extinction phase responses were analysed only for subjects who showed CRs. Mean CR in extinction phase was 3.6 (SD = 1.2) in the tDCS group and 3.0 (SD = 1.3) in the sham group (paired t-test; $P = 0.26$). Representative traces showing unconditioned and conditioned responses are illustrated in Figure 5.3A. Thus placing the cathode electrode over the inion does not appear to have significant cerebellar effects.

Topographic tDCS model.

The model simulation (Figure 5.4) shows two main differences between anodal M1 stimulation with a reference at the inion compared with a supraorbital reference. First, with a 2-mA stimulating current, the current density induced in the region of brain directly below the anode peaks at 0.29 A/m² (Figure 5.4A). In comparison, when the reference electrode was moved to the supraorbital location, the induced current density in the M1 region was modestly smaller, peaking at 0.28 A/m², and in particular the current density decay is greater as the depth into the brain increases. Second, the field lines, which show the current path through the brain, show less shunting through the scalp and CSF, penetrating deeper into the brain (Figure 5.4B). Specifically, the model predicted that the same 2-mA stimulating anodal

current would cause up to 47% less current density beneath the anode using a supraorbital reference electrode.

5.7 Discussion

We present the novel finding that anodal tDCS over the primary motor cortex and premotor leg areas increases the magnitude of the broken escalator adaptation aftereffect by 80% and prolongs its duration [normally observed only in the 1st AFTER trial; (1)] into the 2nd trial. We provide TMS data demonstrating that anodal tDCS over Cz increases cortical excitability in leg muscles bilaterally and also show that our computational model predicts tDCS-induced leg motor cortex excitability changes.

At first sight, the occurrence of the broken escalator effect itself appears incongruous. Why do healthy subjects display a motor response (a forward “stumble” on a stationary platform) apparently inimical for their stability despite full knowledge of the escalator being broken? Since motor aftereffects are a measure of motor learning in general (46, 47), the observed stumble on the stationary platform implies the inappropriate expression of the newly generated motor program acquired when stepping onto the moving platform (8). Viewed in this light, the increased amplitude of the trunk sway aftereffect reflects an enhancement of the motor adaptation aftereffect.

Our results are consistent with previous data using TMS to explore the role of M1 in upper limb force-field adaptation. Repetitive training of a single ballistic hand movement transiently modifies corticospinal excitability, leading to a favoured pattern of motor output (48), although the neural substrate for this change is unknown. Studies of visuomotor

adaptation or learning in animals have implicated the supplementary motor area [SMA; (49)], premotor cortex (49-51), parietal cortex (52), and cerebellum (53), and this has been confirmed using functional imaging in humans (16). We have shown that stimulation of M1 and premotor cortex before skill acquisition increases locomotor adaptation. One may consider three non-mutually exclusive explanations to account for this.

When the brain encounters environmental or sensory changes in the body, it must choose the most appropriate response for the current situation, using a Bayesian motor decision-making process (54). The motor response in the escalator task may be determined by weighing prior experience on the moving sled and the current estimate of the platform motion. Indeed, the proportion of subjects who show an aftereffect on this task can be increased from 80 to 100% when the experiment uses a faster platform velocity (55). Furthermore, autonomic arousal and anxiety about the task all influence the expression of the locomotor aftereffect (55) via a process of “risk assessment.” This assessment is therefore subject to interactions from the physical properties of the sled and the individual's state of arousal. Premotor areas show prominent activation during motor planning (56-59), and there is evidence that the activity of neurons in premotor cortex (60) and SMA (61) during motor planning reflects the dynamics of the upcoming movement. tDCS in its offline mode may thus prevent the selection of a motor program that is contextually appropriate in favour of a cautious approach (“the sled may move after all”), thus generating a larger aftereffect. Recent data have confirmed that premotor regions are involved in involuntary task switching (62, 63), a function that could potentially be invoked in our subjects' decision to select a gait response appropriate for a moving vs. a stationary platform.

Alternatively, neurostimulation paradigms may impact on connected structures distant to the site of stimulation, including subcortical and brain-stem locomotor circuits such as the basal ganglia, brain-stem locomotor and posture regions (e.g., the midbrain locomotor regions), and spinal circuits. Indeed, it has been shown that non-invasive brain stimulation can alter spinal network excitability. Thus one may consider that tDCS is altering excitability of spinal systems involved in sensorimotor integration (sensory and proprioceptive output from muscles, skin, and joints) to modulate motor output. Spinal cord reflexes can be facilitated using rTMS over the motor cortex, presumably occurring as a result of inhibition of corticospinal projections (64). Anodal tDCS has also been shown to have effects on spinal network excitability (65). Thus, in our experiment, anodal tDCS may alter the excitability of spinal reflex responses to enhance adaptive motor responses. In fact, an interesting characteristic of this locomotor aftereffect is that the aftereffect overrides cognitive control, e.g., it cannot be suppressed at will, and yet it will not appear if the subject walks on a surface other than the training sled (6, 8). This suggests the involvement of low-order brain-stem locomotor pathways (66, 67) that are under involuntary, although cortical in that they are context-dependent, gait control. Contrary to this argument, the spinal effects of anodal tDCS appear to operate online and rapidly wear off when stimulation is discontinued (65). In addition, and in contrast to our findings, there is some disagreement in the literature as to whether motor cortex high-frequency rTMS and anodal tDCS increase (68, 69) or decrease (65) spinal cord excitability. Overall, our results suggest that anodal tDCS stimulation may modulate “high-order” cortical networks given the gait parameters that were affected: motor learning, the characteristics of the locomotor aftereffect, and the dissociations between its functional components, namely gait velocity vs. trunk sway. Although tDCS is likely to induce excitability changes over widespread cortical networks, including areas outside M1,

we provide direct TMS evidence that tDCS increases lower limb excitability bilaterally, suggesting that M1 is involved in the locomotor aftereffect.

Lastly, the assumption that applying non-invasive brain stimulation with parameters that increase motor cortical excitability (e.g., anodal tDCS) improves motor performance has become generally accepted (70). However, it has become clear that there are timing-specific effects of tDCS relative to adaptation or training. Thus anodal tDCS applied to M1 during training improves performance (71-74), whereas the application of tDCS before learning or adaptation has produced mixed results with respect to motor performance. It has been proposed that such variability may relate to homeostatic effects when tDCS is applied before training (75). Given that tDCS-associated increases in excitability are likely to be widespread, concurrent synaptic activation induced by motor training could lead to improvements in performance via synaptic specificity (ensuring that the synaptic changes specific to the motor task are enhanced, with pruning of nonspecific synaptic connectivity). A further explanation for our findings, therefore, is that anodal tDCS increased neuronal excitability in a widespread cortical network and that the repetitive locomotor task of walking onto the moving platform reinforced appropriate synaptic changes that led to an enhanced expression of the adaptation aftereffect. This is the first demonstration of enhanced locomotor (lower limb) adaptation aftereffect using anodal tDCS when applied just before adaptation.

One may reasonably assume that the forward trunk displacement component of the aftereffect is directly related to the increased gait velocity, such that a sudden termination of gait leads to the forward overshoot of the trunk. However, gait velocity only contributes to a small degree to forward trunk sway, suggesting that these two aspects of locomotion are largely independent (6), and the current results further support such a view: the most prominent

effect of tDCS was on trunk displacement (largely due to hip flexors) rather than gait velocity. Whether this dissociation is due to tDCS modulation of relevant frontal areas such as the SMA (76, 77) or to the fact that cortical leg areas are deeper than hip/axial structures (although still affected by tDCS; see Figure 7) is not clear. Furthermore, we can exclude a direct effect of tDCS on gait velocity per se, as we observed no significant differences in gait approach velocity in MOVING trial 1 between real and sham groups.

It is perhaps surprising that the large increase in the motor aftereffect was not accompanied by recordable changes during the learning phase (MOVING trials). However, this has been a consistent finding in studies exploring the role of M1 in motor learning and retrieval (24, 78). For example, anodal tDCS to the contralateral M1 did not result in greater adaptation compared with sham during force-field adaptation, but when the force field was turned off, anodal tDCS induced larger errors in reaching performance, suggesting a role for M1 in retention (23). Indeed, M1 appears to have a distinct functional role in retention, rather than acquisition, processes during adaptive motor learning (24), such that anodal tDCS over M1 did not improve the ability to learn from errors but resulted in increased retention (larger aftereffects). This result is consistent with our findings.

Study Limitations

Some methodological aspects of the study deserve mention. It could be argued that a large active electrode (anode) on Cz and a smaller cathode on the inion could cause effects over a number of other central nervous system regions relevant to sensorimotor control and adaptation. In particular, the cerebellum is in anatomic proximity to the inion and is known to be involved in motor adaptation (79). Most studies of tDCS cerebellar stimulation, however, place the stimulating electrode 3 cm lateral to the inion (79, 80) or 2 cm below the inion and

1 cm posterior to the mastoid process (81), locations that we avoided. Furthermore, “open-loop” locomotor adaptation experiments in patients with cerebellar damage have shown reduced, and sometimes absent, motor aftereffects (47). Lastly, anodal cerebellar tDCS has been shown to produce faster adaptation to a visuomotor transformation (24). Thus one would not expect cathodal (inhibitory) stimulation over the cerebellum to cause the enhancement of the locomotor aftereffect that we observed. Indeed, we show that cathodal stimulation over the inion does not alter eyeblink conditioning [a phenomenon that relies on the cerebellum; (33)], although this cannot be taken as definitive evidence that the cerebellum was not modulated by tDCS in this locomotor task. Nevertheless, our computational model predicted that current flow from Cz to the inion was more likely to have an effect on cortical leg areas than with a supraorbitally placed cathodal electrode, a fact that we were able to corroborate neurophysiologically with TMS. Additionally, this electrode montage enabled us to target midline locomotor cortical structures that span both hemispheres (including bilateral M1). It should be noted that an extracephalic reference electrode, while avoiding cathodal effects over the cortex, may shunt electric current through the skin or even displace the current such that it would not reach the desired cortical regions (82). We cannot comment on the specific brain structures directly affected by the stimulation, which may not be strictly limited to leg regions of the primary motor and premotor cortex. Admittedly, the pathway of least resistance for current flow using tDCS is not known, a potential criticism of this and most tDCS studies. Current flow during tDCS depends on the electrode montage, electrode size, and current intensity used; computational models of brain current flow during tDCS provide an estimation of the current flow and hence the anatomic regions affected by the stimulation. Such models range in complexity from concentric sphere models (40, 83-85) to individualized MRI-based high-resolution models (86-88). Our modelling data show that it is possible to predict neurophysiological outcomes with tDCS based on simple models and

suggest that such models could help optimize the potential of non-invasive techniques. Finally, the nature of the broken escalator adaptation process that spans several seconds precludes the use of single-pulse or short-burst TMS approaches. Equally, the widespread cortical circuits involved in gait adaptation phenomena render more spatially selective tDCS and rTMS techniques unsuitable. Indeed, rTMS is likely to affect premotor areas in one hemisphere, not both.

Our results may have clinical implications. The finding of an effect of cortical modulation on involuntary locomotor control is of potential interest for patients with gait disorders as tDCS offers the advantage of ease of access. Its relative lack of focus, an apparent disadvantage for physiological experiments, may be welcomed when attempting to modulate complex and distributed cortical networks such as those involved in gait. Indeed, there is evidence supporting the use of tDCS in the treatment of conditions such as stroke (89) and Parkinson's disease (90), although this is the first study to assess specifically the effect of bihemispheric anodal tDCS on gait. Results from the current finding suggest that direct non-invasive stimulation of primary motor cortex and premotor areas may be suitable sites to target locomotor adaptive learning. Accordingly, our findings support the use of tDCS for experimental treatment of neurological gait disorders.

5.8 References

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C_{hapter} 6

Modulation of gait and balance in Parkinson's disease

6.1 Introduction

Parkinson's disease (PD) is a common cause of gait and postural instability. Although it is defined pathologically by the loss of dopaminergic neurons in the substantia nigra, much of the long-term disability relates to symptoms that do not respond to levodopa (1), and is therefore therapeutically challenging.

While the organisation of antigravity postural tone occurs at the level of the spinal cord (propriospinal and vestibulospinal circuits (2)) and the brainstem (rubrospinal tract (3)), human gait is heavily reliant on the motor cortex (4-6). The pathophysiology of bradykinesia and gait disturbance in PD involves an increase in inhibitory efferent drive from the basal ganglia to the thalamus, with subsequent inhibition of thalamocortical loops. Such inhibitory overactivity reduces motor and premotor cortical activity (7-9). Targeting the motor and premotor cortices using non-invasive stimulation techniques in patient with PD represents an attractive strategy to addressing gait disturbance in these patients (10).

Physical therapy is an established therapeutic adjunctive in patients with PD, with approaches ranging from attentional control (11), sensory cueing (12), Nordic walking (13), and audio biofeedback (14). Both anatomical and physiological changes are seen in primary motor cortex following a period of motor learning (15-17). Non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) are able to improve motor learning and rehabilitation in patients with PD (18, 19). To date, the combination of non-invasive stimulation with simultaneous clinically-relevant gait and balance training has not been studied in patients with PD.

Our objective was to apply bihemispheric anodal tDCS over lower limb M1 and premotor cortex in patients with PD a) during locomotor training, and b) during locomotor performance. Evidence from a previous study (see chapter 4) suggests that a bihemispheric

electrode montage modulates cortical lower limb excitability. Given that a single session of anodal tDCS administered in temporal association to motor skill training improves performance (20-22), we hypothesised that anodal tDCS time-locked to physical training would improve gait and balance in PD above and beyond the effects of PT and tDCS in isolation.

6.2 Materials and methods

Patients

All subjects gave written informed consent according to the study protocol approved by the local ethics committee. 16 patients diagnosed with idiopathic Parkinson's disease were recruited for this study. All patients fulfilled the UK Brain Bank criteria for idiopathic PD and sustained a clear and prolonged beneficial response to treatment with levodopa or a dopamine agonist. Patients were evaluated using the Hoehn and Yahr scale, the motor component of the Unified Parkinson's Disease Rating Scale (UPDRS III) (23). Patients with severe freezing, daily falls, dementia (mini-mental state examination score less than 24/30), clinically significant orthostatic hypotension, orthopaedic, vestibular, visual or somatosensory disorders were excluded.

Patients were randomly assigned to one of two groups (physical training – 'PT' [n=8] or 'No PT' [n=8]) using an online randomisation software tool (Research Randomizer, Version 3.0). Subjects were also randomised to receive either real tDCS or sham stimulation in the first session. All subjects were 'crossed over' to receive either real or sham stimulation in the second session one week later. Physical training (Figure 6.1) was carried out by the main examiner (DK). Both the examiner and patients were blinded to the tDCS protocol, which was delivered and monitored by a second researcher (ROD).

Exercise Programme for PD**Stand up from a sitting position**

Follow a sequence of four actions:

- Shifting the body forward so that the buttocks are close to the edge of the chair,
- Placing the feet flat on the floor so that the heels are well back,
- Leaning the trunk forward, and
- Standing up quickly while thinking of leaning “forward and up” in an arc of movement.

Note: It is useful to start with a chair with a high seat and armrests so the sit-to-stand action is performed independently and to gradually reduce seat height (and presence of armrests).

Walking

Walk with long strides and adequate ground clearance in different walking speed

- Initially, draw some lines on the floor and ask the patient to walk by following the lines with large steps
- Give the patient a rhythmical beat to generate a more normal stepping rate
- Ask the patient to walk with swinging the arms to help balancing

Walk with long strides and take a side step at the end

Step over obstacles while walking

Note: Remind the patient to stand upright and look forward while walking

Turning

Turn in a large arc of movement by using full body movements rather than focusing on rapidly switching directions

- Put an object, such as a chair, in the centre of turning and ask the patient to turn by taking steps around the object

In very small spaces, where turning in a large arc is not possible, the “clock turn” strategy is recommended

Note: Attention is directed to lifting the feet clear in a deliberate stepping action, rather than shuffling or swivelling around

Balance training

Forward reach a target with both hands to different directions, from closer to further distance

Pick up some objects from the floor (or a lower place) to a higher place

Figure 6.1: Training protocol for the physical training group.

Our physical training protocol focused on gait initiation failure, stride length, gait velocity, arm swing, and balance both during gait and during stance. The protocol (Figure 6.1) was designed and approved by our local physiotherapy department based on published practice recommendations (24-27).

The evaluation time points were selected when anti-parkinsonian drugs had some effect (neither *on* nor *off* states) to assess the additive effect of tDCS above standard treatment. All assessments were performed at the same time during the day in each subject to exclude some

of the diurnal variations in clinical state. All patients were assessed whilst ‘on’ medication, and repeat protocols were carried out at the same time (+/- 1 hour) as the initial visit.

18 healthy age-matched individuals took part as controls and performed only baseline tests (without tDCS). All controls were free of disorders that could affect balance or gait control.

6.3 Methods

Timed ‘Up and Go’ (TUG)

Subjects began seated in an armless office chair and were asked to get up, walk 3 metres, turn round, return to the chair and sit down again (Figure 6.3A *right panel*). A verbal “go” signal was given to start the test. Subjects were asked to perform the task at a brisk but safe pace. The total duration of the task was calculated from the moment the subject began to get up until they were comfortable on the chair again.

6 metre walk

Subjects were asked to walk a distance of 6m along a flat surface at a brisk pace (Figure 6.2A). The start and finish were marked with black tape on the floor. An assistant accompanied the subject at a distance of 1 metre to prevent the subject from falling.

Pull test

The pull test is a well-established clinical tool used to evaluate postural instability in patients with Parkinson’s disease (28). Subjects stood in a comfortable stance position with feet at shoulder width, and eyes open (Figure 6.2B). They were warned that they would receive a sudden and firm shoulder pull, delivered by the examiner standing directly behind the subject. The examiner then delivered a single pull using sufficient strength in order to force subjects to take at least one corrective step backwards. The test was repeated a total of 3

times. The same examiner (DK) performed the retropulsion test on every subject to reduce the pull strength variability. The shoulder pull forces were not quantitatively controlled but recordings showed that subjects' backward trunk velocity was approximately equal (mean backward velocity = 32.5deg/s, SD =5.8). Trunk sway recordings were started just prior to the pull and terminated 5 seconds later, or until loss of balance occurred. Subjects were prevented from falling by the examiner and an assistant standing next to the subject.

In addition, all subjects were evaluated using the Tinetti Gait Index and the tasks were video-taped. A tripod-mounted digital video recorder was placed at the far end of the test walkway. A second hand-held camera was used to record the subject's legs during the get up and go task (Figure 6.2A). These recordings were used to assess gait velocity (m/s), stride length (cm), and stride length variability (CoVar). Subjects were instructed to "walk as quickly, but safely, as possible". The duration of walking during the middle 4m of the 6m walk was used to calculate mean gait velocity (m/s). Stride length (distance from the initial contact of one foot with the ground to the following contact of the same foot) was measured against floor markers placed 15cm apart using frame-by-frame video analysis. Stride length variability was calculated using the variability index ($\text{CoVar} = \text{SD}/\text{mean} \times 100$) to express the intra-individual stride-by-stride variability (29). Gait velocity was estimated from task duration data from the Swaystar trunk recording system and cross-referenced with the video data acquisition for validation.

Trunk sway measurement system

A device encompassing two digitally-based angular-velocity transducers arranged to measure angular trunk displacement and velocity in the roll (coronal) and pitch (sagittal) planes (SwayStar System, Balance Int. Innovations GmbH, Switzerland) was used in all subjects. The transducers were encased in a lightweight Bluetooth cordless device attached to an

elasticised motorcycle belt, which was easily fitted on the subjects back at the L2-3 level (Figure 6.2A). Angular deviations were calculated using on-line-trapezoid integration of the angular velocities.

Transcranial direct current stimulation

A DC stimulating rectangular saline-soaked sponge electrode (10cmx4cm; surface area 40cm²) was placed centrally across the scalp to cover a region 10-20% anterior to Cz as measured from the midline of the stimulating electrode. The reference electrode (4cm x 4cm) was positioned at the inion. A 2mA current was delivered by a battery driven, Magstim Eldith DC stimulator (NeuroConn, Ilmenau, Germany) during the exercise session for the PT group, or during the second set of baseline tasks for the No PT group. The current was initially increased by a ramp input over 10 seconds until reaching 2mA (current density 0.05mA/cm²). Stimulation duration of 15 minutes, as chosen, can result in an excitability change lasting approximately 90 minutes (30). We cannot rule out that cortical regions or networks other than M1 and premotor cortex could be affected during stimulation. However, this montage both increases cortical excitability in lower limb areas and improves motor adaptation in healthy young normal subjects (31). The sham stimulation was identical to the real stimulation condition except that the current was delivered for only 30 seconds and then turned off. Participants reported a ‘tingle’ sensation beneath the electrodes at the beginning of the stimulation for both sham and real conditions, which typically faded away after 10-20 seconds in both groups. Naive participants are unable to distinguish between real and sham tDCS, when employed in this fashion (32, 33).

6.4 Data analysis

Video and SwayStar data were acquired simultaneously for all tasks. For the video data, the first three and the last two steps of each gait cycle were eliminated from the data set to remove acceleration and deceleration effects.

	PD	CONTROLS	
	n=16	n=18	p value
Age, yrs (SD)	76.4 (5.67)	76.1 (7.1)	NS
Male/Female	7/9	9/9	NS
Medical history			
Arterial hypertension (%)	3 (19)	5 (28)	NS
Diabetes mellitus (%)	4 (25)	5 (28)	NS
Stroke (%)	0	0	NS
Average disease duration (SD), yrs	10.4 (3.0)	-	-
Patients with falls in the preceding year, %	41.2	4.5	<0.0001
Mini-mental status score (SD) max = 30	29.1 (1.1)	29.4 (0.93)	NS
UPDRS III (SD) max = 56	25.8 (5.74)	0.53 (1.2)	<0.0001
Baseline Tinetti scale score (SD) max = 28	22.0 (4.1)	26.5 (3.8)	<0.001

NS= not significant

Table 6.1 Averaged demographic data for all patients (n=16) and controls (n=18).

For the recorded (angular trunk movements) version of the retropulsion test we report the time taken to regain a trunk angular position within 2 degrees of the baseline (quiet standing), which is easy to measure objectively (Figure 6.4A) and correlates well with the number of falls in the preceding year ($r=0.8$, $p=0.0002$; Figure 6.4B), suggesting it is a clinically relevant measure of imbalance. We also recorded the peak pull velocity and displacement (to ascertain stimulus consistency) and peak recovery phase velocity (see Figure 6.4A inset) within the first second following maximum pitch backward displacement.

We performed a two-way repeated measures ANOVA [INTERVENTION_{tDCS, sham} and PHASE_{baseline, test}; between group factor: TRAINING_{yes, no}] to evaluate overall effects of stimulation and training before and after stimulation. Statistical analysis was carried out using SPSS 18.0 with significance set at $p < 0.05$ (two-tailed).

6.5 Results

16 PD patients and 18 controls completed the experimental procedures. Patients (see Table 6.1 for demographic and clinical data) had a mean age of 76.5yrs (range 67-82yrs) was not statistically significant from those of controls ($p=0.37$) and mean disease duration of 10.4 years (range 6-16). As expected, disease duration correlated with disease severity ($r=0.55$, $p=0.02$).

Patients performed significantly worse than controls in all tasks at baseline. Table 6.2 shows the statistical results for all groups and tasks.

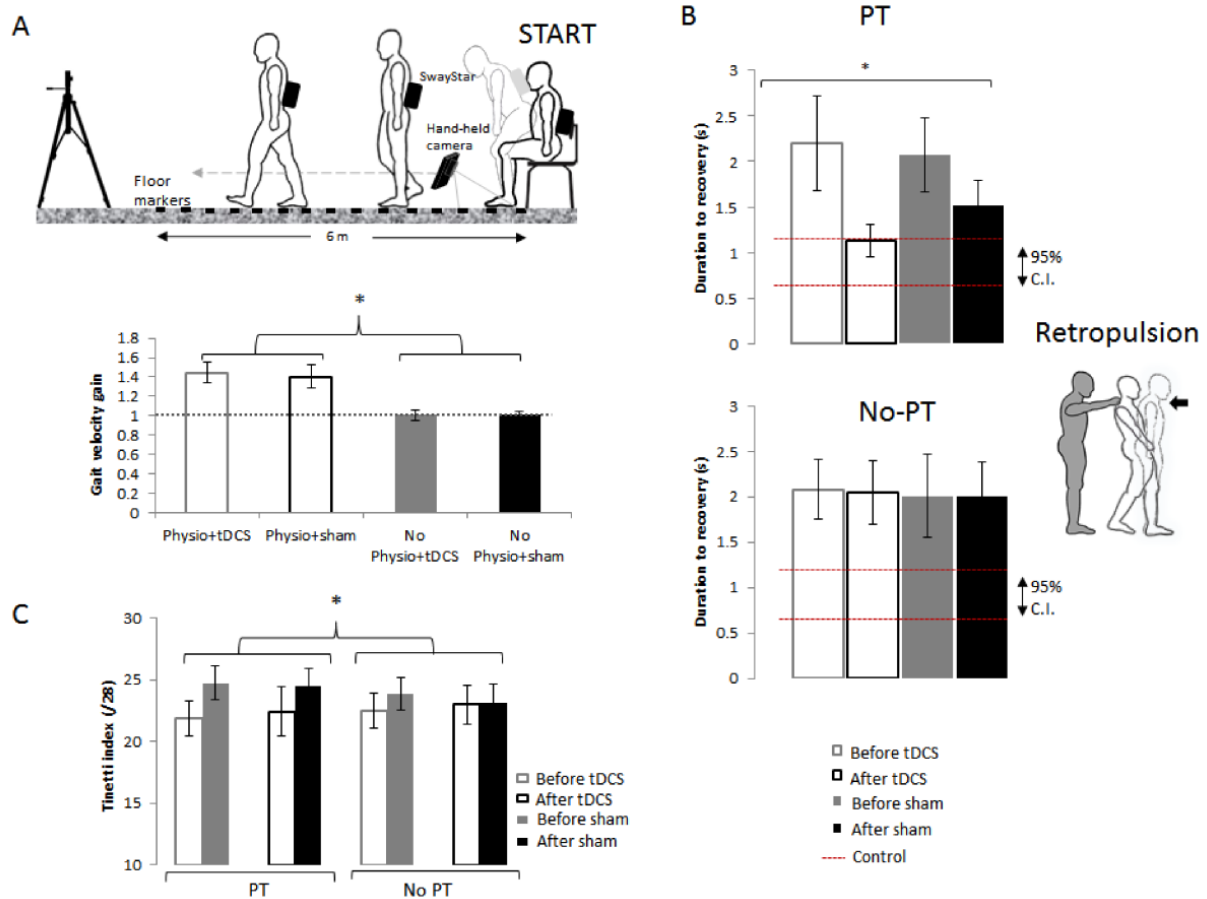


Figure 6.2 (A) 6m walk setup. A tripod-mounted digital video recorder was placed at the far end of the test walkway. A second hand-held camera was used to record the subject's legs during the get up and go task. These recordings were used to assess gait velocity (m/s) and stride length (cm). Subjects started from a standing position and were again asked to walk "as quickly but safely as possible" a total of 6m. Shown below, averaged group data for gait velocity gain (gait velocity post stimulation/gait velocity baseline) calculated from the 6m walk. (B) Time taken to regain posture in the retropulsion test. Values represent averaged group data. Vertical bars show standard errors. Subjects stood in a comfortable stance position with feet at shoulder width, and eyes open. The examiner stood behind the subject and delivered a single pull using sufficient strength in order to force subjects to take at least one corrective step backwards (right cartoon). The test was repeated a total of 3 times. The main outcome measure was time (s) taken to regain posture following the retropulsive stimulus. Horizontal dotted lines show 95% confidence interval (C.I.) for healthy aged-matched controls. (C) Averaged group data for the Tinetti Gait Index, also calculated from the 6m walk.

Gait velocity

Mean "fast-walking" gait velocity in healthy controls was 1.69m/s (SD=0.30) and 0.63m/s (SD=0.13) in the PD group at baseline (paired t-test; $p=0.0001$). As shown in Figure 6.3A, there was an overall effect of training, with faster gait velocity in the PT group than in the

No-PT group (training-phase; $F=6.57$, $p=0.02$) but no effect of tDCS alone (stimulation-phase; $F=4.37$, $p=0.06$). We observed no interaction between tDCS and training (stimulation-training-phase; $F=0.02$, $p=0.88$) suggesting no combined benefit of tDCS with physical training. Gait velocity correlated with UPDRS ($r=0.77$, $p=0.025$) but not with age, Fazekas or MMSE ($p>0.1$ for all).

Stride length

Patients had reduced stride length at first assessment compared to controls ($p<0.001$). Stride length was not statistically different between PT and No-PT groups at baseline (paired t-test: $p=0.43$). Stride length increased with physical training (training-phase; $F=17.5$, $p=0.001$). With tDCS and training stride length increased from 92.7cm (SD = 12.0) to 122.1cm (SD=23.9) but this was not significant in the ANOVA (stimulation-training-phase; $F=7.2$, $p=0.41$). There was no isolated effect of stimulation (stimulation-phase; $F=0.6$, $p=0.45$).

Stride length variability

Stride length variability was greater in patients for the first assessments compared to controls ($p=0.04$). There was no significant interaction between tDCS and PT (stimulation-training-phase; $F=0.03$, $p=0.86$). There was no overall effect of tDCS, irrespective of training (stimulation-phase; $F=0.04$, $p=0.95$) and no decrease in stride length variability with training alone (training-phase; $F=0.02$, $p=0.90$).

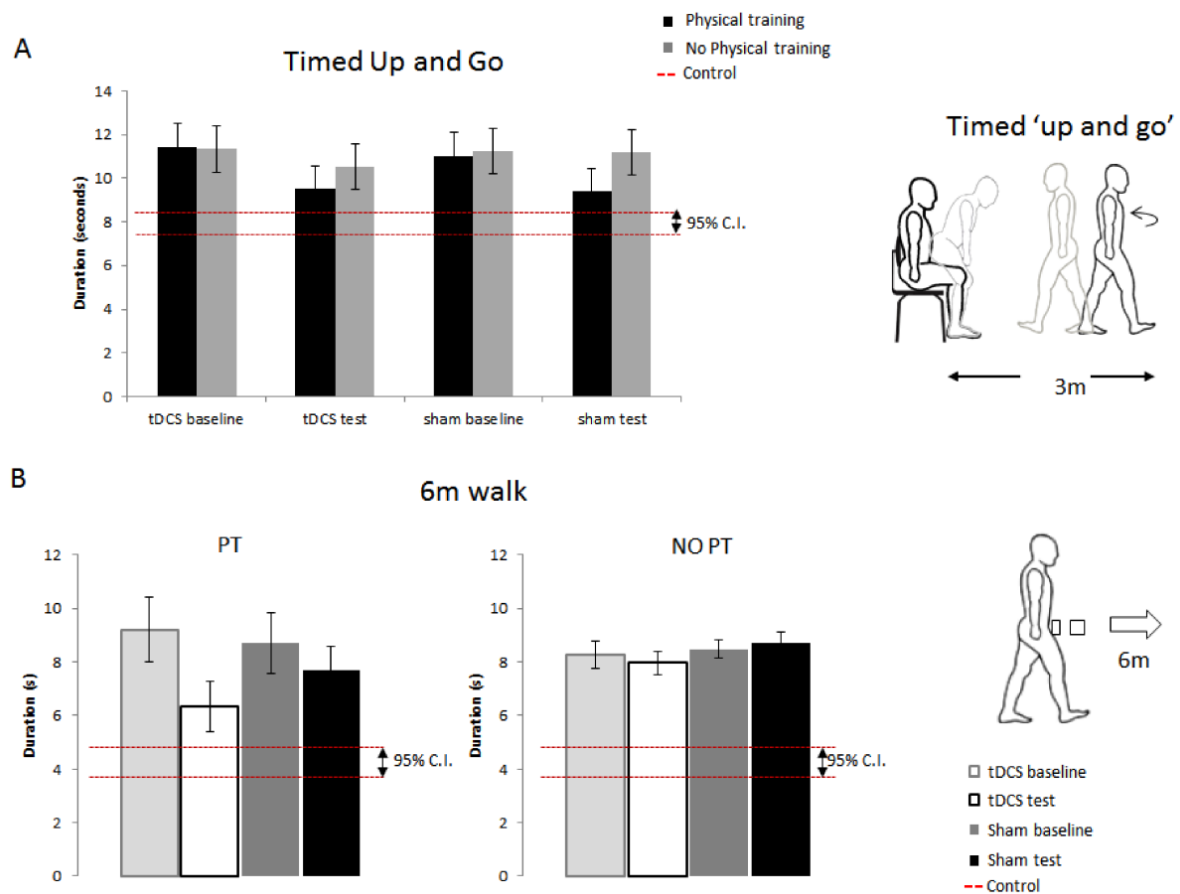


Figure 6.3: Averaged group results for the Timed Up and Go (A) and 6m walk (B) duration.

Pull test

The retropulsive stimulus was of similar velocity between controls and patients ($p > 0.1$), and between patient groups (repeated measures ANOVA, $F = 0.93$, $p = 0.39$) suggesting consistency in the way the pull was delivered. Physical training reduced the time taken to regain stability following the retropulsion stimulus (training-phase; $F = 5.03$, $p = 0.042$). There was no effect of stimulation (stimulation-phase; $F = 0.99$, $p = 0.34$) and no interaction between tDCS and PT (intervention-stimulation-phase; $F = 0.83$, $p = 0.34$) as shown in Figure 6.2B.

Timed Up and Go

There was no difference in baseline TUG duration between real and sham stimulation groups (paired t-test; $p=0.72$ for the PT group, and $p=0.85$ for No-PT group). PT resulted in significant improvements for TUG duration (training-phase $F= 8.85$, $P=0.007$). However, we did not find a significant interaction between training and tDCS (training-intervention-phase; $F= 0.19$, $P= 0.66$), nor any overall effect of stimulation (stimulation-phase; $F=0.91$, $p=0.35$; see Figure 6.3A). The range of pitch angular velocity increased significantly with training (training-phase; $F= 11.43$, $P=0.003$) but was unaffected by tDCS alone, or the combination of tDCS and training ($p>0.1$). No differences were seen for pitch displacement range, roll velocity nor roll displacement within or between groups ($p>0.05$).

6 metre walk

The results are shown in Figure 6.3B. In the PD group, training decreased 6m walk duration (training-phase $F= 4.94$, $P= 0.04$), but tDCS had no effect (intervention-phase $F= 1.07$, $P= 0.32$). Training alone did not augment pitch velocity (training-phase $F= 3.78$, $p= 0.07$) but the combination of training and real tDCS stimulation did (training-intervention-phase $F= 7.59$, $p= 0.016$). Training increased the range of roll motion during the 6m walk (training-phase $F= 4.96$, $p= 0.04$). There was no effect of intervention or training on pitch angular range or roll velocity range during the task ($p>0.05$).

TASK	Training				No training				p value		
	real		sham		real		sham		training effect	tDCS effect	tDCS + training
	baseline	test	baseline	test	baseline	test	baseline	test			
Gait velocity (m/s)	0.63 (0.15)	0.86 (0.25)	0.65 (0.14)	0.81 (0.14)	0.63 (0.11)	0.72 (0.12)	0.59 (0.15)	0.60 (0.12)	0.02	0.06	0.88
Stride length (cm)	90.0 (18.9)	127.3 (17.7)	91.4 (21.7)	120.7 (22.6)	90.9 (16.1)	95.2 (16.1)	89.4 (17.6)	90.6 (16.1)	0.001	0.45	0.41
Retropulsion test											
DURATION TO RECOVERY	2.14 (1.5)	1.07 (0.51)	2.07 (1.2)	1.51 (0.8)	2.08 (0.9)	2.05 (0.9)	2.01 (1.2)	2.00 (1.0)	0.04	0.41	0.46
RECOVERY PEAK VELOCITY	15.06 (8.9)	20.29 (13.9)	15.77 (9.3)	19.85 (17.4)	18.06 (10.0)	19.01 (8.7)	19.10 (13.2)	17.43 (9.6)	0.15	0.57	0.75
Timed Up and Go											
DURATION	11.43 (3.7)	9.50 (3.1)	11.02 (2.4)	9.37 (1.5)	11.34 (4.3)	10.52 (3.6)	11.24 (3.3)	11.17 (2.6)	0.007	0.35	0.66
ROLL ANGULAR RANGE	49.04 (4.4)	40.63 (3.6)	46.37 (3.1)	49.74 (3.6)	40.34 (17.2)	38.24 (22.5)	41.36 (18.0)	39.61 (24.6)	0.07	0.45	0.41
ROLL VELOCITY RANGE	60.71 (10.4)	89.38 (33.6)	68.94 (30.4)	72.74 (34.1)	53.38 (19.8)	64.86 (19.0)	54.13 (14.5)	59.39 (29.1)	0.32	0.37	0.78
PITCH ANGULAR RANGE	47.84 (9.6)	47.46 (7.0)	50.55 (5.3)	53.00 (6.2)	50.14 (10.5)	52.14 (9.0)	46.39 (13.8)	52.94 (13.3)	0.32	0.35	0.88
PITCH VELOCITY RANGE	196.25 (60.6)	246.51 (81.3)	181.52 (75.1)	181.20 (74.4)	202.24 (41.1)	165.01 (39.2)	201.46 (52.5)	163.87 (28.0)	0.003	0.19	0.19
Turn											
DURATION	4.50 (3.7)	2.69 (2.1)	4.11 (2.0)	4.09 (1.9)	4.17 (1.0)	3.95 (1.4)	4.14 (1.2)	4.00 (1.1)	0.03	0.06	0.06
ROLL ANGULAR RANGE	15.09	20.26	16.11	21.96	15.47	13.39	10.84	10.01	0.09	0.84	0.95
ROLL VELOCITY RANGE	44.64 (17.2)	62.00 (28.6)	45.17 (18.7)	58.70 (42.4)	41.55 (16.4)	41.21 (11.0)	32.26 (9.3)	42.49 (15.1)	0.42	0.68	0.34
6m walk											
DURATION	9.20 (3.7)	6.33 (2.8)	8.70 (3.5)	7.66 (2.8)	8.27 (1.5)	7.96 (1.3)	8.48 (1.1)	8.69 (1.3)	0.04	0.32	0.57
ROLL ANGULAR RANGE	7.43 (2.3)	9.27 (2.9)	7.71 (2.7)	9.83 (4.3)	6.04 (1.9)	6.03 (2.1)	5.67 (2.1)	5.60 (0.9)	0.03	0.93	0.97
PITCH ANGULAR RANGE	10.38 (4.8)	11.04 (3.0)	11.43 (4.1)	11.46 (4.5)	8.13 (1.3)	8.02 (1.9)	8.08 (1.9)	8.12 (1.6)	0.73	0.83	0.79
ROLL VELOCITY RANGE	72.00 (33.1)	73.37 (38.1)	68.01 (27.2)	96.07 (54.6)	51.30 (18.5)	52.35 (21.5)	42.29 (12.6)	43.33 (8.9)	0.20	0.42	0.42
PITCH VELOCITY RANGE	90.85 (31.8)	127.94 (52.0)	92.71 (33.9)	104.69 (58.7)	63.81 (18.0)	56.26 (12.9)	58.83 (9.8)	56.97 (13.8)	0.01	0.07	0.13

Table 6.2 Averaged group results for all gait and balance tasks.

Turn

In the PD group, training alone reduced the time taken to turn 180° (training-phase $F= 6.07$, $P= 0.027$; Figure 6.4C). Training alone also reduced roll velocity range towards control values (training-phase $F= 12.81$, $P= 0.03$). There was no effect of tDCS alone (stimulation-phase $F=4.75$, $p=0.06$). The combination of tDCS and training also barely missed significance (stimulation-training-phase $F= 4.26$, $P= 0.058$).

Individual variability

We observed marked between-individual variability in 6m walk duration, TUG duration (Figure 6.5A), and gait velocity in patients receiving tDCS. In this group (tDCS+PT) there was a positive correlation between disease severity and % reduction in walking time (TUG vs. UPDRS; $r=0.74$, $p=0.03$; TUG vs. HY stage; $r=0.62$, $p=0.05$; Figure 6.5B) but not with age (UPDRS vs. age $r=0.26$, $p=0.53$), white matter disease (UPDRS vs. Fazekas $r=0.005$, $p=0.99$), or cognitive impairment (UPDRS vs. MMSE $r=0.24$, $p=0.57$). We performed post hoc analyses on ‘responders’ – patients in the tDCS+PT group that had a moderate effect size (Cohen’s $\delta > 0.5$) in the TUG and 6m walk ($n=6$). In these patients, we found a strong and significant association between improvements in gait and the daily amount of dopamine taken (TUG vs. daily dopamine $r=0.83$, $p=0.02$; 6m walk vs. daily dopamine $r=0.82$, $p=0.02$). In addition, there was a significant correlation between non-motor symptoms and improvements in gait (TUG vs. UPDRS I $r=0.71$, $p=0.05$; 6m walk vs. UPDRS I $r=0.85$, $p=0.01$).

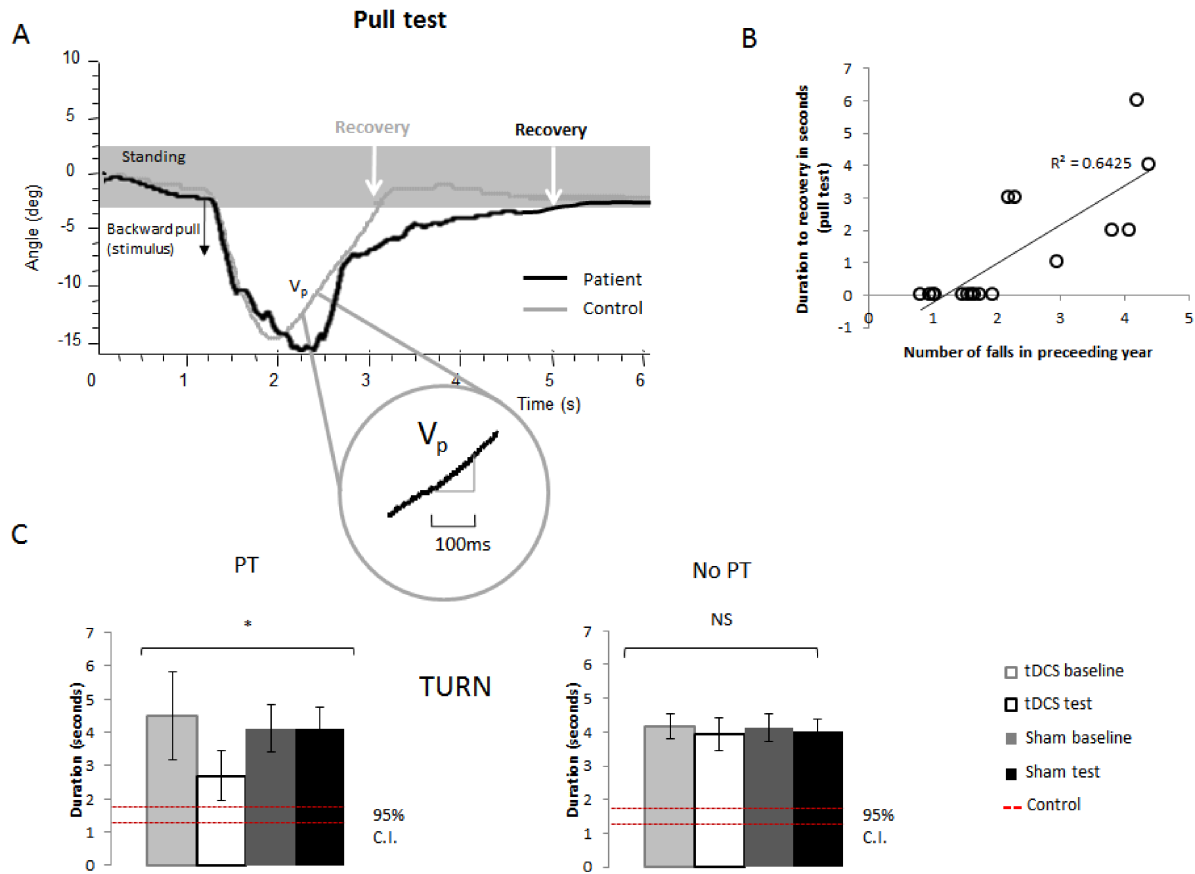


Figure 6.4 (A) Representative traces for a patient (black line) and healthy age-matched control (grey line) for the pull test. Time taken to regain posture (duration to recovery) was calculated in seconds from the onset of the first negative displacement of the trunk pitch trace (small arrowhead) to arriving at ± 2 SD of the baseline pitch trace (large arrowhead). The peak recovery velocity (V_p) within the first 100ms after peak backward displacement was calculated from the differential of the position trace (inset) (B) Correlation between number of falls in the preceding year and the time (s) taken to regain posture following a retropulsive stimulus (objective measure for the retropulsion test). (C) Averaged group duration data for the ‘turn’ phase of the Timed Up and Go. Vertical bars represent standard errors. Horizontal dotted lines show 95% confidence interval (C.I.) for healthy aged-matched controls.

6.6 Discussion

This double-blind, randomised, sham-controlled study evaluated bihemispheric anodal tDCS as a ‘proof-of-principle’ treatment for gait and balance disturbance when combined with physical training in 16 PD patients. We found a significant benefit of training in relation to TUG duration, stride length, gait velocity, and range of roll-plane and pitch-plane trunk movements, compared to patients receiving no training exercises. The main result, however,

is that tDCS alone applied over primary motor and premotor cortices bihemispherically does not improve balance or gait in these patients. Moreover, tDCS did not augment the effects of locomotor training in PD.

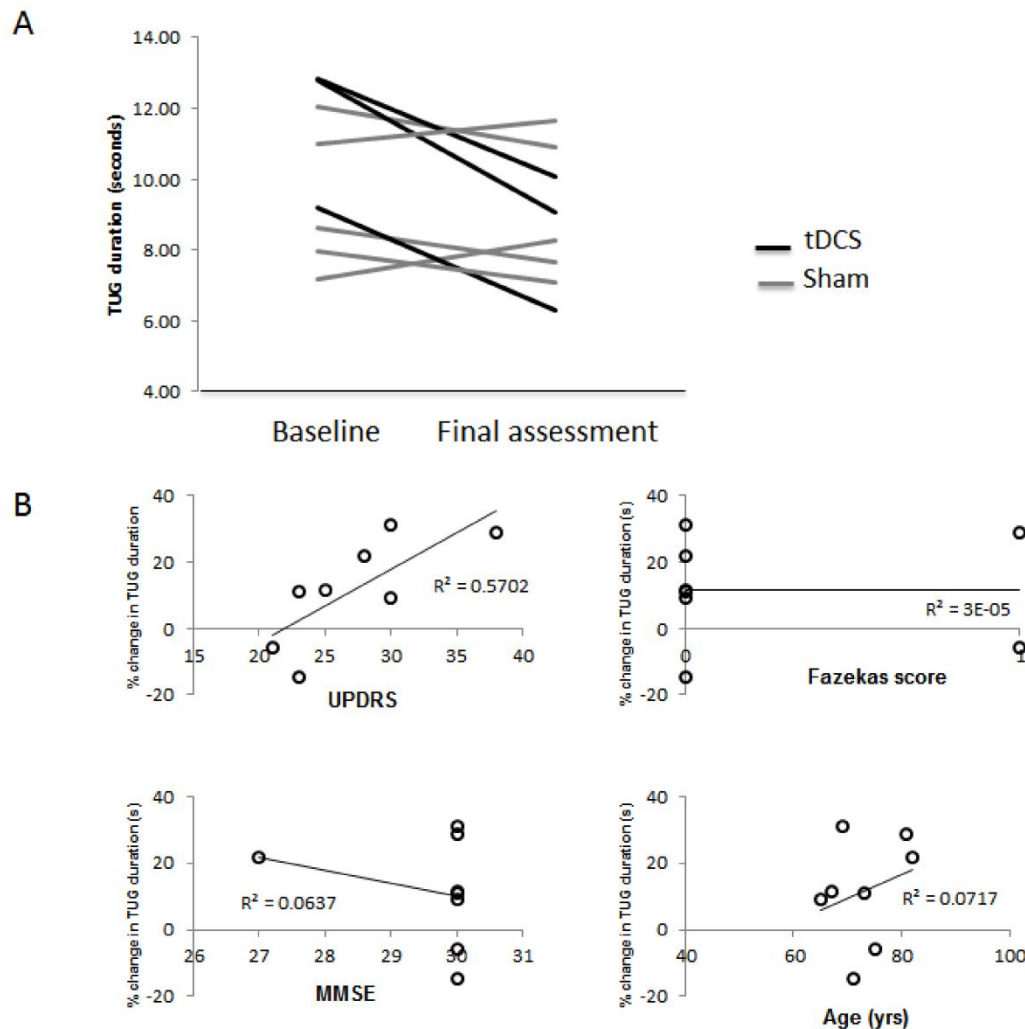


Figure 6.5 (A) Inter-individual variability in TUG duration in the PD group before (baseline) and after (final assessment) receiving the combination of tDCS and physical therapy. (B) Correlation between the percentage change in TUG duration [(baseline duration – test duration)/baseline duration x 100] and UPDRS, Fazekas score, MMSE, and age.

Physical training has been shown to improve gait function in patients with PD. The mechanism by which this occurs is incompletely understood, but may relate to external cueing to reset the walking pattern and reinforce neuronal circuits involved in gait pacing

(34-36). The attempt at combining physical training with tDCS has a physiological basis - physical training induces changes in excitability in relevant motor cortex (37), which may strengthen corticospinal and intracortical networks, whilst tDCS may lower the threshold for these changes to occur. Indeed, the combination of tDCS and skilled motor training improved motor hand function in chronic stroke patients (33). We found however no improvement when combining tDCS with PT in patients with Parkinson's disease. This may relate to the site of tDCS stimulation, the stimulation intensity used, timing of the stimulation, or variability in patient responses within our test population. These will be discussed separately below.

Stimulation protocols

Stimulation site – M1 and premotor regions

The basal ganglia influences volitional motor control by modulating cortical function through basal ganglia-thalamocortical motor loops (7, 8, 38), and deficits herein may account for the motor deficits seen in PD (39). The primary motor cortex (M1) and premotor cortex thus appear logical anatomical substrates for non-invasive neurostimulation in PD to modulate activity in these motor circuits. The application of repetitive TMS (rTMS) over M1 in PD resulted in significant improvements in reaction and movement times as well as upper limb functional performance (10). Subsequent studies demonstrated similar benefits using rTMS over M1 (40-43). Negative results however have also been obtained by groups using similar paradigms (44), and with different stimulation frequencies (45). rTMS at 1Hz (46) and 5Hz (47) over the supplementary motor area in PD patients have also shown modest improvements in upper limb motor symptoms, although intermittent theta burst, a type of rTMS failed to improve motor symptoms in PD when applied over M1 and dorsolateral prefrontal cortex (48). Strikingly, few studies have reported a benefit for gait in patients with

PD using non-invasive stimulation over M1 or premotor regions. Most recently, tDCS applied to M1 and prefrontal cortex improved walking time in the ‘off’ state but only with the exclusion of a patient whose results the authors considered factitious (49). Given the bilateral representation of cortical gait regions, does a clinically-significant improvement in gait require simultaneous modulation of cortical activity *bilaterally*? Can this be achieved with current electrode montages of tDCS? Bihemispheric tDCS as applied in this study indeed enhances lower limb excitability bilaterally (31) in healthy subjects, although we cannot exclude that our stimulation protocol induces different cortical changes in patients.

Stimulation intensity

A second explanation for the lack of tDCS effect on gait is that the intensity of the stimulus (2mA) was inadequate to modulate gait. A preliminary study in patients with small vessel disease revealed significant improvements in walking time (reduction in ‘Timed up and go’ and 6m walk), and balance (time to regain posture in the retropulsion test) when 2mA anodal tDCS was applied bihemispherically (Kaski et al., preliminary data). Admittedly, in contrast with PD(50), these patients’ primary pathology lies in the connectivity between cortico-subcortical locomotor circuits(38) – PD patients may have lower cortical ‘reserve’ and would therefore be less likely to respond to cortical electrical stimulation at 2mA. On the other hand, higher stimulation intensities are contraindicated in humans due to possible adverse events(51).

Timing of tDCS

It has been recently shown using an explicit sequence-learning task, that anodal tDCS over M1 is associated with faster learning, compared to sham stimulation (52). However, application of tDCS prior to performance of the task led to slower learning, irrespective of

polarity (anodal or cathodal) (52). Our results suggest that whether the tDCS is applied online during the *motor learning* training tasks or during *execution* of the gait tasks does not affect walking time. Further experiments are necessary to evaluate the role of combining physical training and tDCS *prior* to motor learning, with possible priming of the motor cortex (53). Our study was not designed to evaluate long-term outcome following a single session of tDCS+/- physical training.

Individual variability of responses

There exists a wide individual variability in walking time and gait velocity (Figure 6.5A). The positive correlation between the severity of motor symptoms (UPDRS III and Hoehn Yahr scale) and percentage improvement in walking time suggests that patients with intermediate disease may be more likely to benefit from DC stimulation than patients with mild disease. Note we did not test patients with advanced disease who were unable to walk unaided. In contrast, gait outcome did not correlate with age, the degree of small vessel disease, or cognitive impairment. This may be congruent with a ceiling effect, whereby patients at the extremes of the disease process are less likely to respond to an intervention. In addition, UPDRS part I correlated with tDCS-related improvements in walking time, implying that the effects of tDCS are greater with increasing severity of non-motor symptoms. Interestingly, we observed a robust association between the amount of daily dopamine taken and improvements in gait in those patients undergoing tDCS+physio. This supports our finding that tDCS may have greater effect in more affected patients, but also points to a potential role for dopamine in tDCS-related motor learning (54). The application of tDCS in clinical practice may thus require a process of pre-selection to identify patients who are most likely to benefit from such an intervention. From a physiological viewpoint, understanding the neuronal mechanisms that underlie such variability may help explain how

neuro-stimulatory paradigms exert their effects. Our results suggest that dopamine may play an important role and warrants further therapeutic studies combining DC stimulation and dopamine.

6.7 References

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C_{hapter} 7

Modulation of gait using in leukoaraiosis

7.1 Introduction

Leukoaraiosis (white matter lesions or small vessel disease) are hyperintensities in the cerebral subcortical white matter and are associated with gait and balance dysfunction in the elderly (1). Beyond measures to reduce the progression of new white matter lesions, there are no evidence-based treatments for the gait disorder and balance dysfunction in these patients. Clinically, these patients have a low gait velocity due to reduced stride length, long double support time and broad based gait (2).

Physical therapy is an established treatment for patients with neurological gait disorders, such as chronic stroke. In humans, upper limb motor skill training increases excitability of the cortical representation of relevant muscles (3,4). Such plastic cortical changes have also been observed in leg areas following physical therapy (5). Non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) have been successfully used to improve motor learning and rehabilitation in patients with stroke (6). Furthermore, physical therapy has been used in conjunction with non-invasive brain stimulation to augment the effects of training alone (7). To date, the combination of non-invasive stimulation with simultaneous clinically-relevant gait training has not been studied in patients with leukoaraiosis.

Human locomotion relies upon a distributed neural network including SMA, primary motor, premotor areas and, importantly, the underlying white matter connections (8). The relevance of the primary motor and premotor cortices in the control of gait in relation to leukoaraiosis has been demonstrated using fMRI (9) and cerebral perfusion (10) techniques. Since leukoaraiosis is liable to decrease activity diffusely in this gait control system, we attempted to facilitate neural activity in this network with anodal tDCS, specifically targeting the primary motor leg area and premotor cortex bilaterally.

7.2 Hypothesis

We hypothesised that tDCS would improve gait and balance, and that the combination of tDCS with physical therapy would augment the benefits of tDCS alone. The primary gait outcomes were velocity and stride length as it has been shown that the severity of leukoaraiosis correlates with these two gait parameters². For balance, our primary outcome was recovery of stance in the retropulsion test, postural instability being a recognised feature of leukoaraiosis (11), and a common cause of falls in these patients (12). Secondary outcomes were test duration (a surrogate measure of gait velocity), and angular trunk velocity and amplitude.

7.3 Methods and Materials

Patients

Local ethics approval and participant informed consent was obtained. Patients were prospectively recruited over a 12 month period. Inclusion criteria consisted of a gait and balance disturbance with onset >1 year, in patients who responded affirmatively to the question: “have you noticed changes in your normal walking or balance?” and had a radiological diagnosis of leukoaraiosis [Fazekas score 2-4 (13), Figure 7.1A for representative scan] constituting the primary cause of the gait and balance disturbance. Eighteen patients were recruited. One patient was excluded from the analysis being unable to attend the second experimental session. Brain scans were reviewed by two independent neuro-radiologists. Patients with severe freezing, daily falls, dementia (mini-mental state examination score <24/30), or other conditions that could affect gait/balance were excluded. Due to the theoretical risk of inducing seizures with tDCS, patients with a co-existing history of epilepsy were excluded, in addition to patients with pacemakers. 18 healthy age-matched

individuals took part as controls and performed only baseline tests (without tDCS). Patients mean age was 79.4yrs (range 71-89yrs), not statistically significant from that of controls [76.1yrs (66-89); $p=0.13$]. Disease duration [mean = 8 years (range 4-12)] was taken as the date of onset of the imbalance. According to the Fazekas scale, 10 patients had moderate (score=2) and 7 severe (score=3) leukoaraiosis at baseline. There were no patients with mild (score=1) leukoaraiosis at baseline. The baseline Tinetti gait index score (14) did not differ between intervention (real vs. sham; $p=0.88$) nor training groups (physical training – ‘PT’ versus ‘No-PT’; $p=0.16$). See Table 7.1 for full demographic and clinical data.

	SVD	CONTROLS	
	n=17	n=22	p value
Age, yrs (SD)	79.4 (5.5)	76.1 (7.1)	NS
Male/Female	7/10	10/12	NS
Medical history			
Arterial hypertension	11	7	NS
Diabetes mellitus	6	5	NS
Stroke	2	0	NS
Ischaemic heart disease	15	4	<0.0001
Hypercholesterolaemia	15	3	<0.0001
Patients with falls in the preceeding year (%)	32	4.5	<0.0001
Mini-mental status score (max = 30)	27.0	29.4	NS
Fazekas score (0-3)	2.4	0.1	<0.001
Baseline Tinetti scale score (max = 28)	19.6 (4.68)	26.5 (3.8)	0.0001

NS= not significant

Table 7.1 Demographic details for all subjects.

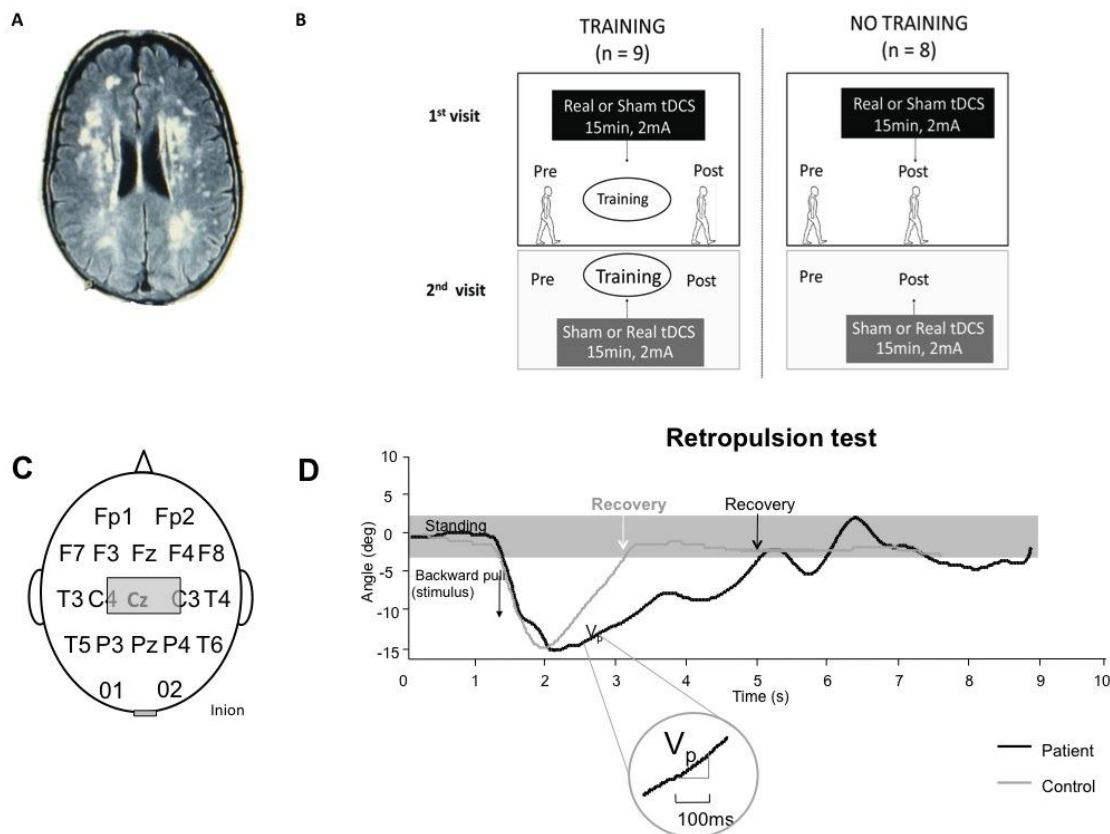


Figure 7.1 (A) Representative axial cut fluid attenuated inverted (FLAIR) sequence magnetic resonance image (1.5 Tesla) of a patient that took part in this study showing multiple areas of white matter hyperintensity (Fazekas score 3). (B) Cross-over study design. (C) tDCS electrode placement with the anode at Cz and cathode at the inion. (D) Retropulsion test. Subjects received a forceful pull backwards from the shoulders (stimulus). The time taken to recover pitch trunk displacement to $\pm 2^\circ$ of baseline was recorded offline using SwayStar. *Inset* The peak velocity (V_p) within the first second following maximum peak pitch displacement was measured for the recovery phase in all subjects as a function of displacement over 100ms.

The cross-over study design is shown in Figure 7.1B. Patients were randomly assigned one of two groups (PT and No-PT) using an online randomisation software tool (Research Randomizer, Version 3.0). Subjects were also randomised to receive either real tDCS or sham stimulation in the first session. All subjects were ‘crossed-over’ to receive either real or sham stimulation in the second session one week later. Both the examiner and patients were blinded to the tDCS protocol, which was delivered and monitored by a second researcher (RD).

For an ANOVA design, based on published neurophysiological data on the effect-size of tDCS on cortical gait regions (15), a sample size calculation revealed that 15 patients or more would be sufficient to observe a proof-of-principle effect ($\alpha = 0.05$ and power = 80%).

Methods

All patients performed a 6m walk, Timed Up and Go (TUG), and retropulsion test, twice in each session ('baseline' and 'final' assessments). Following 'baseline' assessments the PT group underwent a 15 minute balance and gait training session with the examiner (DK) concurrently with stimulation. As there are no validated training programmes for patients with leukoaraiosis, we selected a training schedule used in these patients by our physiotherapists (Figure 7.2). Subjects in the PT group then repeated the gait and balance tests ('final assessment') with no break between training and the final assessment. The No-PT group also started with the 'baseline' tests. This group then underwent tDCS stimulation during the performance of the final assessment gait and balance tests. All assessments were performed at the same time during the day in each subject to minimise diurnal variations in clinical state. Assessments took on average approximately 15 minutes to complete.

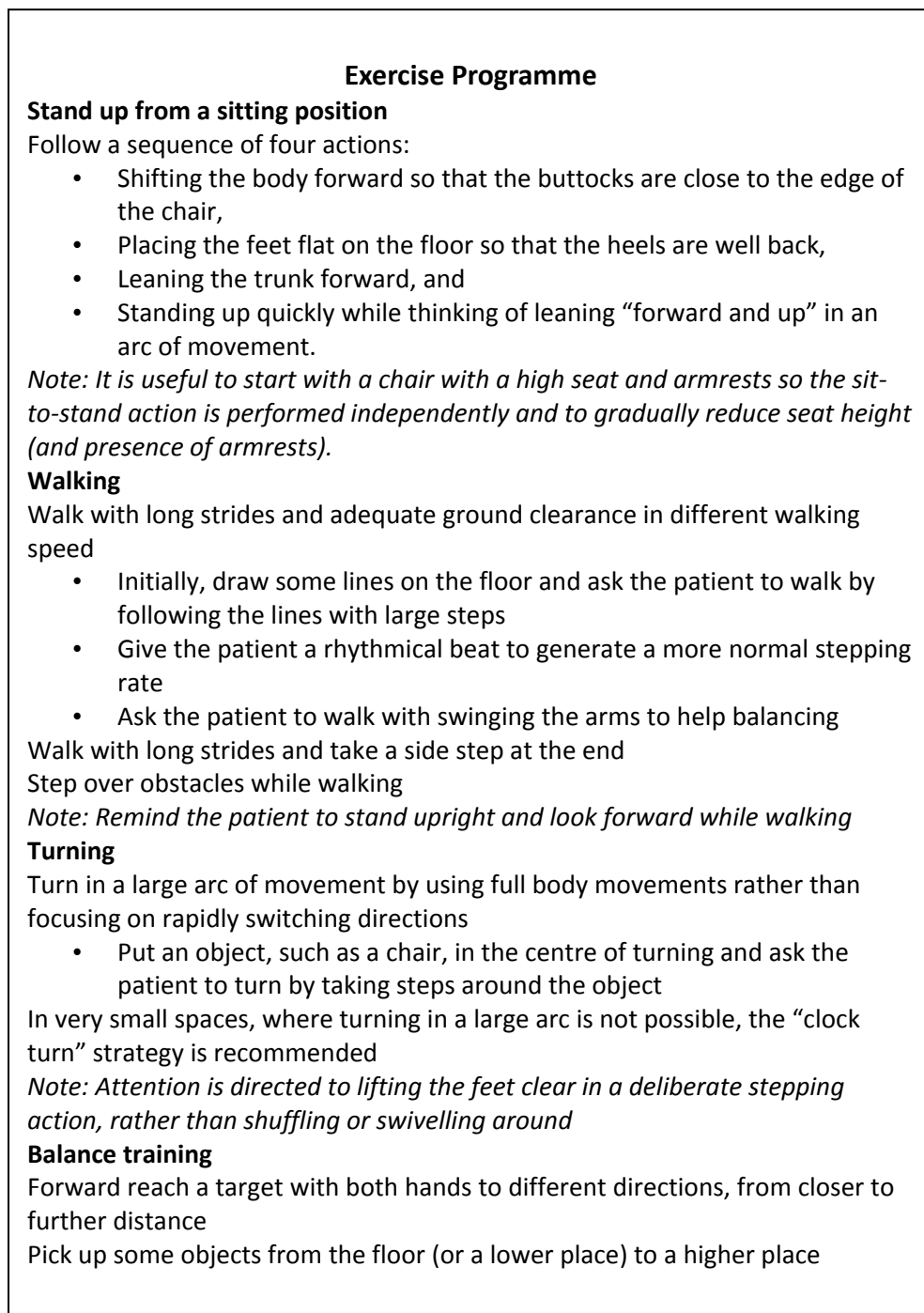


Figure 7.2 Training programme for patients in the physical training group.

Semi quantitative assessment consisted of the modified Tinetti test, which is a reliable measure of gait function in both healthy (16) and patient populations (17). All tests were recorded on video camera. A tripod-mounted digital video recorder (Veho Kuzo HD

camcorder) was placed at the far end of the test walkway. A second hand-held camera was used to record the subject's legs during the TUG. These video recordings were used to assess the following gait outcome measures:

1. Gait velocity
2. Stride length
3. Stride length variability

Subjects were instructed to “walk as quickly, but safely, as possible”. The duration of walking during the middle 4m of the 6m walk was used to calculate mean gait velocity (m/s). Stride length (distance from the initial contact of one foot with the ground to the following contact of the same foot) was measured against floor markers placed 15cm apart using frame-by-frame video analysis. Stride length variability was calculated using the variability index [CoVar = SD/mean X 100 (18)]. Mean gait velocity was estimated from test duration data from the Swaystar trunk recording system (6m walk) and cross-referenced with the video data acquisition for validation (Figure 7.3A).

Trunk sway measurement system

A device comprising two digitally-based angular-velocity transducers arranged to measure angular trunk velocity and displacement in the roll/lateral and pitch/sagittal planes (SwayStar, Switzerland) was used for all subjects (19).

Transcranial direct current stimulation

A DC stimulating rectangular saline-soaked sponge electrode (10cmx4cm; surface area 40cm²) was placed centrally across the scalp to cover a region 10-20% anterior to Cz as measured from the midline of the stimulating electrode (Figure 7.1C). The reference

electrode (4cmx4cm) was positioned at the inion. A 2mA current was delivered by a battery driven, Magstim Eldith DC stimulator (NeuroConn, Germany) during the exercise session for the training group [aim: does tDCS facilitate locomotor learning if applied during training? (20)], or during the final assessment gait and balance tests for the no-training group [aim: can tDCS alone improve motor performance? (20)]. The current was initially increased by a ramp input over 10 seconds until reaching 2mA (current density 0.05mA/cm²). A stimulation duration of 15 minutes was chosen which can result in an excitability change lasting approximately 90 minutes (21). This montage is known to increase cortical excitability in lower limb areas and facilitates locomotor adaptation in healthy subjects without significant effects over the cerebellum (15). Sham stimulation was identical to real stimulation except that the current was delivered for only 30 seconds and then turned off. Participants reported ‘tingling’ beneath the electrodes at stimulation onset for both sham and real conditions, typically fading away after 10-20s in both groups.

7.4 Data analysis

Video and SwayStar data were acquired simultaneously for all tests. For the video data, the first three and the last two steps of each gait cycle were eliminated from the data set to remove acceleration and deceleration effects.

There is currently no consensus regarding neurophysiological objective measures for the retropulsion test. For the recorded (angular trunk movements) version of the retropulsion test we report the time taken to regain a trunk angular position within 2 degrees of the baseline (quiet standing), which is easy to measure objectively (Figure 7.1D). We also recorded the peak pull velocity and displacement (to ascertain stimulus consistency) and peak recovery phase velocity within the first second following maximum pitch backward displacement.

We performed a two-way repeated measures ANOVA [INTERVENTION_{tDCS, sham} and PHASE_{baseline, test}; between group factor: TRAINING_{yes, no}] to evaluate overall effects of stimulation and training before and after stimulation. Statistical analysis was carried out using SPSS 18.0 with significance set at $p < 0.05$ (two-tailed).

7.5 Results

Table 7.3 shows the statistical results for all groups and tests. Baseline and experimental values for the TUG represent averages across 2 trials, for all other tests, values represent single measurements. Patients performed significantly worse than controls in all tests based on the first assessment results. We observed no order effects for any of the variables measured (i.e. no differences between baseline trials in the first and second sessions). The results of gait velocity, step length, and step length variability (Table 7.2) were obtained from the 6m walk, which is discussed separately to the trunk movement results.

PHYSICAL TRAINING (n=9)						NO PHYSICAL TRAINING (n=8)			
	controls	Real tDCS		Sham tDCS		Real tDCS		Sham tDCS	
		Baseline	Test	Baseline	Test	Baseline	Test	Baseline	test
gait velocity, m/s (SD) *	1.62 (0.29)	0.69 (0.19)	1.01 (0.32)	0.72 (0.21)	0.80 (0.22)	0.70 (0.15)	0.69 (0.12)	0.71 (0.20)	0.70 (0.20)
stride length, cm (SD) *	130 (17.4)	67.6 (9.95)	95.8 (23.9)	65.7 (22.5)	77.5 (22.8)	69.2 (20.5)	66.7 (15.0)	69.1 (20.0)	68.8 (18.4)
Co Var stride length * †† (SD)	2.4 (1.5)	9.5 (4.7)	5.9(42)	9.7 (4.7)	7.3 (4.1)	9.7 (2.9)	9.6 (2.8)	10.3 (2.8)	10.3 (2.5)

* training effect (p<0.05)
 † tDCS + training effect (p<0.05)
 † † tDCS effect

Table 7.2 Averaged group data for gait parameters.

1. Gait velocity

Mean “fast-walking” gait velocity in healthy controls was 1.69m/s (SD=0.30) and 0.70m/s (SD=0.24) in the leukoaraiosis group. We observed an interaction between tDCS, training, and phase ($F=6.51$, $p=0.02$) suggesting a combined benefit of tDCS with physical training. There was an overall effect of training, with faster gait velocity in the PT group than in the No-PT group ($F=8.72$, $p=0.01$) but no effect of tDCS alone ($F=3.32$, $p=0.09$).

2. Stride length

Patients had reduced stride length at first assessment compared to controls ($p= 0.047$). With tDCS+training stride length increased from 67.6cm (SD = 9.9) to 95.8cm (SD=23.9) [$F=6.9$, $p=0.018$]. Stride length increased in the PT group (training-phase $F= 29.4$, $p<0.001$), but despite a trend in this direction, there was no isolated effect of stimulation ($F=4.1$, $p=0.06$). Stride length was not statistically different between PT and No-PT groups.

3. Stride length variability

Stride length variability was greater in patients for the first assessments compared to controls ($p= 0.001$). There was a decrease in stride length variability of ~50% with tDCS+PT (intervention-training-phase $F=5.24$, $p=0.04$). There was an overall effect of tDCS, irrespective of training (intervention-phase $F= 4.74$, $p= 0.04$) with a decrease in stride length variability but no effect of training alone ($F=3.76$, $p=0.07$). As expected, stride length correlated well with gait velocity and stride length variability was negatively correlated with gait velocity (Figure 7.3B).

TASK	Training (n=9)				No training (n=8)				p value			
	real		sham		real		sham					
	pre	post	pre	post	pre	post	pre	post	training effect	tDCS effect	tDCS + training	
TUG												
DURATION	12.8 (4.59)	9.08 (4.12)	12.8 (6.13)	8.94 (3.40)	12.6 (4.23)	9.42 (2.87)	12.5 (4.98)	12.4 (3.22)	0.05	0.70	0.02	
ROLL ANGULAR RANGE	38.9 (4.35)	31.1 (3.80)	42.6 (5.20)	34.2 (2.90)	69.6 (11.2)	65.6 (9.80)	56.3 (4.90)	63.1 (7.57)	0.04	0.28	0.23	
ROLL VELOCITY RANGE	53.7 (3.32)	76.6 (5.98)	57.7 (5.56)	62.5 (4.94)	61.2 (3.85)	63.7 (3.19)	59.4 (1.81)	63.6 (2.32)	0.04	0.07	0.03	
PITCH ANGULAR RANGE	51.8 (2.0)	50.8 (1.45)	50.3 (2.01)	50.1 (2.10)	55.6 (2.91)	62.1 (5.05)	49.9 (2.32)	56.2 (4.23)	0.02	0.91	0.86	
PITCH VELOCITY RANGE	154.3 (8.7)	203.3 (13.9)	162.3 (10.9)	185.9 (14.0)	146.9 (7.96)	146.7 (5.13)	141.8 (8.20)	144.1 (10.3)	0.001	0.22	0.15	
Get up												
DURATION	3.19 (0.54)	2.51 (0.36)	3.02 (0.46)	2.77 (0.37)	2.59 (0.26)	2.53 (0.22)	3.16 (0.39)	3.23 (0.40)	0.38	0.44	0.69	
PITCH ANGULAR RANGE	46.52 (2.87)	40.5 (2.37)	43.7 (2.79)	38.5 (2.61)	32.8 (2.64)	39.5 (2.72)	39.9 (1.84)	35.5 (2.81)	0.04	0.30	0.09	
PITCH VELOCITY RANGE	112.4 (14.3)	138.3 (12.9)	116.6 (13.7)	125.1 (12.7)	107.2 (12.3)	112.6 (9.09)	111.0 (14.3)	108.0 (15.6)	0.21	0.51	0.81	
Go												
DURATION	4.25 (1.48)	3.11 (1.10)	4.37 (1.67)	3.35 (1.11)	4.30 (1.49)	4.28 (4.33)	4.55 (5.39)	4.47 (4.60)	0.03	0.53	0.09	
PITCH VELOCITY RANGE	60.84 (5.05)	68.39 (6.85)	59.11 (6.39)	58.99 (4.32)	55.28 (5.55)	63.67 (6.01)	55.81 (5.47)	57.15 (6.53)	0.86	0.26	0.96	
Turn												
DURATION	2.83 (0.26)	1.88 (0.18)	2.68 (0.53)	2.40 (0.38)	2.81 (0.49)	2.85 (0.33)	2.73 (0.52)	2.91 (0.57)	0.05	0.10	0.26	
ROLL ANGULAR RANGE	11.64 (2.04)	18.34 (1.34)	12.53 (1.73)	15.02 (1.20)	13.89 (2.26)	13.59 (1.43)	13.10 (1.29)	14.30 (1.49)	0.046	0.39	0.08	
ROLL VELOCITY RANGE	41.89 (4.91)	57.80 (6.43)	42.42 (5.58)	44.21 (4.75)	13.89 (2.26)	13.59 (1.43)	13.10 (1.29)	14.30 (1.49)	0.88	0.01	0.003	
6m walk												
DURATION	8.91 (3.41)	5.40 (0.96)	9.01 (3.07)	7.13 (2.57)	8.36 (1.786)	8.70 (1.76)	8.87 (2.43)	8.84 (3.67)	0.008	0.12	0.045	
ROLL ANGULAR RANGE	5.94 (1.56)	8.32 (3.92)	6.20 (3.62)	6.14 (1.77)	7.46 (5.10)	7.89 (3.50)	7.07 (3.19)	8.13 (2.61)	0.77	0.41	0.17	
ROLL VELOCITY RANGE	38.51 (3.55)	46.09 (4.89)	39.45 (3.32)	44.39 (3.49)	46.00 (7.88)	50.30 (7.29)	46.15 (5.44)	47.69 (7.05)	0.19	0.51	0.99	
PITCH ANGULAR RANGE	8.99 (0.63)	10.59 (1.00)	10.57 (0.76)	8.95 (0.41)	8.46 (0.77)	8.98 (0.83)	7.59 (0.72)	9.72 (0.87)	0.25	0.39	0.02	
PITCH VELOCITY RANGE	68.81 (6.74)	83.76 (7.03)	67.98 (9.02)	78.27 (5.87)	65.21 (3.28)	61.65 (7.86)	61.12 (7.26)	62.44 (8.17)	0.14	0.06	0.02	
Retropulsion test												
DURATION TO RECOVERY	2.08 (0.65)	1.06 (0.19)	2.28 (0.53)	1.60 (0.36)	2.13 (0.46)	1.17 (0.24)	1.95 (0.29)	1.95 (0.32)	0.35	0.035	0.67	
RECOVERY PEAK VELOCITY	20.40 (5.29)	26.25 (9.55)	19.52 (7.49)	19.23 (5.65)	28.74 (0.79)	24.78 (4.81)	22.71 (4.72)	23.28 (3.17)	0.51	0.93	0.31	

Table 7.3 Grouped results and statistical outcomes for all tasks.

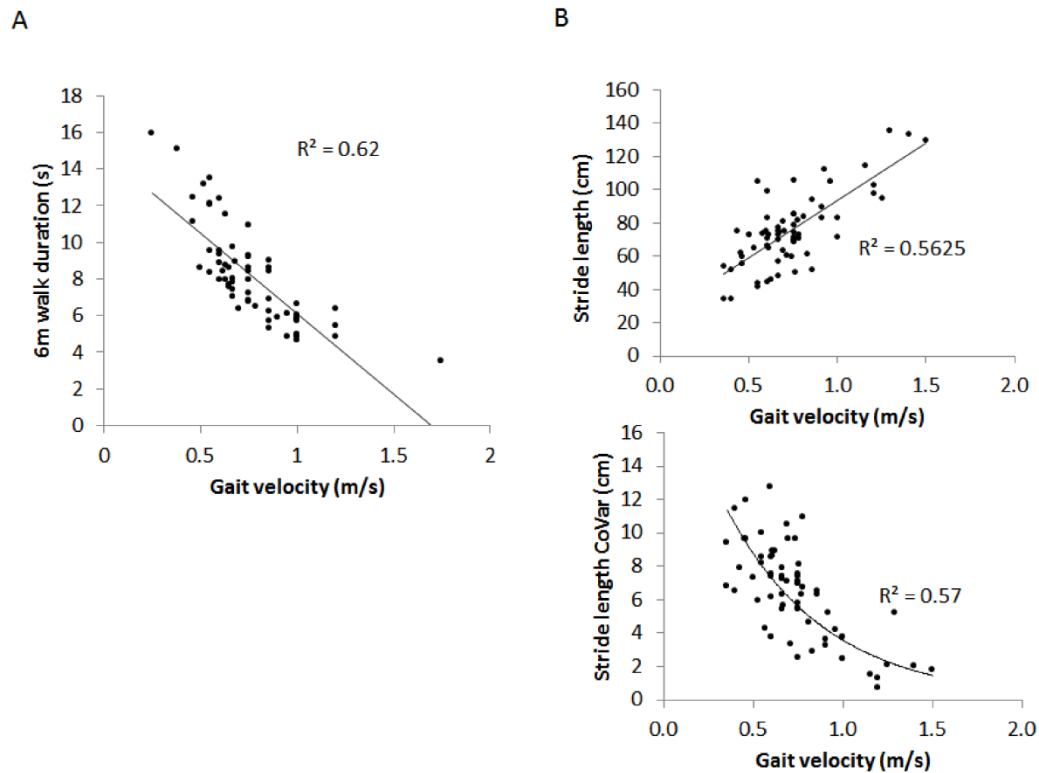


Figure 7.3 (A) Correlation between gait velocity (acquired from 6m walk video data) and 6m walk duration (from trunk sway measurement system) in a representative patient. (B) Roll angular trunk displacement during the 6m walk in a representative patient, derived from Swaystar. Gait velocity is calculated as the distance travelled over the time points between start and finish (vertical arrows). C Correlation between gait velocity and other gait parameters.

4. 6m walk

Again, there was a tDCS+PT effect with a reduced test duration (intervention-training-phase $F=3.08$, $p=0.045$; Figure 7.4) in addition to a training effect (training-phase $F= 32.6$, $p=0.008$). There was no pure effect of tDCS ($F=2.83$, $p=0.12$). Concomitant with the increase in gait velocity (table 1), trunk pitch angle and velocity also increased (figure 2 and supplemental table 2) with both training and combined tDCS+PT.

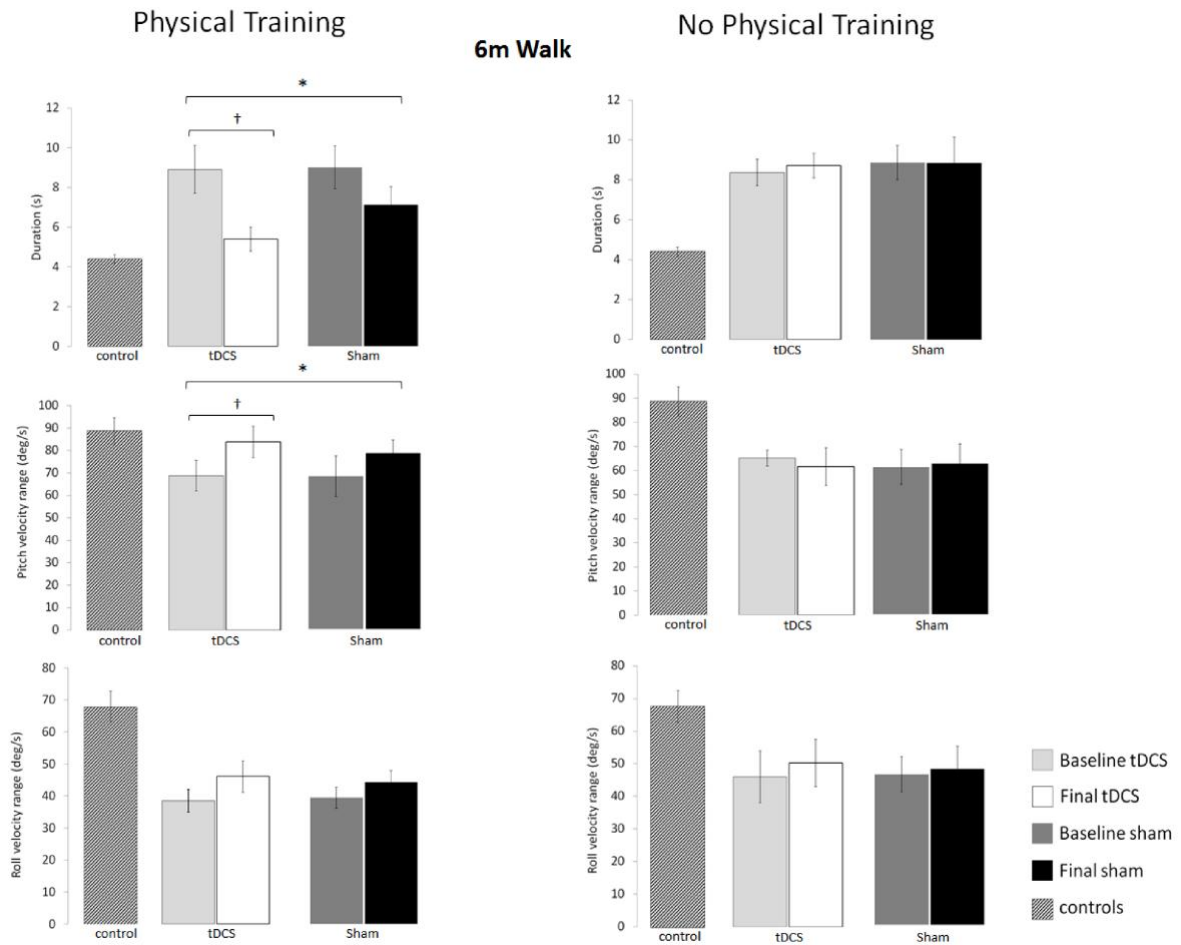


Figure 7.4 Average values of duration, and roll and pitch velocity ranges during the 6m walk in the physical training (PT) and No-PT groups. Vertical bars represent standard errors.

5. Timed Up and Go

Mean data for the TUG is shown in figure 7.5 and Table 7.3. There was a significant interaction between tDCS+PT for total test duration (intervention-training-phase $F=6.08$, $p=0.02$) suggesting an additional benefit of tDCS with training. In addition, training alone significantly reduced TUG duration ($F=4.16$, $p=0.05$). Trunk sway results (Table 7.3) showed an overall increase in roll and pitch motion with training. tDCS+PT improved roll velocity range above training or tDCS alone (intervention-training-phase $F=4.92$, $p=0.03$).

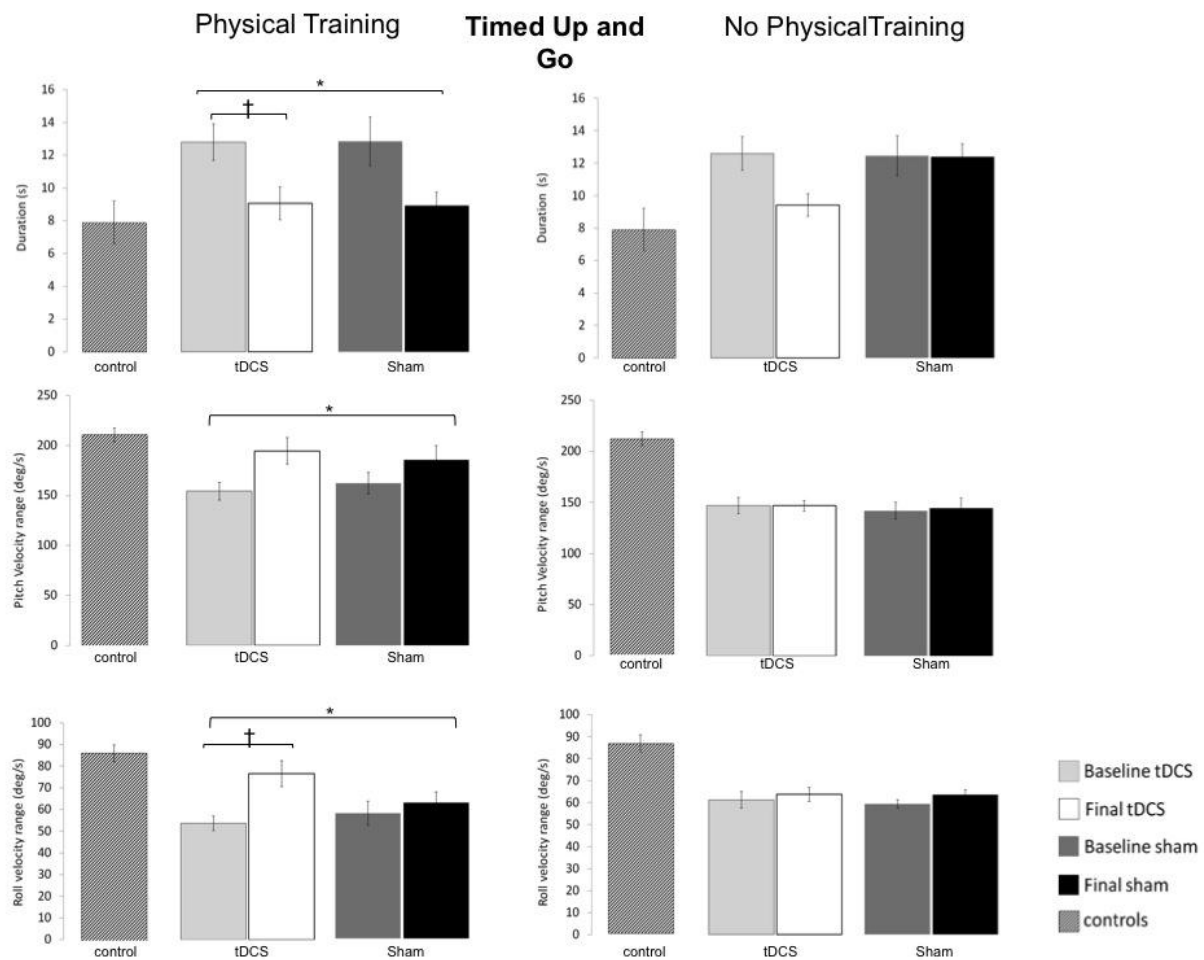


Figure 7.5 Grouped data showing mean and standard error values for the duration, roll, and pitch velocity range in the TUG test. * denotes an overall training effect (comparing PT versus No-PT); $p < 0.05$ † denotes an effect of combining training + tDCS; $p < 0.05$.

Timed Up and Go – ‘Get Up’

Total duration of the ‘Get up’ phase of the TUG did not significantly improve with training, and there was no overall benefit of tDCS alone. The combination of tDCS+PT did not shorten the duration significantly.

Timed Up and Go – ‘Go’

The ‘Go’ phase of the TUG test was significantly shorter in patients receiving training (training-phase $F = 5.82$, $p = 0.03$). There was again a trend to shortening of the duration of the

‘Go’ phase with the combination of tDCS+PT (paired t-test: $p=0.09$) compared to sham+PT ($p=0.98$).

Timed Up and Go – ‘Turn’

Training reduced test duration modestly (training-phase $F= 4.78$, $P= 0.05$). Roll velocity range increased towards control values in patients receiving tDCS+PT compared to all other conditions (intervention-training-phase $F= 12.24$, $p=0.003$) suggesting greater trunk movement that may translate into shorter turn duration (Figure 7.6).

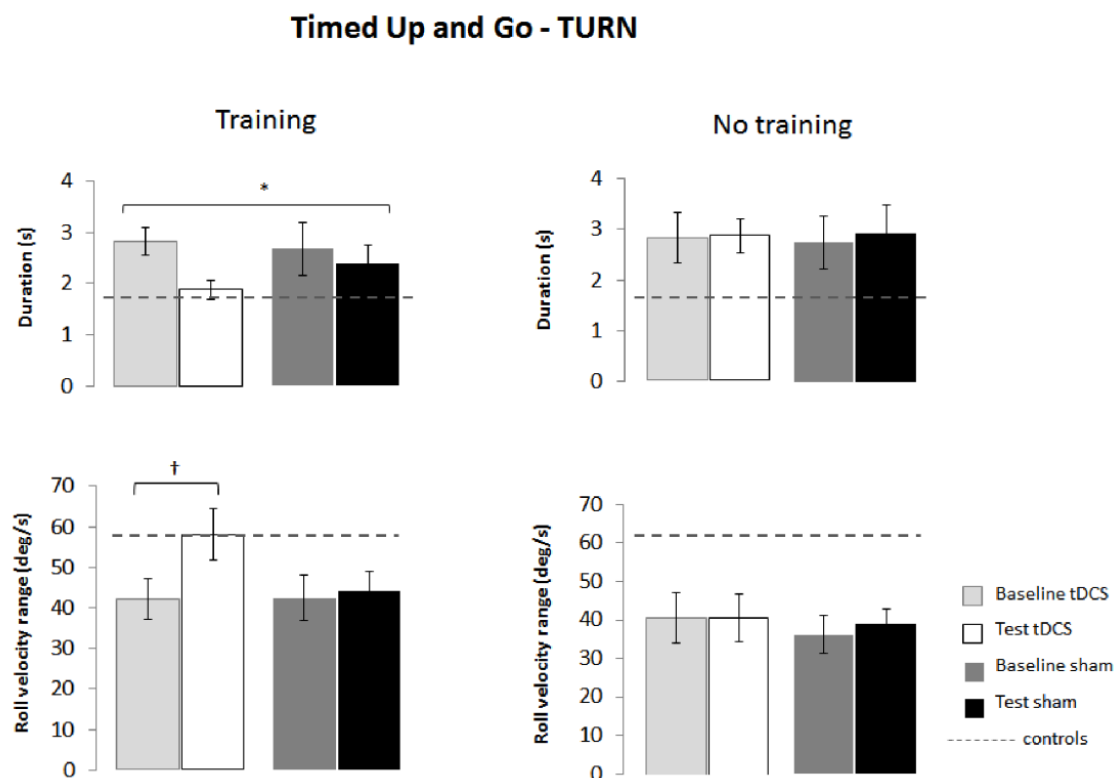


Figure 7.6 Grouped data showing mean and standard error values for the duration, roll, and pitch velocity range in the turn phase of the TUG test. * $p<0.05$ (training effect) † $p<0.05$ (training + tDCS effect).

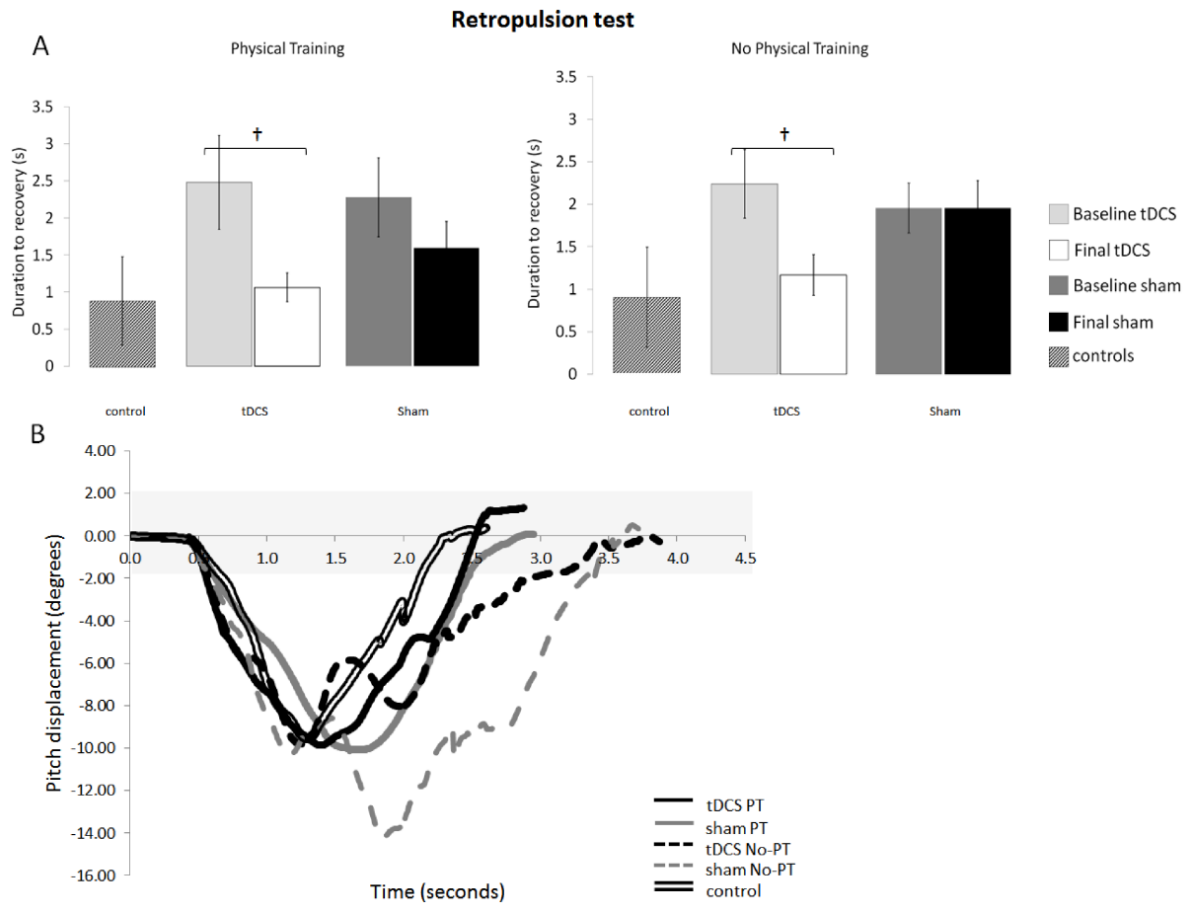


Figure 7.7 Retropulsion test in the physical training (PT) and No-PT groups. A The columns show the time taken to regain a pitch angular displacement of $\pm 2^\circ$ of baseline following a backward pull on the shoulders. Vertical bars represent standard errors of the mean. $\dagger p < 0.01$ (training effect) B Grand averaged group data of retropulsion test responses post stimulation in the PT and No-PT groups.

6. Pull test

The baseline measurement correlated well with both the Fazekas score ($r=0.76$, $p=0.003$) and number of falls in the preceding year ($r=0.79$, $p<0.001$), suggesting it is a clinically relevant measure of imbalance. The retropulsive stimulus was reproducible as the average peak backward displacement and peak backward trunk velocity did not differ across groups (paired t-test real vs. sham groups, $p=0.80$; also see Figure 7.7B - initial backward (negative) stimulus is no different between groups). Irrespective of training, the duration to recovery of

trunk posture was reduced in patients receiving real tDCS compared to sham tDCS (intervention-phase $F= 5.4$, $p=0.035$; [figure 7.7A]). There was no additional training effect.

7. Tinetti Balance Index

There was no overall effect of training, tDCS or the combination of the two in the Tinetti balance index (Table 7.1).

7.6 Discussion

The principal result is that the combination of tDCS and locomotor training improves locomotor performance as measured by stride length, stride length variability, and walking time in patients with leukoaraiosis, which was the main outcome of this study. Secondly, anodal tDCS reduces the time taken to regain balance in the retropulsion test, irrespective of training (our primary balance outcome). Thirdly, physical training independently improved gait parameters in these patients.

In addition to the spinal cord central pattern generator, midbrain locomotor regions, and the basal ganglia, human gait is critically dependent on the cerebral cortex. It is well recognised that the primary motor cortex is involved in the automatic execution of lower limb learned motor plans (22), while loops of the prefrontal cortex regulate and plan complex actions relevant to gait (23).

Gait dysfunction in leukoaraiosis is likely to involve disruption of cortico-subcortical locomotor circuits (24). Therefore, targeting the function of neocortical regions involved with gait using non-invasive stimulation is one therapeutic strategy to overcome the disconnection caused by white matter lesions. The combination of physical therapy with

tDCS (25), and rTMS (26) time-locked with motor training, has shown promise for chronic stroke rehabilitation. Although motor improvement with brain stimulation protocols has been amply demonstrated for upper and lower limb function, such findings are less common for gait, perhaps owing to the more widely distributed cortical locomotor networks, and the difficulty in modulating cortical circuits bilaterally. Thus, the use of anodal tDCS for the treatment of gait disturbance in Parkinson's disease yielded ambiguous results (27). Cortical locomotor centres can, however, be modulated bilaterally with our tDCS montage (15). Therefore, one explanation for our findings may be that physical training induces changes in excitability in relevant motor cortex⁵ that may strengthen corticospinal and intracortical networks, whilst tDCS lowers the threshold for these changes to occur.

It is noteworthy that even a relatively short 15 minute period of task-specific gait training for functional movement is able to improve the quantity (TUG) and quality (stride length, stride length variability) of gait in these patients, and it can be postulated that this is due to increased cortical excitability from the anodal TDCS.

The effect of tDCS on balance has not to our knowledge been previously investigated. Whilst anodal tDCS did not improve gait in the absence of training, the DC improvements in balance may be related to preferential effects on reaction time, rather than overall motor performance (28). Impaired postural reflexes in leukoaraiosis are likely due to subcortical disequilibrium (29) involving dysfunction of white matter connections between the motor cortex, basal ganglia and brainstem (30). Anodal tDCS may enhance cortical excitability of primary motor and premotor cortices to improve postural reaction time or indeed facilitate the selection of an appropriate motor (postural) response (31,32).

Timing of tDCS

Anodal tDCS over M1 is associated with faster learning, compared to sham stimulation (33). However, tDCS prior to performance of a reaction time task led to slower learning, irrespective of polarity [anodal-cathodal (33)]. Our results support the finding that tDCS applied online during the motor learning training tasks improves performance (34,35). We found no effect of tDCS when applied during execution of the gait tests which is an argument against the tDCS effect merely boosting performance execution and favours the idea that tDCS during training enhances motor learning with performance gains which outlast the stimulation. Nevertheless, we observed a pure effect of tDCS in retropulsion and stride length variability irrespective of training, suggesting that some tDCS effects may not be time-locked to physical training.

Study limitations and future implications

As with many studies of neurostimulation, one must be careful not to falsely attribute behavioural effects to the structures directly beneath the electrodes or coil. As such, given the widespread (cortical and subcortical) network involved in gait, and the widespread excitability changes that tDCS induces (36), our effects may not be restricted to the primary motor or prefrontal cortices. A smaller electrode surface area and reduced current density results in more focal cortical stimulation in humans. Conversely, a larger electrode size can induce a more distributed, if less intense, effect beneath the electrode (37). Although a disadvantage when focal stimulation is required, this wide area of effect can be helpful for bihemispheric primary and premotor cortex stimulation, as in this study.

One possible limitation is the use of video recordings of patient's performance to calculate gait parameters. However, our values for control data are consistent with previous published reference values (38,39). Indeed, despite the variability of gait velocity and stride length in patients with leukoaraiosis (2,40), presumably a result of the degree (41) and location (1) of

white matter involvement, our patient baseline gait values also lie within the published range for leukoaraiosis (10,42).

Lastly, our cross-over study design aimed to assess the immediate effects of tDCS in leukoaraiosis patients as a preliminary assessment of its therapeutic value. As such, we were unable to collect longitudinal data, but our results indicate that further studies are warranted to evaluate long-term effects of tDCS in this group of patients. More importantly, despite an improvement trend in the anodal tDCS group vs. sham in our study, we observed a wide variability of improvement in different individuals (Figure 7.8). Thus, the application of tDCS in clinical practice may require a process of pre-selection to identify patients who are most likely to benefit from such an intervention.

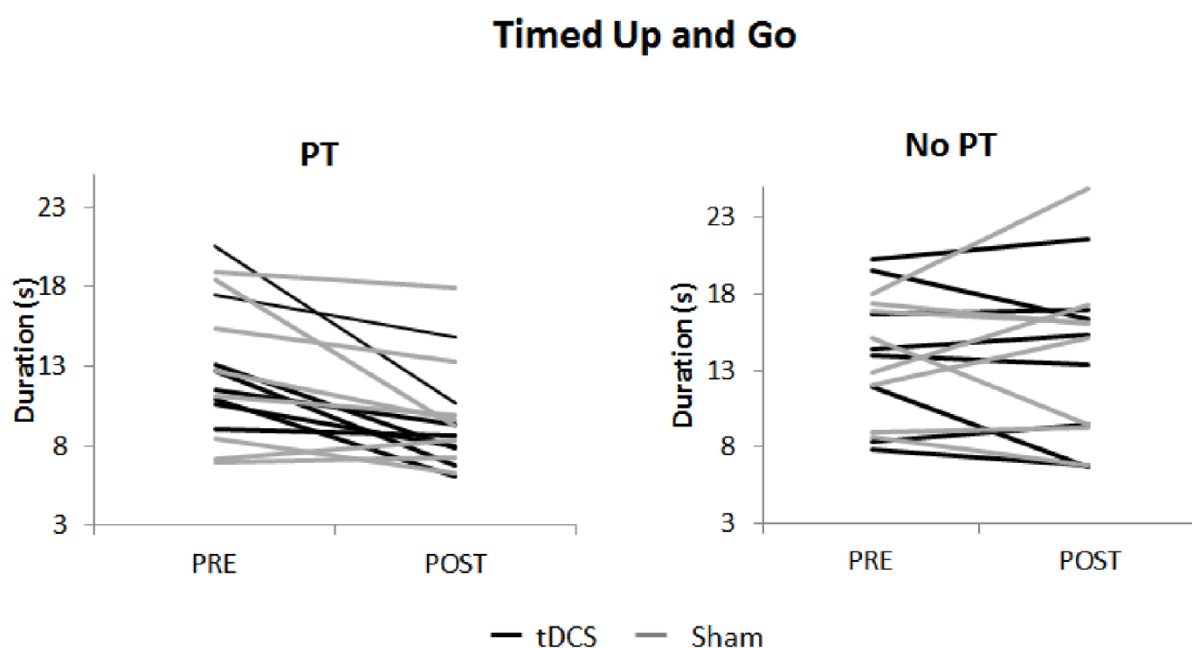


Figure 7.8 Individual variation in physical training (PT) and No-PT groups between baseline and final assessments (for real and sham tDCS) in the Timed Up and Go (TUG) test. There is a general trend for a reduction in test duration in the PT group following both real and sham stimulation, and a greater scatter of response in the No-PT group.

Summary

These results show that locomotor training, tDCS and their combination may offer a treatment option for patients with gait disorder due to leukoaraiosis. Given that gait variability may be a better functional indicator of leukoaraiosis gait dysfunction and risk of falling than gait velocity (25), anodal tDCS as used here may entrain a more symmetrical locomotor pattern that could prove clinically relevant. In order to provide evidence of the effectiveness of these treatments further randomised controlled trials with larger samples of patients are warranted.

7.7 References

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C_{hapter} 8

Summary and outline of future research

Summary

The research described in this thesis examined the cortical mechanisms underlying human spatial navigation, both from perspectives of cortical afferent processing and motor execution (via locomotion), using healthy individuals and patients with focal cortical lesions.

Specifically, the role of the posterior parietal cortex in the neural integration of vestibular signals for self-location perception was examined in a series of behavioural experiments (*Chapter 2*) assessing position, motion, and timing perception during angular rotations in the dark. Hippocampal cells have been associated with spatial navigation involving allocentric (map-based) co-ordinates. A combination of landmark-based orientation and vestibular path integration paradigm was used to evaluate the role of the right hippocampus in vestibular working memory related to allo-, and ego-centric navigation (*Chapter 3*). A new hypothesis relating to theta oscillation synchronisation for binding spatial (and non-spatial) conjunctions is proposed. Vestibular-guided self-motion relies upon visual calibration, for sighted individuals. Blind individuals, however, are said to possess a ‘supersense’ as a result of cross-modal plasticity. Blind versus sighted performance was compared using a vestibular-guided auditory localisation task in footballers (*Chapter 4*), and both in turn compared to sighted non-footballers. When completed, this study will enable a fair assessment of the relative contribution of practice versus innate ‘supersense’ for spatial performance.

Gait is a necessary component of spatial navigation in humans, and the ability to adapt locomotor behaviour to a change in the environment is essential for everyday activity. Using the ‘broken escalator’ paradigm, the role of the primary motor cortex and premotor regions for gait adaptation was assessed in healthy participants, using non-invasive transcranial direct current stimulation (tDCS; *Chapter 5*). This technique was then applied in combination with physical therapy to patients with Parkinson’s disease (*Chapter 6*) and patients with small

vessel disease (*Chapter 7*) – a common cause of gait dysfunction in the elderly –to improve gait and balance function. The complementary study in a single patient with Parkinson’s disease combining tDCS with tango dancing examined whether non-invasive brain stimulation could preferentially augment the effects of this form of physical therapy in a clinically-relevant manner (Appendix 9.1).

Self-location from vestibular signals of motion

Trying to encapsulate the relevance of this work as applied to everyday life brought to mind the story of a Chilean architect, captured under the oppressive Pinochet regime and sent to a concentration camp in the Atacama desert (from *Nostalgia for the light*). There, in an attempt to later reconstruct the details of his imprisonment, he set out to walk the perimeter of every room in the camp, eyes closed, to construct a visual map of his surroundings. He was able to, many years later whilst in exile in Denmark, redraw in exquisite detail every room he had been taken to, with near-exact dimensions. The question of how his mind was able to draw a mental architectural picture struck me at the time as almost magical. One part of this puzzle, at least, may lie in his temporo-parietal junction, and a perceptual neural integrator, able to derive his position in space from vestibular cues of self-motion, as he turned each corner of the room. More poignant still is that his wife developed Alzheimer’s dementia, drawing a black contrast in their abilities to navigate through space. Thus, this work has shed some light on the cortical mechanism underlying the perception of self-location for humans.

Timing signals for self-location perception

In particular, the TPJ appears to function as a perceptual neural integrator converting a velocity signal into one of position, by computing time, thus being analogous to an ‘internal clock’. Recent literature has linked the very rare phenomenon called Out of Body

Experiences (OBEs) provoked by pathological cerebral cortical activity to self-location perception (1, 2). An OBE is defined by the presence of three perceptual phenomena: disembodiment (where the location of the self is located outside one's body), extracorporeal egocentric perspective (seeing the world from an elevated and distant perspective), and autoscopy (the impression of seeing one's own body) from this elevated position. Our data help to resolve two contentious points in the literature, namely:

(i) What is the relevance of OBEs to everyday self-location perception? That OBEs can be evoked by several brain areas perhaps casts doubt on the relevance of the OBE state for the study of a precisely defined function such as self-location perception as the significance of these OBEs for self-consciousness under normal conditions is not clear.

(ii) What is the mechanism(s) underlying everyday self-location perception? Ionta et al. (Neuron 2011) stated that OBEs result from "a disintegration between somatosensory...and visual signals ...with an additional visuo-vestibular disintegration...yet this has not been tested experimentally." But it remains unclear if the OBE mechanisms relate to self-location perception under normal conditions.

Our anatomical results are relevant for self-location under normal conditions. None of the previous studies in the literature can be considered normal conditions and note the ambiguity of neuronal loci underlying the OBE phenomenon in point (i) above. OBEs also include 'autoscopy' (looking at one's own body from the outside) a state which is difficult to reconcile as being part of the normal everyday self-location perception in which one looks egocentrically, i.e. from within one's own body out towards the world. In contrast to OBE studies, our experimental protocol unambiguously probes self-location perception and no philosophical inferences are required to link our data with the everyday experience of making one's way to the bathroom at night.

Binding spatial cues for self-location

Whilst position signals appear to be encoded in the temporo-parietal cortex, other sensory afferent information, such as proprioceptive, auditory, tactile, and visual information, relevant also to spatial navigation, need to generate a congruent representation of the environment to allow us to navigate through it. Indeed, incongruent afferent signals often induce symptoms of disorientation, as evidenced by patients with visual vertigo following a peripheral vestibulopathy (e.g. vestibular neuronitis), whereby signals of self-motion and external motion become tangled and confused. Such afferent ‘binding’ appears to occur in the hippocampus. This may offer an underlying mechanism for the topographical memory impairment seen in patients with Alzheimer’s disease and other focal hippocampal lesions, in the context of world-based navigation that depends upon drawing spatial maps based on visual landmarks, and updating these maps in the context of our own motion (path integration). The underlying neural mechanisms will likely require intracellular recordings (electrode implantation in epileptic patients undergoing surgery for example) during spatial navigation and non-spatial multi-modal tasks to assess the role of theta and gamma oscillatory behaviour in the human hippocampus.

Non-invasive brain stimulation to improve gait

As Francis Bacon once projected, science and technology would enhance man’s control over nature, and social progress, prosperity, and the conquest of disease would follow (3). The Marquis de Condorcet (1743-94) predicted that future medical advances would extend longevity, perhaps even to the point of immortality (4). Unlike physicians in the Enlightenment period, for whom advances in pathology underpinned a paradox: “I know better perhaps than another man, from my knowledge of anatomy, how to discover disease, but when I have done so, I don’t know better how to cure it”, we are entering an era of

therapeutics in neurology that are beginning to cast a welcome shadow over the prevailing Voltairian concept that neurology is the ‘art of entertaining the patient whilst nature takes its course’. Nevertheless, neurological conditions remain amongst the most intractable, and the need for research increasingly poignant with an ageing population. Whilst treatments targeting afferent pathways are still some way away, non-invasive brain stimulation has shown great promise in enhancing motor control via efferent pathways. Most clinical studies, however, have focussed on upper limb motor rehabilitation in stroke patients given that the upper limb primary motor cortex (M1) lies more superficially and laterally than the lower limb M1 and is easier to target with transcranial methods. Nevertheless, lower limb function, particularly gait, is amongst the most common cause of disability in neurological practice. Firstly, this work has shown that it is possible to target lower limb muscles cortically, and that this can be done for both legs simultaneously by placing a central large anodal electrode over the motor strip, and a smaller cathode electrode over the inion. Thus, using a combination of TMS with tDCS it has been possible to show in this thesis that such a montage increases cortical excitability of lower limb muscles of both legs. This was supported by computational modelling showing a greater depth of stimulation and greater current density over the motor strip than changing the reference cathode electrode to a supraorbital location.

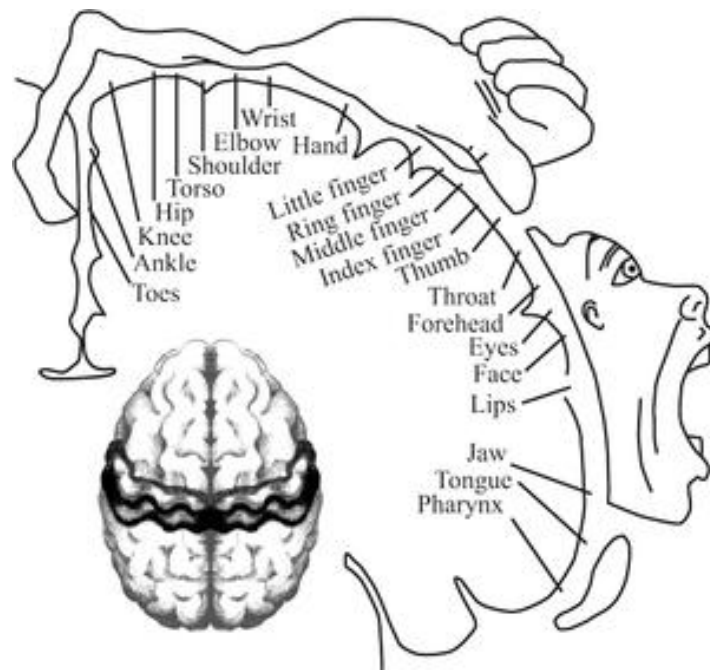


Figure 8.1 The human homunculus showing the location and relative allocation of motor cortical regions to the different body parts.

Secondly, such cortical stimulation can be combined with physical therapy to increase the benefits on gait and balance that are achieved with physical activity alone, for patients with small vessel disease and gait disturbance – an increasing cause of falls in the elderly.

Interestingly, tDCS irrespective of physical therapy, appears to shorten the time taken to regain balance after a forceful backward pull on the shoulders (“retropulsion test”). The neural mechanisms underlying differential effects on balance and gait will require further investigation.

For Parkinson’s disease the results have been less clear. Whilst physical therapy has, at least short-lived, benefits on gait and balance, the combination of tDCS with physical training did not augment these effects. Nor did tDCS alone result in any improvements in these patients. Of note, in a single patient with moderate Parkinson’s disease who was an avid Tango dancer, applying anodal tDCS during dancing increased gait velocity, suggesting possible

improvements in bradykinesia with the combination of non-invasive brain stimulation and dance therapy. Again, these effects need to be reproduced in a larger cohort of patients over repeated sessions before any conclusions about the clinical significance are drawn.

Original contribution to the field

Spatial navigation is a complex task requiring on the one hand the amalgamation of sensory afferent cues from vestibular, visual, proprioceptive, auditory, and motor signals, and on the other a reliable motor output to execute the desired trajectory. This work has illustrated that self-location perception relies upon timing signals, via a process of neural integration that, for angular rotations, occurs in the temporo-parietal junction. Moreover, medial temporal lobe structures are required for allocentric navigation, with the specific involvement of the hippocampus in vestibular working memory. Lastly, we have shown that it is possible to modulate gait function in both healthy individuals, and more importantly, in patients with neurological gait disturbances using transcranial direct current stimulation.

8.2 References

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C_{hapter} 9

Appendices

Appendix 9.1

Perception and cortical plasticity in the blind: supersense or nonsense?

9.1. Introduction

The visual cortex of the blind has been the subject of significant research in attempts to uncover the mysteries regarding the extent of activity in such a large area of the brain. What role, if any, does the visual cortex perform in the blind? Does the time of onset of blindness affect the functionality of the primary visual cortex? Is there any evidence that the visual cortex is used for non-visual functions in the blind (i.e. cross-modal plasticity)? Answers to these questions have recently begun to emerge, aided by the advent of innovative techniques for measuring cortical activity. A second perhaps related issue, is that of superior performance, i.e. a supersense, in the blind, particularly the congenitally blind. Recent studies seem to suggest that increased cortical representations inherent to cross-modal plasticity, may directly relate to enhanced psychophysical performance. We review the evidence for cross-modal plasticity, the evidence for a supersense in blind humans and in particular, assess the relationship between cross-modal plasticity and performance differentials between sighted and blind humans.

9.2. Visual cortex neuronal activity

9.2.1 Metabolic activity

Studies of cerebral metabolism show that the visual cortex in the congenitally blind is not dormant but remains highly active. Whilst total cerebral glucose metabolism in early blind (EB) subjects was shown to be comparable to that of normally sighted subjects, the resting metabolic activity in visual cortical areas of the EB subjects was elevated above that in (blindfolded) sighted subjects (34, 147, 151). This elevated metabolic activity in EB compared to blindfolded sighted subjects was also maintained during auditory and tactile tasks. Interestingly, the glucose utilisation in visual areas of human subjects who became blind following completion of visual development (late blindness) was found to be lower than in blindfolded sighted subjects (147).

9.2.2 Abnormal neuronal population in visual cortex of early blind

Why might there be elevated metabolism in visual cortex in the EB? Firstly, early blind cortex may possess higher neuronal densities since visually driven maturation of visual cortex involves significant neuronal death (11, 103). Secondly, visual cortex maturation involves a refinement of connections including an increase of intra-cortical inhibition (11, 103, 128). Hence, a lack of early visual input results in a surfeit of connections and relatively less intra-cortical inhibition. Lastly, early visual loss may result in increased projections from some sub-cortical relays providing non-specific input to visual cortex (9). Thus changes in visual cortex maturation and to visual cortex inputs may account at least in part, for the elevated resting metabolism observed in early blind visual cortex.

9.2.3 Effect of experience upon visual cortex neuronal population

Loss of visual input results in disruption of the normal maturation throughout the visual system, from the retina to the visual cortex (11, 138). The extent of changes to visual cortex depends upon the time of onset of blindness (66, 147). Such changes do not affect the macroanatomy of visual cortex (151) but may influence its parcellation into histologically and functionally defined regions in addition to their intra-cortical connectivity, e.g. prenatal blindness leads to a marked reduction in area 17 with consequent shift in the area 17-18 boundary zone and increased the number of trans-callosal projections in area 18, a region already rich in such projections (35, 103, 128). Synaptic density in newborn human visual cortex is comparable to that in the adult, but is known to undergo significant changes during normal, visually-driven development, in particular ‘synaptic pruning’ (11, 103, 112). This synaptic pruning can be seen as a refinement of connectivity within and between different cortical areas, essential for the interaction and function of the various brain regions. Studies in rhesus monkeys and kittens show that peak synaptic density is reached in the early postnatal period with slow decline to puberty and a subsequent more rapid post-pubertal loss to adult level (14, 15, 33, 134, 156, 157). The increase in synaptic density is followed by an increase in synaptic revision, which is thought to be crucially dependent on visual inputs (156). Indeed, the elimination of supernumerary synapses in visual areas decreases in the absence of competition between visual afferent inputs (15, 156), which may manifest itself in an elevated synaptic density. It is likely that the elevated synaptic or neuronal density, reflected in a high glucose utilisation rate, seen in blindness of early onset, is the result of suppression of visual afferent inputs prior to synaptic revision. Correspondingly, the low metabolic rate observed in the visual cortex in late-onset blindness is explicable on the basis of a normal (i.e. less dense) post-pruning synaptic density in combination with decreased synaptic traffic and thus neuronal activation.

9.3. Cross modal plasticity

9.3.1 Neuronal connections and function in the ‘de-afferented’ visual cortex

Compensation to early visual loss may occur at several levels, e.g. cortically (enlarged representation in the vibrissae somatosensory cortical barrel field; 110), sub-cortically (visual tectal neurones show auditory responsiveness; 126) and even peripherally with whisker hypertrophy (109). The interesting observation of complementary vibrissae and cortical expansion of vibrissae representation does however suggest a practice-dependent plastic phenomenon whatever the locus of such compensation (109, 110).

Recent animal studies suggest that the development of the sensory cortex is strongly influenced by ascending sub-cortical input (91, 117, 126, 135). The surgical removal of target regions for optic-nerve fibres, with co-incidental destruction of auditory or somatosensory afferent fibres, revealed innervation of auditory thalamic regions by optic nerve fibres (89, 117). These animals retained the ability to orientate in the direction of a given visual stimulus, despite the absence of their visual cortex and optic tectum. Artificial redirection of ascending retinal axons to the auditory pathway resulted in similarities in topography and receptive field properties between the primary auditory cortex and visual cortex (117). Gao and Pallas (44) have also shown that early visual inputs to the auditory thalamus can alter the modality and thus the pattern of activity of the inputs to the auditory cortex. The primary auditory cortex in “rewired” ferrets developed visual orientation-selective cells and an orientation map but with remnants of normal auditory cortical connections and a less well defined orientation map as that in normal visual cortex (126). von Melchner et al (148) suggest that animals in whom the auditory cortex receives visual radiations ‘perceived’

activation of the auditory cortex by visual stimulation as a visual sensation. If visually activated auditory cortex can subserve visual perception, it is reasonable to assume visual cortex can be used for hearing.

Apart from re-directed sub-cortical input, the other possible drive to cortical plasticity in de-afferented visual cortex is from cortico-cortical connections. This may arise either from the enhancement of pre-existing, dormant, non-visual cortico-cortical afferents to the visual cortex, or the direct sprouting of new synapses from adjacent cortical areas (8, 20, 45, 46, 47, 68). Visual input to secondary visual (extra-striate) cortex is derived primarily from the primary visual cortex, although sub-cortical input (e.g. the lateral geniculate nucleus), albeit sparse, does exist, (19, 43, 71, 128, 160). Baseler et al. (8) examined the extent of reorganisation of topographical maps in human extrastriate areas, following damage to the striate cortex. They concluded that when extrastriate neurons are deprived of their normal V1 inputs, they are colonised by other neurons in nearby healthy cortex. A recent study (39) has also shown in visually competent primates, the existence of projections from auditory cortex to areas of the primary visual cortex subserving peripheral visual field function. Ecologically, such a projection is most likely to mediate rapid detection and localisation of peripheral targets, whose nature would be discerned, at least in the sensorially replete animal, via a head-eye gaze shift with visual capture of the target. Whilst there is no direct evidence that such projections exist in visually deprived humans, such a pathway (and similar feedback inputs from polysensory cortex) could provide an alternative route for sensory input to drive cross-modal plasticity in visual cortex. A recent study in sighted humans showed that tactile stimuli produced occipital activation after only a few days of visual deprivation implying that such latent connections between polysensory and primary visual cortex may mediate rapid cross-modal plasticity (136). In summary, sensory inputs may access visual cortex not only

from ascending sub-cortical sensory input, but also via cerebro-cerebral interaction, either via horizontal interaction with higher visual cortex or feedback connections with polysensory cortex.

9.3.2 Human studies of cross-modal plasticity

The earliest studies of human cross-modal plasticity following early sensory deprivation, involved ERP studies in early deaf subjects who were found to process visual stimuli using not only visual but also auditory cortex (94). These findings studies prompted ERP studies in early blind humans which found that auditory processing took place in the visual cortex (1, 77, 78). Other ERP studies (119, 140) also found a similar cross-modal occipital cortex activation with somatosensory stimuli and Braille reading.

Using positron emission tomography (PET), Sadato et al., (121) demonstrated the activation of primary and secondary visual cortex in early blind subjects during Braille reading. Normal controls showed deactivation of these areas during Braille reading. It has been proposed that selective attention to one sensory modality is associated with decreased activity in areas dedicated to processing information from other sensory modalities, thus explaining the somatosensory cortex deactivation. In a subsequent PET study, Sadato et al. (122) demonstrated bilateral activation of ventral occipital regions, including the primary visual cortex, during both Braille and non-Braille discrimination tasks in early blind subjects. The opposite was true for sighted subjects where activity in the ventral occipital regions were suppressed. The conclusion was that fine tactile discrimination, including Braille reading in the early blind, involves visual cortex with deactivation of the somatosensory cortex implying the re-routing of somatosensory information from the somatosensory to visual cortex. In contrast to Sadato et al (121, 122), Büchel et al. (18) showed (using PET) that Braille reading

activated parieto-occipital regions but not V1 in the congenitally blind, whilst the late blind group showed additional V1 activation. The nature of Büchel et al.'s study (18) may have invoked visual processing amongst the visually-experienced subjects hence explaining their V1 activation. The lack of V1 activation in the early blind subjects is not explicable upon a failure to invoke visuospatial processes given their lack of visual experience. It must be noted that the control tasks for Büchel et al and Sadato et al were very different, with that of Büchel et al being language-based (auditory and Braille tasks) and those of Sadato et al. involving somatosensory and motor confounds. One interpretation was that blind subjects used V1 for tactile processing but not necessarily for language processing. However, a subsequent study complicated matters by showing that *sighted* subjects utilised V1 during spatial tactile orientation (Zangaladze et al). This TMS study contrasted with the TMS study of Cohen et al. (31) who found no involvement of V1 in their control group of sighted subjects during a Braille and embossed letter, reading task. One explanation for these differential findings could be a difference in tasks, viz. that required by Cohen et al (31) may have invoked language processes (letter identification) whilst that of Zangaladze et al required spatial processing (tactile orientation). TMS-specific parameters could also have lead to differential findings although the loci of occipital stimulation were essentially the same and the study finding no effect in sighted subjects (31) utilised a more robust set of TMS parameters (10Hz for 3,000ms at 110% motor threshold for Cohen et al. vs. 200µs cosine TMS pulse at 150% motor threshold for Zangaladze et al.). Whatever the differences between these two studies, it appears that use of use of occipital cortex for non-visual functions, in particular somatosensory, may not be the exclusive preserve of the blind.

Subsequent studies have provided evidence for language-related processes during Braille as separate from somatosensory processing per se (22, 23). Burton et al (22), using fMRI in a

well-controlled task of verb generation from Braille nouns, showed activation of primary, secondary as well as higher visual areas in all blind subjects, irrespective of age of blindness onset. They noted that the intensity of activation in V1 to be higher in late blind than early blind although the areas of activation were the same across both groups. In a companion study, using an auditory verb generation task, Burton et al. (23) found identical activation to the Braille task. Hence the occipital activations noted were thought to represent language processing and not merely due to somatosensory processing. Indeed Burton and Maclaren (21) showed occipital activation in auditory language processing tasks in Braille naïve late-onset blind subjects confirming that Braille reading is not a pre-requisite for development of language-specific cross-modal plasticity in the occipital lobe.

Language-related processes such as verbal memory may be associated with occipital lobe function in the blind. Amedi et al. (3) showed that the magnitude of activity in an fMRI study in human occipital cortex was correlated with superior verbal memory in EB (but not sighted subjects). Functional imaging evidence remains circumstantial in terms of proving causality, however Amedi and colleagues followed this study with another using a virtual lesion approach via repetitive TMS (rTMS). In this separate study, Amedi et al. (2), disrupted verb generation performance in early blind subjects by applying repetitive TMS 500ms following verbal noun presentation. Whilst Amedi et al. (2) suggest that they disrupted verb generation, it is also feasible that they may have disrupted noun encoding since ERP studies show that verbal recognition begins at 450ms and peaking at 600ms following word presentation (154, 155). In sighted subjects, encoding of visually presented nouns activated visual cortex versus motor cortex for verbs (105). Thus, if the sighted and blind both utilise posterior cortical areas for noun encoding, then this, could potentially explain Amedi et al.'s (2) results. This

study however, provides further evidence for the involvement of visual cortex in language function in blind subjects.

The effect of stroke in congenitally blind patients is potentially a very useful area of research in terms of assessing topographic functionality of blind subjects' cerebral cortex.

Unfortunately, for obvious reasons, the numbers of reports are few. Hamilton et al (57) report Braille alexia in an early blind patient following bilateral watershed infarcts in the occipital cortices. Signoret et al. (127) report another patient with left temporal and inferior parietal (not occipital) stroke with Wernicke's aphasia and Braille alexia. Perrier et al. (99) report a patient with late onset blindness with a stroke right parieto-occipital cortex that developed Braille dyslexia in the setting of completely normal verbal language function. Given the paucity of data, further large-scale studies are required if lesion data is to provide any insight into cross modal plasticity in the blind.

The distribution of activation within visual cortex may allude to the origin of non-visual inputs and hence mechanisms underlying cross-modal plasticity. Reports suggesting only V1 activation only in early blind (and not late blind) were suggestive of cross-modal plasticity occurring in sub-cortical loci in a bottom-up fashion (120, 121, 122). This is consistent with animal studies showing that re-routing of sub-cortical inputs during early development may modify target cortical characteristics (91, 117, 126, 135). On the other hand, other studies have shown that V1 may be activated by non-visual stimuli in late blind suggesting that top-down process (given that sub-cortical inputs are relatively fixed post-development) may be involved, i.e., V1 input derived from other cortical loci (18, 21, 22, 23,88). In support of these findings, animal studies have suggested that cortical association areas are more likely to be subject to cortical reorganisation, e.g. lid-sutured monkeys showed cross modal reorganisation of extrastriate and parietal areas (25) whilst neuronal recordings from area 17

showed no response to tactile stimuli (112). However, PET, ERP and TMS evidence show that visual cortex in sighted humans may be specifically utilised for perception of tactile orientation as opposed to tactile stimuli in general. Cross-modal integration may also occur during shifts of attention, one putative mechanism of use-dependent cross-modal plasticity (86). Such evidence suggests that cross-modal activity may be a feature of normal visual cortex perhaps by cortico-cortical connections with such connections being strengthened in blind subjects (161, 162). Hence the normal flow of visual signals from V1 to higher order visual cortex may be reversed in early visual loss with a stronger top-down influence of multimodal extrastriate cortex upon V1 in terms of incoming non-visual sensory processing.

9.4. Psychophysical performance in the congenital blind

9.4.1 Auditory performance

The current consensus appears to be that blind subjects possess better auditory localisation than the sighted (5, 81, 94,123) via use-dependent cross-modal plasticity with occipital cortex recruitment in addition to auditory cortex for auditory processing, viz. a ‘more (cortex) is better’ concept being invoked (see Section 3.2 though). An alternative view of worse auditory localisation in the blind has also been proposed (41, 82, 83, 164, 165). This latter view has been buttressed by animal data particularly seminal work by Knudsen who showed that blind-reared barn owls have impaired auditory spatial localisation and degraded auditory representation maps in the superior colliculus (74, 75).

Lessard et al. (81) showed a superior ability to localise sounds in early blind as compared to both sighted and late blind subjects. One puzzling result in Lessard’s data is that late onset partially sighted subjects performed worse than sighted subjects. We are not told the

aetiology of the blindness, but systemic conditions associated with blindness [e.g. the commonest cause of acquired blindness in the developed world is diabetes mellitus (29)], may be associated with central nervous dysfunction. The finding of worse performance in late blind subjects has not been duplicated; indeed Voss et al. (149) found equivalent auditory localisation performance between early and late onset blind subjects. Thus the results of the late group blind sub-group in Lessard et al (81) must be viewed with caution. The results of the early blind group however, support the prediction that compensation through the functioning senses occurs in the blind, enabling them to form accurate spatial representations of the external world (112).

Gougoux et al (51) findings are consistent with Lessard et al (81) and Doucet et al. (36) with roughly half early blind subjects (5 out of 12) showing superior monaural hearing localisation in azimuth. In addition Gougoux et al (51) showed a correlation between degree of occipital activation and performance in the blind, but not sighted. Unfortunately, Gougoux et al. (51) used unequal numbers of blind and sighted subjects particularly since 2 out of 7 sighted subjects were superior performers (an observation not mentioned by the authors). It is feasible that a similar number of sighted subjects could have been superior performers had the size of the blind and sighted groups been equal (i.e. 12 each). On the other hand for the blind group, performance is correlated to occipital activation and not for the sighted group. Again the problems of small control numbers, normally the non-limiting factor in subject recruitment, make interpretation difficult. The control data becomes more problematic when one compares this to previous findings. That is, the finding 2 out of 5 sighted subjects showing superior performance as demonstrated by Gougoux et al. (51) is highly incongruent when compared to Lessard et al. (81) and Doucet et al. (36) who found no sighted subjects with superior auditory localisation after testing 36 and 5 sighted subjects respectively. This

observation casts some doubt over the variability in the control (sighted subject) auditory localisation data.

Roder et al. (116) showed that congenitally blind subjects demonstrate better sound localisation ability in the far lateral space than sighted subjects. However, sighted subjects were actually more accurate ($P < 0.001$) in the central frontal plane than blind subjects. Hence, it would also be true to say that sighted subjects' sound localisation ability, whilst apparently superior than early blind subjects in the straight ahead, also showed a more dramatic performance fall-off than the blind in the far lateral space. Why might this be? One explanation was based upon the evidence for a differential connectivity between peripheral and central auditory space and visual cortices seen in primates (39, 136). A more prosaic, but no less valid explanation, is based upon normal responses in the sighted to stimuli in peripheral visual space. For example, a peripheral auditory target greater than $20\text{-}30^\circ$ from the horizontal midline will induce a sighted individual to make a combined eye-head saccade (maximum ocular range is $\pm 50^\circ$ from midline) towards the stimulus with fine-tuning of the response carried out under visual control (49, 80). Indeed even in echolocating bats, the primary function of passive sound localisation is to direct the eyes to the sound source (59). Hence, although auditory space undergoes constant recalibration by retino-visuomotor feedback in the sighted (82), the necessity for anything but an approximate calibration of peripheral auditory space is made redundant by retinal-slip feedback. In contrast, central auditory space, almost by default, will receive continuous high fidelity visuospatial feedback. It follows that in sighted humans, auditory localisation will be most acute frontally. Hence, in a sighted subject, an alerting auditory stimulus in the $70^\circ\text{-}90^\circ$ range (as tested by Roder et al., 116) would always result in a large head-eye saccade towards the target. Given that auditory spatial localisation can be improved in sighted individuals receiving special training (95), the

observed differences between sighted and blind subjects (including within group differences) in auditory localisation may be heavily dependent upon the individual's prior experience (e.g. vision) and daily routine (e.g. musicianship).

Lessard and colleagues (81) suggested that the supranormal monaural sound localisation ability of the blind may have arisen from increased use of spectral auditory information. However it is known that perceived sound intensity varies with distance (163), a fact that may explain Lessard et al (81) findings given that they used differently positioned auditory targets of identical intensity. Indeed, Doucet et al. (36) did not find a decrement in auditory localisation in azimuth in blind subjects when the sound transfer characteristics of the pinnae were changed by application of acoustic paste. Given that the pinnae are crucial in determining the spectral shape of incident sound, these findings would suggest that in fact, the blind subjects tested by Doucet et al. (36) (and by possibly those reported by Lessard et al., 81), were not predominantly using spectral cues in sound localisation. In fact, auditory localisation in the vertical plane as opposed to in azimuth, is a much better test of spectral cue usage. Normal humans show a dramatic degradation of sound localisation in the vertical plane with the application of moulds to the pinnae (64). Healthy subjects are however able to adapt to their modified pinnae, with auditory localisation performance returning to baseline within weeks (64). Two separate groups have now found that the blind are actually less good than the sighted (83, 165) in localising vertical auditory targets. Hence, the existence of superior auditory spectral performance in the blind remains unclear.

Gougoux et al. (50) report superior pitch discrimination in blind subjects with early blind subjects showing higher abilities compared to late blind. Of note was that the average

duration of blindness in the congenital group was 28.1yrs (range 1-36 yrs.) and late onset was 14.4yrs (range 21-40); in addition four late onset subjects were 40yrs age and over, and of these, three had relatively recent onset blindness (1-3 yrs.) hence the two groups (congenital and late blind) may not have been well matched. The correlation between performance and age of blindness onset found by Gougoux et al. (50) could thus also have been related to number of years of exposure to no vision. The distribution of duration of blindness was clearly bimodal in the late blind versus a more normal distribution in the early blind group. When the confound of duration of blindness was removed only 0.24% of the performance data variance ($r = 0.49$) was explained by age of blindness onset. In the conclusion of this article, the authors state, “a large part of the variance (42%) could be accounted for by the age of blindness”; here the authors should have quoted 24% and not the 42% variance since a co-factor (here duration of blindness) was a major contributor to the quoted r^2 value. In fact the correlation between age of blindness onset and duration of blindness was not trivial with an r value of 0.86 ($P < 0.0001$; regression calculated from supplementary information supplied online). The data as presented by Gougoux et al. (50) was thus confounded by duration of blindness and hence possibly by other concomitant associations (e.g. experience-dependent practice). In addition, recent data in other aspects of auditory perception has shown no differential between early and late blind subjects (149). Further studies which control for duration of blindness are thus required to answer the original question that the blind inherently possess better sound perception capabilities as a result of their blindness and not because of the effect of continuous practice.

9.4.2 Somatosensory performance

Congenitally blind subjects have been reported as having normal sensory thresholds for fine touch discrimination (60, 61, 98, 132) vibration (60), length discrimination (133), or

electrical pulses (98). Several authors have suggested that early blind subjects possess heightened higher cognitive somatosensory function; e.g. enhanced fingertip detection of a grating orientation in early blind Braille readers than in sighted control subjects (48, 142). Explanations proposed for these findings included enlarged sensorimotor cortical representation of the Braille-reading fingertip and/or enhanced working memory capacity. Given the above, it is not clear why early blind subjects have been consistently shown to be impaired in haptic form recognition and rotation tasks and perception of embedded figures (7, 93, 115), both higher cognitive tasks. Grant et al. (55) found that a blind group initially outperformed a sighted group in a Braille-like tactile recognition task but this performance differential was obliterated with practice. Bliss et al. (12) devised an elegant solution to the problem of correcting for experience between blind and sighted groups. They compared working memory using visual and tactile modalities for sighted and blind subjects. As expected the blind group were better at the tactile task and the sighted better at the visual task. They then compared tactile and visual performance between blind and sighted respectively and found no performance differential. They concluded that “*The performance level of blind persons relying on their tactile skills is just about the same as that of sighted subjects relying on their visual skills*”. Ptito et al. (104) used a tactile orientation task with the tongue as the orientation detector, a truly novel task for both sighted and blind alike. They found that not only did blind and sighted learn the new task at the same rate but also that their final performance levels were equal. The only difference between sighted and congenitally blind groups was the location of brain activation during PET acquisition associated with learning the task; i.e. occipital for the blind and somatosensory cortex for the sighted. Thus the results of Ptito et al. (104) demonstrate that cross-modal plasticity may occur in the blind without any performance differential over and above that of sighted subjects. Overall, the evidence suggests that blind and sighted groups show equivalent performance in tactile acuity

and where there are differentials, the effect of practice may be effective in abolishing such differentials. Crucially however, novel somatosensory tasks show no performance differential between blind and sighted groups; compelling evidence for the effect of modality specific practice and hence suggesting that early blindness may not confer a generalised superspatial somatosensory sense; it appears specific to tasks perfected by practice (123).

9.4.3 Olfactory performance

Despite the comparative dearth of studies examining the effect of early blindness on olfactory and gustatory threshold perception, back in 1889 (52, 53, 54) the subject stirred scientific interest, although the finding then was of a null result. Later studies reported similar findings (28, 118, 129). In a study using the Elsberg blast-injection procedure (38), the authors reported enhanced olfaction in congenitally blind subjects and those blinded for six years or longer (10). In this experiment, however, Bertoloni's measure of olfactory sensitivity has come under some criticism (69). Mahner (87) reached a similar conclusion to Bertoloni, although again, the methods employed were suspect (69). Two studies found better odour discrimination in EB with either impaired (96) or unchanged (118) olfactory threshold detection. This implies that the basic sensory transduction process of detecting smell is no different between EB and sighted subjects, but higher order aspects of odour identification, are enhanced in the EB. Indeed Wakefield et al. (150) provide evidence that superior performance in naming a familiar odour in EB subjects is due to enhanced non-visual memory rather than any differential in olfactory transduction. There is evidence that practice amongst sighted subjects improves performance on both odour detection and identification (96, 118, 129, 150). Since EB subjects rely upon odour for a variety of daily tasks in particular navigation, they may develop with practice, superior odour discrimination, primarily from an enhanced repertoire of memorised odours.

9.4.4 Locomotor navigation performance.

The ability to spatially navigate assumes crucial importance in the everyday life of the blind person. Navigating whilst walking in the dark is particularly reliant upon somatosensory and vestibular input, the latter particularly for turns (30). Vision is known to be important in calibrating brainstem vestibular mechanisms (4) implying that vestibular function may be impaired in these subjects. Despite this, the congenitally blind possess intact vestibular perceptual function and can utilise this during simple passive angular reorientations with accuracy equivalent to that of sighted subjects (124). This is consistent with the observation that early blind subjects demonstrate equivalent performance to blindfolded sighted subjects during walking navigation tasks (in the absence of audition) between spatial locations previously directly linked by locomotor activity (85, 137). This type of navigation (called "route navigation") may rely upon a representation of the "path structure" since the spatial dimensions of the route are not referenced to landmarks; e.g. "100 metres straight ahead, turn 90° right and proceed for 50 metres" (137). When locomotor tasks require the derivation of novel spatial relationships ('inferential task') from those previously experienced spatial measures held in memory, then congenitally blind subjects show a decrement in performance compared to sighted subjects in most, but not all, studies (85, 137). Impaired performance in 'inferential' navigation tasks suggests a disruption of external spatial awareness supporting the notion that vision is a prerequisite for the development of spatial concepts (6). Overall, the results do not show a supersense, but either worse or equivalent performance for inferential locomotor navigation. Thinus-Blanc and Gaunet (137) have suggested that individual factors e.g. use of different potentially modifiable strategies or previous experience may be important in explaining the diverse results in the literature.

9.5. Cross-modal plasticity and supersense

9.5.1 Expansion of cortical maps - is bigger really better?

The causal link with changes in cortical representation at various levels and superior function has invoked differing explanations but perhaps the commonest is that of increased cortical representation where found. Hence the occurrence of cross-modal activity in visual cortex is often interpreted as beneficial in terms of psychophysical performance since there is extra cortex available for the relevant task. Quite apart from non-visual processing within visual cortex, there is evidence that in the congenitally blind brain, non-visual sensory cortical representations are expanded (37). The assumption that expanded cortical representations is *sine qua non* for enhanced neuronal processing and hence sensory acuity makes intuitive sense. The idea that “more cortex is better” is also based upon the observation that in normal development, those areas of the sensorium with the highest spatial acuity (e.g. tactile (135) and visual (32)) also have relatively larger cortical representations.

The evidence that post-development expansion of cortical representation equates to enhanced sensory performance is less robust. Vega-Bermudez and Johnson (146) found no improvement in tactile acuity in an adjacent digit following digit amputation despite evidence in primates and humans that there is an expansion of surviving digital cortical representations following single digit amputation (13, 73, 90, 92). Braille readers have been shown to possess an enlargement of cortical digit representation (98) as well as enhanced spatial tactile acuity (143) in the dominant reading finger however, no change in cortical representation was seen in the digit adjacent to the dominant reading finger as well as the contralateral hand despite enhanced spatial acuity in these areas. In addition, Spengler et al (130) found a contraction of

somatosensory representation with training-induced tactile discrimination enhancement. Repetitive movements per se may result in expanded cortical motor representations even in the absence of skill acquisition (56). Hence, expansion of motor or sensory representations could occur via repetitive cortical activation associated with motor repetition or repeated exposure to sensory stimuli. Since such repetition may separately lead to improved psychophysical performance, any associated expansion of cortical representation may not be necessary for enhanced performance.

It thus becomes clear how causal associations between cortical expansion and performance may be illusory, at least in some situations. For example, Pascual-Leone and Torres (98) found that somatosensory representation was expanded for those digits used in Braille at the expense of the other fingers. This allied with findings of superior tactile performance in the blind (48) seems to argue for a causal correlation between size of cortical representation and performance. However, Goldreich and Kanics (48) specifically found no effect of Braille experience on tactile performance. This discrepancy could be explained by the cortical expansion related to repetitive motor tasks, here Braille reading (56).

Recent animal studies (40) have indeed shown the “more cortex is better” concept to be a gross oversimplification in addition to helping to explain other counter-intuitive findings in human studies such as the contraction of cortical representations with training. Importantly, recent studies have shown that use-dependent plasticity may not always be Hebbian. Repetitive stimulation of vibrissae may result in weakened and shrunk somatosensory whisker representations (40). Transfer of rats into enriched natural environments is also

associated with shrinking of whisker representations but here the whisker maps are more robust and indeed more precise in their spatial encoding (101).

Current evidence thus suggests that the assumption that enlarged cortical representations necessarily equate to improved performance is not valid. The assumption that enlarged sensory representation equates to superior performance is widely used in explaining enhanced performance cross-modal activation studies. Thus the comment that the observed expansion of the tonotopic representation in the auditory cortex is “consistent with and well suited to mediate the well demonstrated ability of the blind to accurately localize acoustic sources” (37) does not necessarily follow.

9.5.2 Activation studies during psychophysical tasks: the confound of strategy.

Functional imaging studies (e.g. PET, fMRI, ERP) in task performance rely upon a correlation analysis between brain activity and psychophysical performance. These studies although useful, lack the ability to prove causality between the observed associations. Thus one interpretation of the brain activation study by Amedi et al. (3) demonstrating superior verbal memory in the blind in association with posterior cortical areas is indeed a causal link between the locus of brain activation and performance. Another interpretation of these data could be a specific cognitive strategy developed through practise and unrelated to visual experience per se (see also section 4.4). Hence the use of specific cognitive strategies, could explain different loci of brain activation seen in the blind during a specific cognitive task. For example, in a working memory task that allowed differing strategies to be employed, Vanlierde et al (144) found no difference between early blind, late blind and sighted subjects.

When asked to memorise the locations of a verbally presented 2-dimensional patterns that were placed in a grid, late blind and sighted subjects unsurprisingly utilised a mental imagery strategy whereas early blind subjects used an x,y co-ordinate system. Thus sighted subjects are disadvantaged in cognitive tasks in which they are unable (or unprepared by prior exposure) to utilise mental imagery whilst at the same time advantaging early blind subjects (144, 150). Performance in tactile mental rotation was unaffected by visual experience but was rather determined by the strategies employed (141). Strategy and indeed performance are closely linked to prior experience in a given cognitive task. Indeed, there is consensus that the early blind are at least no better than sighted subjects in locomotor spatial navigation, a very important aspect of blind subjects' lives (85, 114, 137). This may well be related to individual exposure to locomotor tasks from an early age. Overall, the evidence for a causal influence of cross-modal plasticity in performance differentials between early blind and sighted subjects remains circumstantial. Virtual lesions using rTMS (see Amedi et al., 2005; Section 3.2) is one methodology by which causal relationships between cortical loci and psychophysical performance may be explored.

9.5.3 Attention and supersense

One important surrogate factor may be increased attention to non-visual modalities. Studies using oddball paradigms in auditory tasks have shown the P3 component of auditory evoked potentials, an attentional marker, to be deviated towards occipital regions in the early blind (76, 100, 116). This suggests that the blind may outperform the sighted in various auditory tasks as a result a greater capacity of focusing on the task requirements using the appropriate modality. One explanation for blind subject's superior ability to focus attention could be related to task-specific experience. It is known that prior experience can have dramatic effects

on attentional processes as demonstrated by the differential performance between novices and ‘experts’ in an attentional blink study (17, 70).

Leclerc et al. (79) suggests that the purported enhanced attentional focussing capacity of the blind may due be to cross-modal plasticity itself. An alternative hypothesis of visually-induced ‘distraction’ during learning of non-visual tasks may be supported by data in sighted subjects. Kauffman et al (72) found that sighted subjects who were visually deprived learnt to read Braille at a faster rate than a non-visually deprived sighted group. Somewhat supportive of the distraction engendered by vision is the account by Fine et al (42) who reported an adult patient who regained vision after early blindness who still found it easier to perform some tasks with his eyes closed. On the other hand Ptito et al. (104) found no difference in the rate of learning of a novel tactile orientation task (tongue; see Section 4.2) between sighted and blind. The highly novel nature of the task required of subjects by Ptito et al (104) may have resulted in subjects applying near maximal attentional resources. In contrast, the use of the fingers for a tactile task, certainly a less novel task than that requiring the use of the tongue for orientation discrimination (104), may garner less attentional resources. Hence discrepancies in differential learning rates between e.g. visually-deprived sighted vs. sighted (72) or sighted vs. blind (104), may be related to use of attentional resources.

9.5.4 Subject factors and supersense

There are several subject factors that confound the research output in the area of performance in congenitally blind subjects. Differences in the coping abilities of blind subjects may result in selection bias of early blind subjects. Those who do not feel disadvantaged by their blindness, and thus strive to make maximal use of their remaining senses, may be the very subjects who are more willing to participate in scientific studies. The act of volunteering may

result in a remarkable group of individuals being studied, with ‘remarkable’ performance having more to do with the subjects themselves than with their early blindness. A few researchers have tried to account for such confounds; e.g. Jack Loomis’ well established group at the University of California (85) repeated a previously published locomotor navigation paradigm (114) in a different group of congenitally blind subjects and accounted for their divergent results based upon participants’ differences and selection bias. In particular Loomis et al. (85) noted that all of their 12 congenitally blind subjects were independent in all aspects of daily living. Another important consideration alluded to in section 5.2, is the use of expert versus novice subjects (sighted or blind). Large differences in cognitive performance can be accounted for by prior experience in a particular task (17, 70).

9.6. Conclusion

The visual cortex of early blind subjects has been shown to be metabolically active. Modern neuro-physiological and neuro-imaging studies have unequivocally demonstrated extensive cross-modal plasticity in the brains and specifically in the occipital cortex, of EB, late blind or even in sighted subjects visually deprived for a few days. The evidence for a supersense in EB subjects is strongest for auditory and spatio-tactile tasks but the body of evidence is not heterogeneous. Further studies are required to confound for the effects of duration of blindness and hence the effects of practice. It follows that the effects of subject selection or recruitment may have large effects on a study’s outcome. The explanation for supersense amongst the EB, when demonstrated, is unclear. The most popular explanation that more brain being utilised via the cross-modal activation has limited evidence for its instantiation despite its mantra-like invocation. Whilst any observed supersense could indeed be due to cross-modal plasticity itself, given current evidence, this cannot be resolved at present. Equally, superior performance could result from increased practice in specific tasks,

enhanced cognitive functions such as improved attentional focusing or working memory, and selection bias amongst subjects. The timing, degree, and cause of visual impairment may be crucial in all of these factors. The recruitment of congenitally blind subjects with absent or near absent vision is onerous. Hence the literature is populated with studies of small subject numbers and a tendency to group analysis with the commensurate risk of a ‘select’ few outstanding (good or poor) individuals distorting the results. Analysis of both grouped and individual results in addition to more attention to subject characteristics, will aid in a critical appraisal of future research.

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Appendix 9.2

Modulating gait and balance using tDCS and dance therapy

Introduction

A hallmark of progression of Parkinson's disease (PD) is postural instability and its associated falls (1). Dance and movement therapy may improve balance and gait in patients with gait disturbance (2). The Argentine tango has recently received particular interest in PD (3, 4).

Non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) applied over primary motor and premotor cortices improve upper limb bradykinesia (5) in PD patients, although the effects on gait are more ambiguous (5). One may therefore expect additive benefits with the combination of anodal tDCS and physical therapy (6). Our aim was to apply anodal tDCS in its “online” modality (during physical therapy) over primary motor and premotor cortices during partnered tango dancing in a patient with moderate PD.

We applied anodal tDCS over the primary motor and premotor cortices bilaterally (7) in a 79 year old gentleman with moderate Parkinson's disease during partnered Argentine tango dancing. The patient performed 2 dances, one during tDCS, another during sham. This was done in a double-blind fashion, and repeated one week later in a randomised order. Sagittal

(pitch) and coronal (roll) trunk velocity was measured using digitally-based angular-velocity transducers attached to the patients back(8) (Figure 1A). We recorded a Tinetti Gait index questionnaire (scored on the patient's ability to perform specific tasks) and obtained a subjective measure of performance before and after each dance session from the patient's professional dance partner. We also assessed the effects of tDCS on gait in separate experimental sessions.

Methods

6 metre walk

The patient was asked to walk a distance of 6m along a flat surface at a brisk pace. The start and finish were marked with black tape on the floor. An assistant accompanied the patient at a close distance.

Timed 'Up and Go' (TUG)

The patient began seated in an armless office chair and was asked to get up, walk 3 metres, turn round, return to the chair and sit down again. A verbal "go" signal was given to start the test. He was asked to perform the test at a brisk but safe pace. The total duration of the test was calculated from the moment the patient began to get up until he was comfortable on the chair again. The time taken to 'turn', as part of the TUG, was also specifically analysed.

Tango

Two 3-minute dances were performed during either tDCS or sham stimulation. Both the patient and assessor were blinded to the stimulation. This was repeated one week later with tDCS and sham applied in a randomised order. The same music ("la mariposa", Orquesta

Osvaldo Pugliese, music by Pedro Maffia and lyrics by Celedonio Flores) was used for all dances. Although both the patient and his dance partner were instructed to perform equivalent dance routines for all dances, it was not possible to control for this. Additionally, we did not wish to influence performance by restricting the patient's repertoire, or invoking an explicit motor memory task. Sessions took place at the same time and the patient was instructed to take the medication at the same time during both days of testing to minimise diurnal clinical variability.

Transcranial direct current stimulation

A DC stimulating rectangular saline-soaked sponge electrode (10cmx4cm) was placed centrally across the scalp to cover a region 10-20% anterior to Cz as measured from the midline of the stimulating electrode. The reference electrode (4cmx4cm) was positioned at the inion. A 2mA current was delivered by a battery driven, Magstim Eldith DC stimulator (NeuroConn, Germany) during the Tango dance. The current was initially increased by a ramp input over 10 seconds until reaching 2mA (current density $0.05\text{mA}/\text{cm}^2$). This montage is known to increase cortical excitability in lower limb areas and facilitates locomotor adaptation in healthy subjects without significant effects over the cerebellum (7). Sham stimulation was identical to real stimulation except that the current was delivered for only 30 seconds and then turned off.

Results

Trunk peak velocity across the two sessions was significantly greater during tDCS than sham ($p=0.0174$ for pitch and $p=0.0189$ for roll; figure 1B) implying less trunk rigidity (9). The questionnaire data revealed subjective improvements in dance performance (figure 1C and semi-quantitative gait function (Tinetti Gait Index: $p=0.04$; figure 1D). Similar improvements

were observed on gait, with a reduction in time taken to complete the 3m ‘timed up and go’ and 6m walk, and an increase in overall gait velocity and peak pitch trunk velocity with tDCS compared to sham (Figure 2A and B). The gait data support an effect of tDCS on tango performance rather than the improvements being confounds of improvisation and variability inherent to tango.

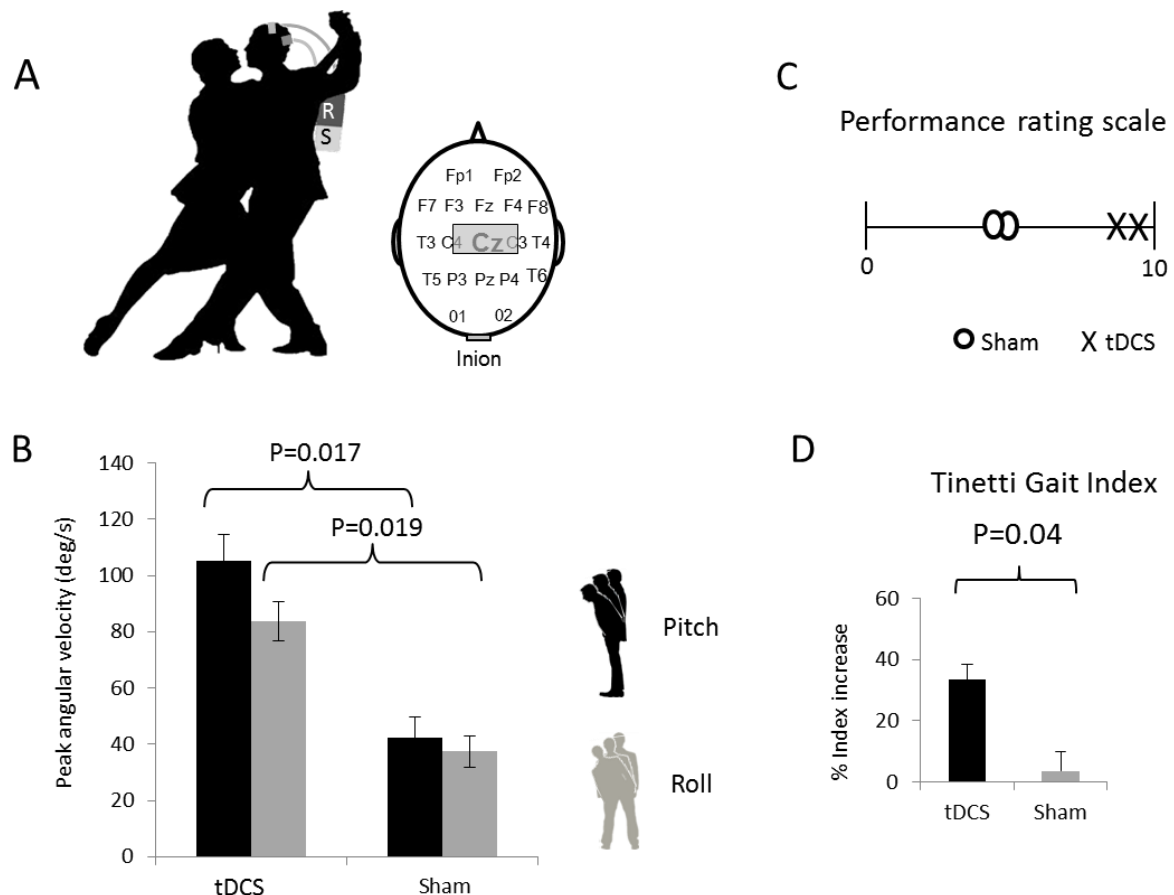


Figure 1 (A) The tDCS electrodes were placed over the scalp, and secured using an adapted scuba diving cap. The tDCS battery was encased in a rucksack (R). Angular trunk movements were recorded using gyroscopes (Swaystar, S), secured at L1 on the patient’s back, using an elasticated belt. The tDCS anode was placed over Cz and 10% anterior, over the primary motor cortex and frontal premotor cortex, including SMA. (B) Averaged data for the 4 tango dances showing increased trunk velocity in coronal (roll) and sagittal (pitch) planes in the real tDCS sessions, compared to sham. (C) The visual analogue scale charting performance completed by the professional dance partner, also blinded, following each dance. (D) The % increase in Tinetti gait index scores for sham and real tDCS sessions comparing baseline (prior to stimulation) with test conditions.

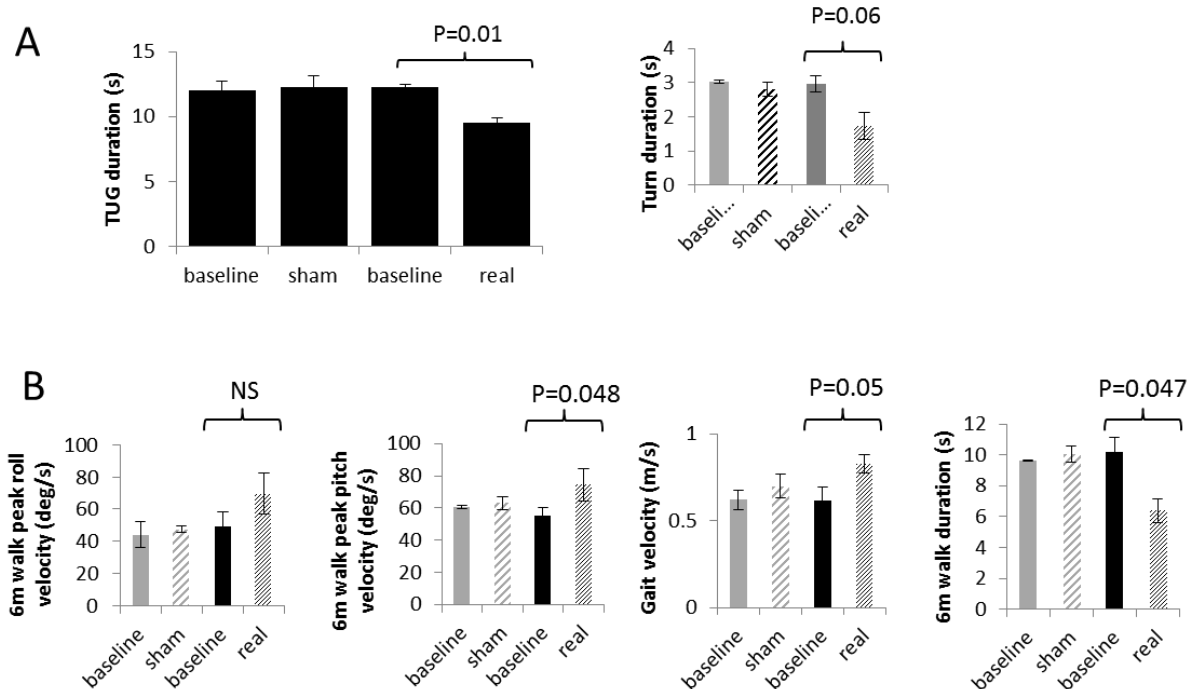


Figure 2 (A) Timed Up and Go (TUG) duration for baseline, sham and tDCS stimulations. Separate analysis of turn duration within the TUG (inset). (B) Gait analysis for sham and tDCS sessions compared to baseline, for the 6m walk duration, gait velocity, and trunk velocity.

Discussion

Investigating a Tango dancer with PD offers a unique opportunity to assess the combined effects of anodal tDCS and physical therapy on trunk and lower limb bradykinesia. Evidence from imaging data suggests that the basal ganglia may be particularly relevant in the control of dance movements (10). The basal ganglia appears to influence volitional motor control through basal ganglia-thalamocortical motor loops (11) and deficits herein account for the motor deficits seen in PD. In this patient, tDCS applied over the primary motor and premotor cortices (including SMA) may have facilitated the generation of these motor signals for the trunk and lower extremities. In addition, dancing involves the co-ordination of movement to music, which may provide an external auditory cue to facilitate movement in individuals with PD (12).

This pilot data suggests that tDCS may be a useful adjunct in gait and balance training for patients with movement disorders. Further studies are needed to evaluate the therapeutic use of non-invasive brain stimulation during music rehabilitation in patients with Parkinson's disease, in particular the effect of repeated sessions, in a larger cohort of patients.

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10. List of publications

This thesis

1: **Kaski D**, Quadir S, Patel M, Yousif N, Bronstein AM. Enhanced locomotor adaptation aftereffect in the "broken escalator" phenomenon using anodal tDCS. *J Neurophysiol.* 2012 May;107(9):2493-505.

2: **Kaski D**, Nigmatullina Y, Malhotra P, Bronstein AM, Seemungal BM. Human angular gyrus mediates angular path integration. *Current Biology* (under review).

3: **Kaski D**; Dominguez RO, Allum JHJ, Bronstein AM. Modulating gait and balance in patients with leukoaraiosis using tDCS and physical therapy. *Neurorehab Neural Repair* (under review).

4: **Kaski D**; Dominguez RO, Allum JHJ, Bronstein AM. Direct current stimulation and training in Parkinson's disease: better outcomes in more advanced disease. *Mov Dis* (under review)

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