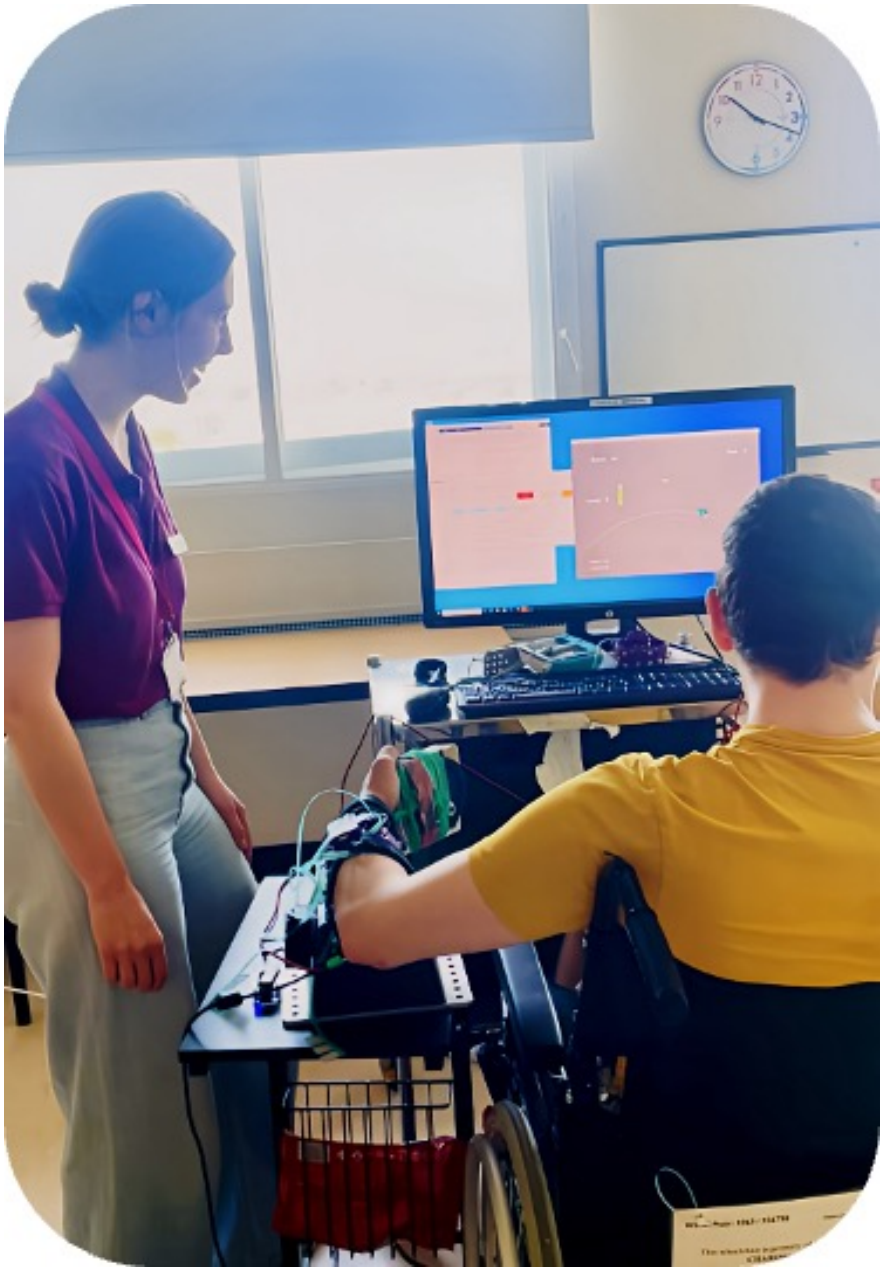
IMPERIAL

Hybrid robotic and electrical stimulation-based neurorehabilitation after stroke



Lucille Madeleine Marie Cazenave

Department of Computing – October, 2025

Submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy at Imperial College London

Lucille Cazenave: Hybrid robotic and electrical stimulation-based neurorehabilitation after stroke. October, 2025.

Funding: This work was supported by the UKRI Center for Doctoral Training in AI for Healthcare (EP/S023283/1).

Statement of originality

This is to certify that the work in this thesis has not been previously submitted to any other university or technical institution for a degree or award. I confirm that the research included within this thesis comprises my original work, and that when carried out in collaboration with, or supported by others, this has been duly acknowledged in the text and my contribution stated. Previously published material has also been acknowledged. I attest that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge break any UK law, infringe any third party's copyright or other Intellectual Property Right, or contain any confidential material.

Copyright Declaration

The copyright of this thesis rests with the author. Unless otherwise indicated, its contents are licensed under a Creative Commons Attribution-Non Commercial-No Derivatives 4.0 International Licence (CC BY-NC-ND). Under this licence, you may copy and redistribute the material in any medium or format on the condition that; you credit the author, do not use it for commercial purposes and do not distribute modified versions of the work. When reusing or sharing this work, ensure you make the licence terms clear to others by naming the licence and linking to the licence text. Please seek permission from the copyright holder for uses of this work that are not included in this licence or permitted under UK Copyright Law.

Abstract

Stroke is a leading cause of adult disability, with over 70% of survivors experiencing upper-limb impairments. While rehabilitation can reduce these deficits, its intensity and availability often remain insufficient, motivating the development of technology-assisted approaches.

Rehabilitation robots enable task-specific motor training, while functional electrical stimulation (FES) supports movement by eliciting muscle contraction and providing sensory feedback. However, FES is limited by rapid muscle fatigue and can be uncomfortable over time. Hybrid systems combining robotics and FES may address these limitations by allowing consistent kinematic guidance from the robot while preserving the neurophysiological engagement provided by FES. This could enable rehabilitation training to be effective and tolerable across a range of impairment levels.

This thesis investigated the effects of hybrid robot-FES assistance and training on motor behaviour, physiological responses, and user experience in unimpaired individuals and stroke survivors, with a focus on clinical applicability. To this end, a simple and portable one-degree-of-freedom robot-FES system was developed to assist wrist flexion/extension, with both systems acting on the same joint. A series of experiments explored how robotic, FES, and hybrid assistance affect performance, effort, fatigue and user experience. Moreover, the effect of a three-week hybrid robot-FES rehabilitation training on functional and physiological recovery after stroke was evaluated.

Overall, the findings indicate that the hybrid system can effectively assist movement while remaining comfortable in unimpaired and stroke individuals, with limited fatigue increase. A three-week intervention of daily hybrid training, in addition to usual care, produced clinically meaningful improvements in impairment, function, and movement quality, alongside high patient engagement and satisfaction. Together, these results support the clinical relevance of such hybrid robot-FES rehabilitation as a safe and effective complement to conventional physiotherapy.

This thesis advances our understanding of hybrid robot-FES assistance and training, informing the development and implementation of clinically viable and efficient neurorehabilitation technologies.

Acknowledgements

I would like to thank my supervisors Etienne Burdet and Paul Bentley for giving me the opportunity to conduct this research and supporting me throughout this PhD. I express my sincere gratitude to Etienne Burdet for his guidance on how to conduct this research, and for the many opportunities he has given me in the last years to grow as a researcher. I also thank my medical supervisor Paul Bentley, who made it possible for me to access the hospital and acquire invaluable insights into stroke care. I am thankful to Aaron Yurkewich as well, for his guidance at the start of my PhD.

The translation of my work to a stroke ward has also been greatly encouraged and facilitated by my colleagues at the Schön Klinik, Bad Aibling, Carmen Krewer and Chiara Höhler, who have always been keen to help me in achieving my goals and by my colleagues at TUM, Satoshi Endo and Hossein Kavianirad. I would also like to thank their colleagues Alexandra de Crignis, Lisa-Marie Huber, Roxana Wüchner and Oliver Plechinger for their dedication in this project and their invaluable work in recruiting patients and collecting data. Additionally, I am extremely thankful to Victoria Reboredo for conducting the final experimental work of my thesis at Charing Cross Hospital with me, and for her extensive support and effort. I would also like to extend my thanks to Victoria Atherton, Ankita Shah, and Davina Richardson for allowing us to work their therapy teams and successfully complete our study, as well as Jennifer Crow and Michelle Broderick for kindly sharing their clinical experience with me and helping me shape this final study.

I am also truly appreciative of my lab mates, whom I have shared this incredible experience with: Aaron, Alexis, Anirvan, Aran, Bella, Benedetta, Camille, Ciara, Dorian, Emanuele, Gero, Hector, Jingwen, Jon, Josh, Katja, Laura, Martin, Matteo, Natalia, Nuria, Pakorn, Patrick, Peter, Pilar, Rejin, Xiaoxiao, Yanpei, Yihan, Yiming, and many more, as well as my friends and colleagues from the ReHyb project. It has been a privilege to work and learn alongside of you, thank you for the amazing time we have spent together in and out of the office. A heartfelt special thanks go to Alexis, Katja, and Nuria, who have been with me since the start of this journey, for their consistent support, kindness, and laughs. I am also immensely grateful to my friends in London and Paris for their encouragement throughout this long journey and who were always present when I needed them.

Finally, my deepest gratitude and love go to my family. My parents and my brother have loved, supported, and encouraged me from the very beginning, I could not have achieved this without them.

Contents

1 Introduction **20**

1.1 Thesis motivation and aim . . . 20

1.2 Research strategy . . . 22

1.3 Thesis structure . . . 24

2 Background **27**

2.1 Stroke and upper-limb impairments . . . 27

2.1.1 Neurophysiological Mechanisms of Upper-Limb Impairments . . . 28

2.1.2 Recovery mechanisms after stroke . . . 30

2.2 Neurorehabilitation principles . . . 32

2.2.1 Motor learning in stroke rehabilitation . . . 32

2.2.2 Dose-Response in Neurorehabilitation . . . 33

2.2.3 Patient Engagement and Motivation . . . 33

2.2.4 Assessment in Stroke Rehabilitation . . . 35

2.2.5 Quality of evidence in neurorehabilitation research . . . 36

2.3 Technology-Aided Rehabilitation . . . 37

2.3.1 Robotic Systems for Upper-Limb Stroke Rehabilitation . . . 37

2.3.2 Functional electrical stimulation (FES) for upper-limb rehabilitation . . . 39

2.3.3 Hybrid Robotic and Functional Electrical Stimulation Systems . . . 43

3 Experimental system and analyses **47**

3.1 Hybrid robot-FES system . . . 47

3.1.1 Wrist robotic interface . . . 47

3.1.2 Functional electrical stimulation (FES) device . . . 48

3.2 Tracking task . . . 49

3.3 Metrics . . . 50

3.3.1 Kinematic metrics . . . 50

3.3.2 Muscle activity metrics . . . 51

3.4 Clinical scores . . . 53

4 Proof of concept of hybrid robot- and FES-assisted training in unimpaired participants **59**

4.1 Methods . . . 60
4.1.1 Participants . . . 60
4.1.2 Hybrid robot-FES system . . . 60
4.1.3 EMG recording . . . 61
4.1.4 Experiment task . . . 61
4.1.5 FES and EMG Calibration . . . 62
4.1.6 Control of robot-FES system . . . 62
4.1.7 Protocol . . . 63
4.1.8 Performance analyses . . . 63
4.1.9 Effort and fatigue . . . 63
4.1.10 Questionnaire . . . 64
4.1.11 Statistical analysis . . . 65
4.2 Results . . . 66
4.2.1 Performance results . . . 66
4.2.2 Effort and Fatigue . . . 66
4.2.3 Questionnaire Answers . . . 68
4.3 Discussion . . . 69
4.4 Conclusion . . . 73
4.5 Additional figures . . . 75

5 Feasibility of hybrid robot-FES system with subacute stroke patients in a clinical setting **76**

5.1 Methods . . . 78
5.1.1 Participants . . . 78
5.1.2 Protocol . . . 78
5.1.3 Hybrid Robot-FES system . . . 81
5.1.4 Data analysis . . . 81
5.1.5 Statistical analysis . . . 83
5.1.6 Estimating FM-UE scores from extracted metrics . . . 83
5.2 Results . . . 88
5.2.1 Participants . . . 88
5.2.2 Assistance . . . 88
5.2.3 Training . . . 90
5.2.4 User experience . . . 93

5.2.5 Assessment . . . 94
5.3 Discussion . . . 95
5.4 Conclusion . . . 100
5.5 Additional figures . . . 101

6 Fatigue induced by FES and voluntary movements in unimpaired and stroke participants 103
6.1 Methods . . . 105
6.1.1 Study in unimpaired participants . . . 105
6.1.2 Study in stroke patients . . . 109
6.2 Results from unimpaired study . . . 110
6.2.1 Questionnaire Answers . . . 110
6.2.2 MVC differences before and after each condition . . . 111
6.2.3 FES-induced torque differences before and after each condition . . . 112
6.2.4 M-wave parameters differences before and after each condition . . . 112
6.2.5 Changes in performance metrics across conditions . . . 113
6.2.6 Changes in effort across conditions . . . 113
6.3 Results from stroke study . . . 117
6.3.1 Questionnaire answers . . . 117
6.3.2 Changes in performance metrics across assisted trials . . . 117
6.3.3 Changes in EMG metrics across assisted trials . . . 118
6.3.4 Frequency-based EMG metrics differences before and after each condition . . . 120
6.4 Discussion . . . 122
6.5 Conclusion . . . 126
6.6 Additional figures . . . 127

7 Clinical study to evaluate the effects of additional hybrid robot-FES rehabilitation 130
7.1 Methods . . . 131
7.1.1 Participants . . . 131
7.1.2 Experimental design and procedure . . . 133
7.1.3 Hybrid robot-FES system . . . 134
7.1.4 Clinical study outcomes . . . 138
7.1.5 Kinematics and physiological outcomes . . . 138
7.1.6 Statistical analysis . . . 139
7.1.7 Subjective outcomes . . . 140
7.2 Results . . . 142
7.2.1 Participants . . . 142

7.2.2 Clinical scores improvements . . . 143
7.2.3 Increase in range of motion and strength . . . 145
7.2.4 Task performance improvements . . . 145
7.2.5 Patients' subjective feedback . . . 146
7.2.6 Controller evaluation . . . 148
7.3 Discussion . . . 150
7.4 Conclusion . . . 155
7.5 Additional figures . . . 156
7.6 Questionnaire answers . . . 156

8 Discussion **162**
8.1 Summary of results . . . 162
8.2 Limitations and future directions . . . 164
8.3 Application and considerations . . . 167

References **171**

A Associated publications **194**
A.1 Proof of concept of hybrid robot- and FES-assisted training in unimpaired participants 195
A.2 Feasibility of hybrid robot-FES system with subacute stroke patients in a clinical setting 205
A.3 Fatigue induced by FES and voluntary movements in unimpaired and stroke participants 211

List of Figures

1.1 Technologies that can aid upper-limb rehabilitation post-stroke. **A.** ArmeoSpring (Hocoma, Switzerland) robot to train whole-arm movement with game-like interactive exercises. **B.** FesiaGrasp (Fesia Technology, Spain) FES system that generates flexion and extension of the wrist and fingers, designed for people with motor impairment of the upper extremity. 21

1.2 Two upper-limb stroke rehabilitation robots. **A.** Upper-limb robot allowing movement in three-degree-of-freedom at the shoulder as well as elbow flexion/extension with a distal module that can be integrated to accommodate forearm supination/pronation and wrist flexion/extension (Klein et al., 2010). It is suitable for large rehabilitation centres and lab-based testings. **B.** Portable one-degree-of-freedom wrist robot, weighing less than 5kg and easily dismountable and transportable in a case, suitable for home-use and rehabilitation centres with restricted space. 23

1.3 Small hybrid system combining FES with electrodes placed on the wrist flexor and extensor muscles and the wrist HRX-1 robot providing torque to the wrist. The hybrid system is used to assist participants in tracking a randomly moving target on-screen using wrist flexion/extension movements. 24

2.1 Subacute stroke therapy at Charing Cross Hospital London. **A.** Physiotherapists with stroke patients practising walking. **B.** Occupational therapist with a stroke patient practising making tea in a kitchen. 32

2.2 Physiotherapist performing the Fugl-Meyer Upper-Extremity Assessment (FM-UE) with a stroke patient. **A.** Assessing patient's ability to perform shoulder flexion from 0° to 90° as part of the volitional movement mixing synergies test in the FM-UE (section A-II). **B.** Assessing patient's ability to perform shoulder flexion from 90° to 180° as part of the volitional movement with little or no synergy test in the FM-UE (section A-III). **C.** Assessing patient's ability to perform thumb adduction grasp as part of the hand test in the FM-UE (section C-b). **D.** Assessing patient's ability to perform cylinder grasp as part of the hand test in the FM-UE (section C-d). 34

2.3 Physiotherapist performing the Action Research Arm Test (ARAT) with a stroke patient. **A.** Assessing patient's ability to grasp objects, here a 10 cm cube (top), and place them on top of a shelf (bottom). **B.** Assessing patient's ability to grip (top), here pouring water from glass to glass (bottom). **C.** Assessing patient's ability to pinch objects, here using the thumb and index to pinch a 6 mm ball bearing (top) and a 1.5 cm marble (bottom), and place them on top of a shelf. 35

2.4 Example of robotic devices for upper-limb rehabilitation. **A.** End-effector device (MIT-Manus) (Krebs et al., 2004). **B.** Exoskeleton device (ArmeoSpring, Hocoma) **C.** Soft wearable exosuit (Lotti et al., 2020). 38

3.1 HRX-1 robotic device for wrist flexion/extension, featuring an ergonomic handle and an adjustable forearm support with straps to secure the hand and forearm, in its compact casing. . 47

3.2 FES device with the stimulation module and the 16-electrode array with the anode electrode positioned on the dorsal and ventral side of the wrist near the ulnar head and the cathode array positioned around the arm in line with the belly of the wrist flexor and extensor muscles. . . . 48

3.3 Hybrid system combining FES with electrodes placed on the wrist flexor and extensor muscles and the wrist HRX-1 robot providing torque to the wrist. The hybrid robot-FES system is used to assist participants in tracking a randomly moving target on-screen using wrist flexion/extension movements. 49

4.1 Experiment description. **A.** Participants track a randomly moving target on-screen with wrist flexion/extension and receive four different assistance conditions: no assistance, robot-only assistance, FES-only assistance and hybrid (robot + FES) assistance. **B.** Overview of experimental protocol, where four assistance conditions were presented randomly to each participant: no assistance, FES-only assistance, robot-only assistance and hybrid assistance. Each block represents one trial of the target tracking task. 61

4.2 Performance, motor adaptation and quality of motion metrics during the tracking task with four different assistance conditions. (**A**) Tracking performance indicated by the Root Mean Square Error (RMSE). (**B**) Tracking performance improvement indicates the difference in participant's tracking performance before and after training; a positive result indicates that they are performing better after training. (**C**) Time Delay indicates the temporal shift between the target and participant trajectories. (**D**) Smoothness of participant's trajectory, evaluated using Spectral Arc Length (SPARC) (Balasubramanian et al., 2015). A SPARC value closer to zero corresponds to a smoother motion. $* : p < 0.05, ** : p < 0.01, *** : p < 0.001$. Comparisons not shown are not significant. 66

4.3 Voluntary effort (A,B), muscular effort (C,D) and changes in muscle fatigue (E,F) during the tracking task assisted with four different assistance conditions. The effort metrics are estimated as the mean envelope amplitude of the torque-normalised EMG signal. Fatigue is obtained from the median frequency of the EMG signal, a decrease in frequency indicates increased fatigue. (**A**) Voluntary effort in the flexor muscles. (**B**) Voluntary effort in the extensor muscles. (**C**) Total muscular effort in the flexor muscles (including M-wave contribution). (**D**) Total muscular effort in the extensor muscles (including M-wave contribution). (**E**) Fatigue changes in the flexor muscles. (**F**) Fatigue changes in the extensor muscles. $* : p < 0.05, ** : p < 0.01, *** : p < 0.001$. Comparisons not shown are not significant. 67

4.4 Answers to the 10-point NASA-TLX questionnaires on perceived workload after the trajectory tracking task with four different assistance conditions, with answers from very low (1) to very high (10). $* : p < 0.05$. Comparisons not shown are not significant. 68

4.5 Answers from a 5-point ordinal Likert scale questionnaire on comfort (**A** and **C**) and usefulness (**B** and **D**) of robotic force (top row) and electrical stimulation (bottom row) after trajectory tracking with four different assistance conditions. Agreement level from 'Strongly Agree' (2) to 'Strongly Disagree' (-2) was provided for each statement. 69

4.6 Motor adaptation during the tracking task with four different assistance conditions. Tracking performance improvement indicates the difference in participant's tracking performance before and after training; a positive result indicates that they are performing better after training. . 75

4.7 Muscle fatigue was evaluated during the EMG calibration at the start and end of the experiment, where participants had to track four different levels of torque. Fatigue is calculated as the median frequency of the EMG signal, a decrease in frequency indicates an increased fatigue. Level of fatigue for (**A**) the flexor muscles and (**B**) the extensor muscles. 75

5.1 Experiment description. **A.** A patient tracks a randomly moving target on-screen with wrist flexion/extension. **B.** Overview of experimental protocol, where a patient performs a series of calibration and assessment steps followed by unassisted trials (U), where no stimulation or robotic assistance are provided, and assisted training trials (A), where patients receive hybrid assistance. 'x10' refers to the number of trials for each block, here ten. 'Q' refers to the questionnaire step. 78

5.2 Consolidated Standards of Reporting Trials (CONSORT) diagram, showing participants screening, group allocation, participation and data analysis. 87

5.3 Assistive effect of the FES and robot during the target-tracking task. **A.** Effect of the assistance on the normalised RMSE between the patient and target trajectories. **B.** Effect of the assistance on the correlation between the frequency spectra of the patient and target trajectories. **C.** Effect of the assistance on the cocontraction of the wrist flexor and extensor muscles. **D.** Effect of the assistance on the reciprocal activation of the wrist flexor and extensor muscles. 89

5.4 Temporal evolution of the unassisted performance and muscle activity during the target-tracking task. **A.** Effect of the training on the normalised RMSE between the patient and target trajectories. **B.** Effect of the training on the correlation between the frequency spectra of the patient and target trajectories. **C.** Effect of the training on the cocontraction of the wrist flexor and extensor muscles. **D.** Effect of the training on the reciprocal activation of the wrist flexor and extensor muscles. 91

5.5 Subjective perception of the unassisted and assisted target-tracking task for each intervention group, reported by patients through a 5-point Likert Scale questionnaire, from 'Strongly disagree' (-2) to 'Strongly agree' (2). **A.** Answers to the questions (figure from left to right): 'The use of the device was comfortable', 'I enjoyed doing this activity very much', 'I would like to use this system for my upper-limb therapy in the clinic'. **B.** Answers to the questions 'During the experiment, I felt assistance' after the unassisted and assisted trial. **C.** Answers to the questions 'The use of the device improved my performance'. 93

5.6 Estimating FM-UE scores of patients using kinematic and EMG data collected in the first five unassisted baseline trials of the first session. **(A)** Models performance (mean absolute error) across the three datasets. Models compared include: baseline mean predictor (base), random forest with surrogate splits (rf surr.), linear regression (linear), random forest (rf), boosted trees with surrogate splits (bt surr.), support vector regression (svr), ensemble of learners (ensemble), boosted trees (bt), ensemble with surrogate splits (ensemble surr.), and neural networks (nn) **(B)** Frequency of feature selection algorithms applied across regression models and outer folds, for the three datasets. Feature selection methods included: no feature selection (none), recursive feature elimination (RFE), principal component analysis (PCA), least absolute shrinkage and selection operator (LASSO), correlation-based selection with thresholds of 0.9 (Corr. 0.9) or 0.7 (Corr. 0.7), principal component analysis (PCA), reliefF, chi-squared test–based feature selection, and Kruskal–Wallis test–based selection. 94

5.7 Correlation between FM-UE scores and assistance effect (assisted performance – unassisted performance) on various metrics: normalised RMSE **(A)**, spectral correlation **(B)**, cocontraction **(C)**, and reciprocal activation **(D)**, for each group individually and the whole population. A performance improvement is indicated by a negative RMSE difference and a positive spectral correlation difference. A negative cocontraction or reciprocal activation indicates a reduction in physiological measures with assistance. 101

5.8 Correlation between FM-UE scores and improvement in unassisted trials over sessions (S3 – S1) on various metrics: normalised RMSE **(A)**, spectral correlation **(B)**, cocontraction **(C)**, and reciprocal activation **(D)**, for each group individually and the whole population. A performance improvement is indicated by a negative RMSE difference and a positive spectral correlation difference. A negative cocontraction or reciprocal activation indicates a reduction in physiological measures from Session 1 to 3. 102

5.9 Estimating FM-UE scores of severely impaired patients (FM-UE $\leq$ 25) using kinematic and EMG data collected in the first five unassisted baseline trials of the first session. **(A)** Models performance (mean absolute error) across the three datasets. Models compared include: baseline mean predictor (base), random forest with surrogate splits (rf surr.), linear regression (linear), random forest (rf), boosted trees with surrogate splits (bt surr.), support vector regression (svr), ensemble of learners (ensemble), boosted trees (bt), ensemble with surrogate splits (ensemble surr.), and neural networks (nn) **(B)** Frequency of feature selection algorithms applied across regression models and outer folds, for the three datasets. Feature selection methods included: no feature selection (none), recursive feature elimination (RFE), principal component analysis (PCA), least absolute shrinkage and selection operator (LASSO), correlation-based selection with thresholds of 0.9 (Corr. 0.9) or 0.7 (Corr. 0.7), principal component analysis (PCA), reliefF, chi-squared test–based feature selection, and Kruskal–Wallis test–based selection. . . . 102

6.1 Experimental protocol for the study on fatigue with unimpaired participants. The three conditions were presented in random order for each participant and consisted of 25 trials of a 30-second wrist target-tracking task. MVC refers to three repetitions of maximum voluntary wrist flexion and extension, followed by three repetitions of maximum flexor and extensor stimulation while participants were instructed to relax. 106

6.2 An example M-wave response from a participant during the 3 s maximum flexor stimulation while at rest, with the measurements of the M-wave parameters: amplitude, duration, and area of the first (Amp_MW1, Dur_MW1, and Area_MW1) and second (Amp_MW2, Dur_MW2 and Area_MW2) phases. These parameters are also computed for the full M-wave, where the absolute sum of the parameter from each phase is computed (MW amplitude, MW duration and MW area). 108

6.3 Answers to the 10-point NASA-TLX questions on physical demand **(A)** and mental demand **(B)**, with answers from very low (1) to very high (10). Each participant performed all three conditions and the dotted line represents their ratings. $***$: $p < 0.001$. Comparisons not highlighted are not significant. 111

6.4 Difference in mean normalised EMG during MVC trials for each condition for the flexor MVC **(A)** and extensor MVC **(B)**. A negative difference indicates a decrease in MVC after the condition compared to before the condition. 111

6.5 Difference in mean normalised FES-induced torque for each condition for the flexor stimulation **(A)** and extensor stimulation **(B)**. A negative difference indicates a decrease in FES-induced torque after the condition compared to before the condition. 112

6.6 Difference in mean normalised M-wave parameters when the maximum comfortable stimulation is applied while at rest, for each condition, for the flexor stimulation **(A,C,E)** and the extensor stimulation **(B,D,F)**. The M-wave parameters presented are the M-wave peak-to-peak amplitude **(A,B)**, the M-wave duration **(C,D)** and the M-wave area **(E,F)**. 114

6.7 Evolution of performance metrics across trials for each condition: root mean square error between the subject's and target's positions **(A)**, correlation between the subject's and target's positions **(B)**, SPARC metric capturing motion smoothness **(C)**. The lines represent the median of each metric computed over all participants and the shaded areas represents the data from the first to third quartile of the metric. The first three trials are excluded as they were used as familiarisation trials and were not considered in the analysis. 115

6.8 Evolution of the normalised EMG envelope across trials for each condition for the wrist flexor **(A)** and the extensor **(B)** muscles . The lines represent the median of each metric computed over all participants and the shaded areas represents the data from the first to third quartile of the metric. The first three trials are excluded as they were used as familiarisation trials and were not considered in the analysis. 116

6.9 Answers to the 10-point NASA-TLX questions on physical demand **(A)** and mental demand **(B)**, with answers from very low (1) to very high (10), averaged over the three sessions. . . . 118

6.10 Evolution of performance, i.e. normalised RMSE between the target and patient trajectories **(A)** , and the correlation between the frequency spectra of the target and patient trajectories **(B)**; and EMG metrics, i.e. the cocontraction **(C)** and the reciprocal activation **(D)** of the wrist flexor and extensor muscles. The metric values across the assisted trials in Session 1 for each intervention group are plotted. The lines represent the median of each metric computed over all participants and the shaded areas represents the data from the first to third quartile of the metric. The dotted line represents the LME fit characterising the effect of `trial` on each metric for each session × group. 119

6.11 Difference in frequency-based EMG metrics between the last three and first three trials for each condition for the wrist flexor (A, C, E) and the extensor (B, D, F) muscles: the difference in median frequency (A,B) and in the mean of the instantaneous median frequency (C,D), as well as the Dimitrov index (E,F) are presented. A negative difference in the median frequency (A,B) and in the mean of the instantaneous median frequency (C,D) would indicate fatigue. A positive difference in Dimitrov index (E,F) would indicate fatigue. 121

6.12 Difference in mean normalised EMG during MVC trials after each condition, presented in chronological order for the flexor MVC **(A)** and the extensor MVC **(B)**. 127

6.13 Difference in mean normalised FES-induced torque after each condition, presented in chronological order for the flexor stimulation **(A)** and the extensor stimulation **(B)**. 127

6.14 Difference in mean normalised M-wave parameters when the maximum comfortable stimulation is applied while at rest, after each condition, presented in chronological order for the flexor stimulation **(A,C,E)** and the extensor stimulation **(B,D,F)**. The M-wave parameters presented are the M-wave peak-to-peak amplitude **(A,B)**, the M-wave duration **(C,D)** and the M-wave area **(E,F)**. 128

6.15 Difference in mean performance metrics between the last three and first three trials for each condition: root mean square error between the subject's and target's positions **(A)**, correlation between the subject's and target's positions **(B)**, SPARC metric capturing motion smoothness **(C)**. $*: p < 0.05, **: p < 0.01, ***: p < 0.001$. Comparisons not shown are not significant. . 129

6.16 Difference in the mean of normalised EMG envelope between the last three and first three trials for each condition: for the wrist flexor **(A)** and the extensor **(B)** muscles. 129

7.1 A patient tracks a randomly moving target on-screen with wrist flexion/extension. 132

7.2 Consolidated Standards of Reporting Trials (CONSORT) diagram, showing participant screening, group allocation, participation and data analysis. 141

7.3 Evolution of the FM-UE **(A-C)** and ARAT **(D-F)** over sessions for the intervention group **(A,D)** and the control group **(C,F)**, and the relative score changes **(B,E)**. In figures A,C,D,F, each dot and line represents one patient's score over time. For figures B and E, the dot represents the mean change with respect to baseline and the bar represents the standard error of the mean. 143

7.4 Passive range of motion **(A)** and active range of motion **(B)** over sessions. Each patient is represented by a different colour, where the dots indicate the ROM value at each session and the lines show the linear regression for each patient. The black dashed line represents the population-level trend estimated by the linear mixed-effects model. 144

7.5 Torque generated during the maximal voluntary contraction task in the flexion **(A)** and the extension **(B)** directions, at the start, middle and end of the intervention. Each patient is represented by a different colour, where the dots indicate the torque value for that session. . 144

7.6 Tracking performance across sessions quantified by the normalised RMSE between the patient and target trajectories **(A)**, the spectral correlation between the two trajectories **(B)** and the motion smoothness of the patient **(C)**. Each patient is represented by a different colour, where the dots indicate the performance value at each session and the lines are the linear regression for each patient. The black dashed line represents population-level trend estimated by the linear mixed-effects model. 146

7.7 Cocontraction **(A)** and reciprocal activation **(B)** during the baseline unassisted trials at the start, middle and end of the intervention. Each patient is represented by a different colour, where the dots indicate the metric value for that session. 147

7.8 Example trial for a representative patient. **(A)** Patient and target trajectories. **(B)** Assistive torque from the robot and FES, with the coefficient α indicating the shared load between actuators. **(C)** FES amplitude applied to the wrist flexor (negative amplitude for visualisation) and the wrist extensor. The comfortable amplitude range is marked by the grey areas, where the maxima and the motor thresholds for each muscle contraction were calibrated during the FES calibration phase of the experiment. 147

7.9 Evolution of the tracking performance (normalised RMSE in blue) and the difficulty level (in red) during the assisted training trials (30 trials) across several sessions for a representative patient. 148

7.10 FES calibration procedure showing the torque response to FES at specific amplitudes and wrist angles, which is used to model a three-dimensional map applied throughout the tracking task to determine the FES amplitude required. 149

7.11 Controller parameter changes over sessions. **A.** Changes in α which defines the share between the FES and robotic assistance where higher values indicate greater FES contribution. **B.** Evolution of the difficulty level over time. 150

7.12 Evolution of the FM-UE shoulder/elbow (subsection A) **(A,B)** and FM-UE wrist/hand (subsections B,C) **(C,D)**, for patients in the intervention group **(A,C)** and the control group **(B,D)**. Each dot and line represents one patient's score over time. 156

List of Tables

2.1 Example of sensing, control inputs, and common types of controllers used in robotic, FES, and hybrid systems for upper-limb rehabilitation. 40

5.1 Patient demographics 88

7.1 Difficulty levels 137

7.2 Patient demographics 142

Chapter 1

Introduction

1.1 Thesis motivation and aim

Stroke is one of the most common neurological disorders, and is a leading cause of adult disability worldwide (Feigin et al., 2019), resulting in upper-limb impairments in over 70% of post-stroke individuals (Nakayama et al., 1994; Lawrence et al., 2001). Rehabilitation can help reduce impairments but the rehabilitation needs of stroke patients are currently unmet (Royal College of Physicians, 2015; Chen et al., 2019; Cieza et al., 2020). Enhancing the efficacy of rehabilitation services and increasing exercise intensity could lead to improved motor recovery, helping more people after stroke live independently.

Technology-aided rehabilitation has been proposed as a means to promote functional recovery while complementing typical one-on-one physiotherapy or occupational therapy sessions. More specifically, rehabilitation robots have been increasingly used for motor training, providing assistance to users during tasks and thus leading to performance improvements (Ganesh et al., 2015; Ivanova et al., 2020; Bertani et al., 2017) (see Fig. 1.1 A). Functional electrical stimulation (FES) is also used in stroke rehabilitation (see Fig. 1.1 B). As there is strong evidence that FES can increase upper-limb activity and enhance recovery after stroke (Howlett et al., 2015; Thrasher et al., 2008; Alon et al., 2008), it is recommended by many national clinical guidelines worldwide (Royal Dutch Society for Physical Therapy, 2014; Royal College of Physicians, 2015; Intercollegiate Stroke Working Party, 2023; Salbach et al., 2022; Stroke Foundation, 2024; Veterans Affairs/Department of Defense, 2024).

While FES provides sensory feedback and can elicit muscle contractions, it may lead to rapid muscle fatigue as it constantly stimulates the same motor units, unlike the naturally varying recruitment pattern seen in voluntary movements (Gorgey et al., 2009; Maffiuletti, 2010; Bickel et al., 2011; Miura et al., 2016; Zhang et al., 2011). On the other hand, robotic systems help users perform a desired task by acting on joint torques, resulting in well-controlled limb motion. In this hybrid approach, both modalities could help facilitating recovery and providing an enjoyable and comfortable rehabilitation

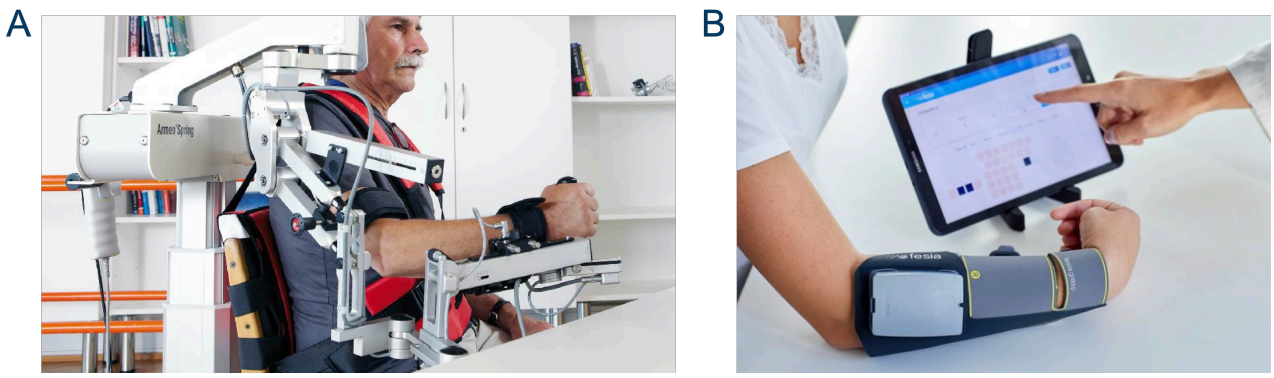


Figure 1.1: Technologies that can aid upper-limb rehabilitation post-stroke. **A.** ArmeoSpring (Hocoma, Switzerland) robot to train whole-arm movement with game-like interactive exercises. **B.** FesiaGrasp (Fesia Technology, Spain) FES system that generates flexion and extension of the wrist and fingers, designed for people with motor impairment of the upper extremity.

experience. FES directly activates the patient's own muscles, generating contractions and peripheral sensory feedback, which can reinforce voluntary motor pathways. The robotic assistance, meanwhile, ensures precise and smooth control of movement trajectories, compensating for the variability and delayed response inherent to FES. It also enhances comfort and safety, particularly during continuous tracking tasks that may require fine corrective motions, where relying solely on FES could result in overshooting or discomfort due to fluctuating torque responses. By integrating both forms of assistance, the system allows for consistent kinematic guidance from the robot while preserving the neurophysiological engagement provided by FES, creating a rehabilitation training that can be effective and tolerable across a range of impairment levels.

Hybrid systems have previously been developed and tested in stroke populations and have shown positive outcomes in aiding functional recovery (Resquin et al., 2016; Höhler et al., 2024). These systems typically rely on FES as the main means of assistance, while using robotic devices only to promote stability and gravitational support (Ambrosini et al., 2017; Alon et al., 2003; Ring et al., 2005; Fujiwara et al., 2009; Barker et al., 2008; Wu et al., 2011; Meadmore et al., 2014; Westerveld et al., 2014; Resquín et al., 2016), or to contribute to other joint movements than the one supported by FES (Alon et al., 2003; Ring et al., 2005; Meadmore et al., 2014; Resquín et al., 2016). Hence, they may not exploit the full potential of hybrid systems for rehabilitation (Resquin et al., 2016). Moreover, simple solutions such as push-buttons have been used to trigger assistance (Resquin et al., 2016), which can limit the therapeutic benefits as the patient may not be engaged in the task (Kroon et al., 2005; Rushton, 2003; Kahn et al., 2006; Blank et al., 2014). On the other hand, advanced controllers have recently been introduced to provide more optimal combinations of FES and robotic assistance, which have been successfully tested in simulations (Bardi et al., 2021) and unimpaired participants (Wolf et al., 2017; Dunkelberger et al., 2022; Burchielli et al., 2022). However, most of these controllers have not yet been tested in a rehabilitation scenario with stroke patients. Furthermore, complex controllers requiring a lengthy calibration or based on models of intact muscles may not transfer well to a stroke population, and may not be suitable for use in a clinical setting, where patients cannot sustain long

therapy sessions.

Finally, most studies conducted using a hybrid system have focused on changes in clinical scores capturing functional recovery after stroke. This is justified as it is the ultimate goal of developing new rehabilitation systems for patients after stroke. However, further understanding the effects of each sub-system and their combination on the motor behaviour and physiological outputs of stroke patients may help in designing more efficient rehabilitation systems that could target different aspects of recovery, e.g. range of motion, muscle strength, volitional output, etc.

In this context, my aim is to **investigate the effects of hybrid robot-FES training on physiological and behavioural changes in unimpaired individuals and stroke patients, as well as whether and how it can lead to functional recovery after stroke**. Specifically, my thesis focuses on investigating how hybrid robot-FES assistance affects performance, user experience, effort and fatigue in both unimpaired and stroke individuals. The effect of hybrid robot-FES rehabilitation, designed based on these results, on functional and physiological recovery after stroke is also explored. This work can provide foundational knowledge to inform the development of hybrid neurorehabilitation technologies based on neuromechanical evidence from stroke data.

1.2 Research strategy

Hybrid robot-FES systems designed for upper-limb stroke rehabilitation often involve multiple degrees-of-freedom (DOFs) to assist full-arm movements (Resquin et al., 2016). Bulky robotic systems (as shown in Fig. 1.2 A) are typically required for this purpose, which are difficult to move and manipulate. Such systems are not suitable for home use by stroke patients and are primarily intended for clinical settings, to be used by individuals in the subacute phase of stroke recovery. However, such large systems may not be usable in typical clinical environments, where space is commonly limited and shared with the care team, patients, family members, etc.

Additionally, these large systems may require a lengthy calibration and adjustments for each patient and at each session, decreasing the duration of effective training. Such necessary preparation may be particularly restrictive for patients in the subacute phase, who may fatigue very quickly (Intercollegiate Stroke Working Party, 2023). A simple, portable system that can be easily set up and controlled is thus preferable for such a demanding environment (see Fig. 1.2 B). This can also facilitate the use of the device by the hospital care team. Furthermore, evidence suggests that single-joint training may be as effective as multi-joint approaches for upper-limb stroke rehabilitation (Milot et al., 2013; Fluet et al., 2014). These studies compared single-joint and multi-joint robotic training and found that the two approaches lead to similar clinically significant improvements in upper-limb outcomes, with no significant differences between training modes in functional measures (Milot et al., 2013; Fluet et al., 2014). Here, wrist flexion and extension training was selected because distal motion

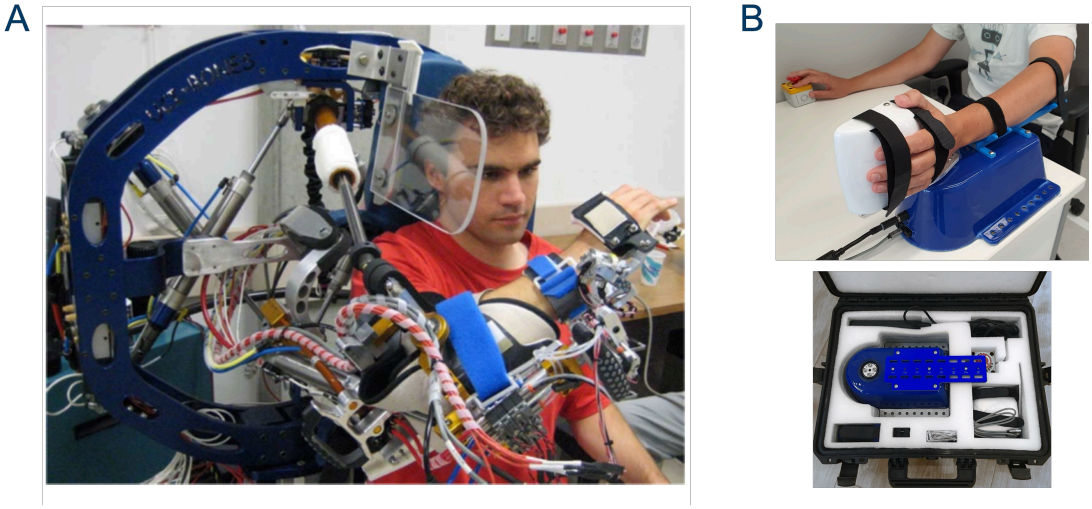


Figure 1.2: Two upper-limb stroke rehabilitation robots. **A.** Upper-limb robot allowing movement in three-degree-of-freedom at the shoulder as well as elbow flexion/extension with a distal module that can be integrated to accommodate forearm supination/pronation and wrist flexion/extension (Klein et al., 2010). It is suitable for large rehabilitation centres and lab-based testings. **B.** Portable one-degree-of-freedom wrist robot, weighing less than 5kg and easily dismountable and transportable in a case, suitable for home-use and rehabilitation centres with restricted space.

is essential for the functional use of the upper limb. While restoring proximal movements at the shoulder and elbow can contribute to gross motor control, meaningful independence in ADLs typically requires coordinated wrist and hand motion, such as during grasping and object manipulation.

Moreover, when the FES and the robot are used to control or support different joint motions, the effect of each sub-component on the recovery of stroke patients, or their combined action, may not be easily identifiable. The use of systems with a larger workspace may also introduce additional confounding factors, which cannot always be controlled for. To further understand the underlying principles behind robot- and FES-based assistance to movement, I thus preferred using a one-DOF system with the FES and robot acting on the same joint motion (as shown in Fig. 1.2 B).

To evaluate the potential of hybrid robot-FES training for post-stroke functional recovery, it is essential to assess performance metrics, physiological responses, and the user's subjective experience. This allows us to characterise behavioural and physiological changes during and after assistance from the robot-FES system as well as the perception of the user. Previous studies mostly evaluated the change in clinical scores assessing functional recovery, but have rarely systematically investigated the neuromechanical changes induced by robot-FES assistance and training. Investigating the underlying principles of hybrid robot-FES assistance may further inform the design of clinically and physiologically efficient rehabilitation systems.

In this thesis, I have developed a simple and portable one-DOF robot-FES system, suitable for clinical environments illustrated in Fig. 3.3. I used it to explore how such assistance and training can affect the motor strategies, learning and perceived experience of unimpaired individuals and stroke patients. I have conducted a series of studies to address the following research questions:



Figure 1.3: Small hybrid system combining FES with electrodes placed on the wrist flexor and extensor muscles and the wrist HRX-1 robot providing torque to the wrist. The hybrid system is used to assist participants in tracking a randomly moving target on-screen using wrist flexion/extension movements.

- QA: How does robotic and/or FES assistance affect unimpaired individuals' behavioural and physiological features?
- QB: Can a hybrid robot-FES system be used to aid the rehabilitation and assessment of sensorimotor functions in stroke individuals?
- QC: Should muscle fatigue be considered when using a hybrid robot-FES system for stroke rehabilitation?
- QD: How does hybrid robot-FES rehabilitation affect functional and physiological recovery after stroke?

1.3 Thesis structure

This thesis follows a structured and progressive experimental approach, with each chapter building upon the findings of the previous one to gradually explore the potential of a hybrid robot-FES system for stroke rehabilitation. The work begins with a study in unimpaired participants to safely explore how the system works and affects users' motor strategies. This enables an informed transition to clinical testing, where a feasibility study with stroke patients is conducted. Finally, a three-week clinical trial with stroke patients is conducted to evaluate changes in recovery over time. This structured progression ensures that each phase provides useful insights to support the next, while enabling the research to be conducted in a responsible and effective manner.

This chapter introduced the motivation for this work, and related research questions and objectives. It also presented the research approach and structure of the thesis.

Chapter II reviews existing literature on upper-limb neurorehabilitation after stroke. It details the neurophysiological mechanisms underlying upper-limb impairments after stroke as well as the recovery process and related neurorehabilitation principles. An overview of existing rehabilitation approaches analyses the benefits and limitations of technologies such as robots and FES to aid the rehabilitation process.

Chapter III presents the hybrid robot-FES device, used to conduct the experimental work of this thesis. It consists of a wrist robotic interface and an FES device, with associated sensors and the training tasks. The metrics employed to characterise users' behavioural and physiological changes during training are also presented, including performance, learning, effort and fatigue in both unimpaired and stroke individuals.

Chapter IV serves as a proof of concept for this hybrid robot-FES system to assist participants' movements, addressing the question QA. Combining FES with robotic assistance could mitigate the discomfort and fatigue induced by FES, while enhancing sensorimotor engagement through muscle activation. Existing clinical implementations typically use FES as the primary actuator, with robots offering only support or assistance to other joint motions (Resquin et al., 2016; Alon et al., 2003; Meadmore et al., 2014; Fujiwara et al., 2009; Barker et al., 2008; Wu et al., 2011; Resquín et al., 2016; Ambrosini et al., 2021). Recent hybrid control strategies have begun to optimise this combination (Dunkelberger et al., 2023; Burchielli et al., 2022; Bardi et al., 2021), but they have rarely been tested in clinical populations and mainly focus on motor output rather than user behaviour and experience. To assess the potential of a truly integrated hybrid approach, where both FES and robotic assistance act on the same joint motion, the effect of each modality, and their combination, on motor performance, muscle effort, fatigue, and perceived workload should be investigated. In this chapter, the hybrid robot-FES system is used to assist unimpaired participants in a continuous target tracking task. Both qualitative and quantitative data are collected and analysed to understand the impact of the assistance on the user, informing the development of a suitable rehabilitation approach.

Chapter V investigates the feasibility of using the hybrid robot-FES system in a clinical context to support upper-limb assessment and rehabilitation in subacute stroke patients (QB). Combining two active assistive devices introduces significant technical complexity, and current clinical systems often underutilise this potential as mentioned above, using simple triggering methods like push-buttons (Resquin et al., 2016), which may reduce patient engagement and therapeutic effectiveness (Kroon et al., 2005; Rushton, 2003; Kahn et al., 2006; Blank et al., 2014). Other more advanced hybrid controllers have shown promising results but remain largely untested in clinical settings. Furthermore, prior studies using hybrid assistance in stroke populations often overlook user experience and qualitative outcomes (Hu et al., 2015). To address these gaps, this chapter adopts a patient-centred approach to

evaluate the use of a simple hybrid controller during wrist tracking in stroke patients. First, the impact of the robot and/or FES assistance on motor performance, learning, and effort is investigated. These results are used to infer the benefits of using a hybrid robot-FES approach in stroke neurorehabilitation. Second, it explores whether the kinematics and muscle activity recordings from the device can be used to estimate motor impairment.

Chapter VI investigates how muscle fatigue may develop when a user is performing a tracking task assisted by FES and/or robotic support, to better understand its impact on rehabilitation and inform the design of suitable hybrid control (QC). FES is known to cause rapid muscle fatigue due to its constant motor unit recruitment, unlike the naturally varying patterns seen during voluntary movement (Gorgey et al., 2009; Maffiuletti, 2010; Bickel et al., 2011; Miura et al., 2016; Zhang et al., 2011). Although commonly used in stroke rehabilitation, FES is typically applied alongside voluntary effort and with regular breaks, which may help limit fatigue (Eraifej et al., 2017). To investigate how fatigue develops under different assistance modes, this chapter first examines the effects of FES- and volitionally-induced movement on unimpaired participants' muscle fatigue. Second, it analyses muscle fatigue in stroke patients using data introduced in Chapter V, focusing on how robotic and/or FES assistance influences muscle fatigue during training. These results can help clarify whether and how fatigue should be considered within hybrid neurorehabilitation systems, particularly when combining robotic and FES assistance in continuous tasks.

Chapter VII investigates the benefits of a three-week hybrid robot-FES rehabilitation training on motor recovery in subacute stroke patients (QD). While previous work has primarily evaluated the outcomes of hybrid neurorehabilitation based on clinical assessments alone, this chapter aims to further examine the potential mechanisms contributing to recovery. Here, changes in clinical scores are used to quantify functional improvements and motor impairment, while muscle activity and kinematic data are analysed to assess physiological changes and behavioural adaptations throughout the training. These findings address how robotic and FES rehabilitation affect motor behaviour and physiological adaptations, and may provide insights for a data-driven design of hybrid technologies.

Chapter VIII summarises the key research findings, highlighting their strengths and limitations, and discusses potential directions for future research stemming from this work. It also discusses potential applications and considerations related to this work.

Chapter 2

Background

2.1 Stroke and upper-limb impairments

Stroke is one of the leading causes of mortality and long-term disability worldwide and represents a major global health burden. It is defined as a sudden onset of neurological dysfunction resulting from an interruption of blood supply to the brain, either due to a blockage (ischaemic stroke) or a rupture of a blood vessel (haemorrhagic stroke) (Feigin et al., 2019). Ischaemic strokes account for approximately 85% of all cases and haemorrhagic strokes for 15% (Feigin et al., 2019).

In 2019, there were approximately 12.2 million new stroke cases and over 101 million stroke survivors globally (Feigin et al., 2021). Furthermore, recent estimates suggest that one in four adults over 25 is at risk of experiencing a stroke during their lifetime (Feigin et al., 2019). Although advancements in acute stroke care have improved survival rates, the global burden of stroke is projected to rise further due to the ageing populations and the increasing prevalence of risk factors such as hypertension, diabetes, and sedentary lifestyles (Feigin et al., 2019; Cieza et al., 2020).

Stroke is also one of the main causes of long-term disability. Approximately 70–80% of stroke survivors experience upper-limb impairments (Nakayama et al., 1994; Lawrence et al., 2001), often leading to significant functional limitations that impact activities of daily living (ADLs) and overall quality of life. This creates a substantial economic burden: in the United Kingdom alone, the total societal cost of stroke was estimated at £26 billion per year (Patel et al., 2020). Within this cost, £15.6 billion was attributed to informal care and £1.6 billion to lost productivity, primarily due to stroke survivors' reduced ability to return to work, and premature mortality (Patel et al., 2020). Indeed, up to 50% of stroke survivors need long-term support for basic activities such as dressing, eating, or personal hygiene (Royal College of Physicians, 2015; Cieza et al., 2020). This places a considerable strain on healthcare systems worldwide and highlights the critical need for effective rehabilitation strategies to enhance recovery and promote independence.

2.1.1 Neurophysiological Mechanisms of Upper-Limb Impairments

Brain lesions and sensorimotor deficits

The severity and nature of motor and sensory impairments after stroke are highly dependent on the location, size, and extent of the lesion (Bentley et al., 2014; Chen et al., 2000). After a stroke, the descending pathways responsible for the initiation and modulation of voluntary movement may be disrupted, resulting in motor deficits such as weakness, spasticity, and impaired coordination (Balasubramanian, 2015; Raghavan, 2015). Sensory pathways are also often disrupted, particularly those responsible for proprioceptive and somatosensory feedback, which prevent individuals from perceiving their joints' and limbs' position and movement, hence significantly affecting their motor control (Connell et al., 2008).

Common upper-limb deficits after stroke

Upper-limb impairments after stroke are diverse and depend on the patient and the lesion. However, they often share common features that reflect the underlying neurological disruption. Weakness, or paresis, is a common motor deficit and is characterised by reduced motor drive, voluntary muscle activation and strength (Bourbonnais et al., 1989; Gray et al., 2012). Muscle weakness can affect both the proximal (shoulder, elbow) and distal (wrist, fingers) segments of the upper-limb, although distal recovery may be affected by the proximal arm capacity in the acute phase of stroke, where early shoulder shrug abilities can predict dexterity and hand function months after stroke (Katrak et al., 1998; Nijland et al., 2010; Houwink et al., 2013)

Spasticity is another type of upper-limb impairment after stroke and is defined as a velocity-dependent increase in muscle tone (Lance, 1980). It is commonly linked to the hyperexcitability of the stretch reflex pathways and often leads to high tone, abnormal postures, and difficulty in executing smooth voluntary movements (Pandyan et al., 2005; Li, 2015).

Alongside weakness and spasticity, abnormal muscle synergies can also develop. They are typically characterised by involuntary coactivation of muscle groups, or the stereotyped muscle activation pattern of shoulder adduction, internal rotation, elbow, wrist, and finger flexion (Canning et al., 2000; Li, 2015). This can impair the ability to perform isolated joint movements, essential for performing functional tasks. This can also be associated with impaired motor coordination and dexterity, which can hinder the execution of precise, goal-directed movements (Canning et al., 2000). Together, these motor deficits significantly reduce stroke survivors' abilities to perform ADLs independently.

Sensorimotor integration deficits

Efficient motor control relies on intact motor pathways as well as on the seamless integration of sensory feedback into movement planning and execution. This somatosensory processing and sensorimotor integration are often impaired after stroke and can substantially contribute to patients' difficulty in executing coordinated movements (Carey et al., 2018).

The lack of proprioceptive and tactile information can impair a patient's ability to accurately perceive limb position, movement trajectories, and contact forces, which may result in poorly controlled actions (Rand et al., 1999; Findlater et al., 2017). This can alter sensorimotor feedback loops, making it more difficult for stroke survivors to perform fine error detection and correction.

In addition, stroke survivors may experience impairments in spatial attention and sensory integration, such as reduced awareness of the affected side. This can be linked to spatial neglect, where patients fail to attend to or acknowledge stimuli on the impaired side, and is not necessarily associated with primary sensory or motor deficits (Ting et al., 2011; Gammeri et al., 2020).

Importantly, since somatosensory feedback is critical for updating internal models during motor learning (Vidoni et al., 2010), these impairments may be associated with reduced function and slower recovery trajectories after stroke (Connell et al., 2008; Kessner, 2016; Gammeri et al., 2020).

Cognitive and psychological consequences of stroke

In addition to sensorimotor impairments, stroke can frequently affect individuals' cognitive and psychological functions. Cognitive deficits, including impairments in attention, memory, executive function, and visuospatial abilities, are observed in up to 50% of stroke survivors (Barker-Collo et al., 2006; Lo et al., 2019). These impairments can limit a patient's capacity to engage with rehabilitation, follow instructions, and maintain motivation over time.

Post-stroke fatigue is another common consequence of stroke, with approximately 23–75% of stroke survivors affected (Choi-Kwon et al., 2011). It can severely restrict participation in therapy sessions, essential for improving outcomes.

Furthermore, decreased motivation and depressive symptoms are often present, with approximately one third of patients experiencing clinical depression (Robinson et al., 2016). These psychological factors can be associated with lower quality of life and slower recovery (Choi-Kwon et al., 2011; Robinson et al., 2016).

Although cognitive and psychological impairments can strongly influence recovery trajectories, the restoration of sensorimotor function after stroke ultimately depends on biological and activity-driven processes of neuroplasticity.

2.1.2 Recovery mechanisms after stroke

Spontaneous recovery and neuroplasticity

Despite the severity of initial impairments, some degree of spontaneous recovery typically happens in the weeks and months following stroke. Early cellular and molecular processes occur post-stroke, which favour axonal sprouting and neuronal generation (Carmichael, 2006; Nudo, 2006). These mechanisms can induce cortical reorganisation, which can in turn contribute to functional improvements (Byrnes et al., 2001). This spontaneous recovery tends to be most prominent within the first three to six months post-stroke, a period considered a critical window of heightened plasticity (Dimyan et al., 2011; Dromerick et al., 2021; Krakauer et al., 2012). During this time, the brain shows increased responsiveness to behavioural interventions, and rehabilitation can be particularly effective in driving functional gains (Maulden et al., 2005; Coleman et al., 2017).

While spontaneous mechanisms can lead to improvements, particularly in gross motor functions, they are often insufficient to recover complex skills. Additionally, although traditional clinical reasoning assumes that upper-limb recovery post-stroke follows a proximal to distal progression, this view has been challenged by both acute and chronic stroke studies. Early reports suggested that proximal function returns more readily (Bard et al., 1965; Twitchell, 1951), and some studies in chronic stroke individuals observed greater weakness in distal joints (Colebatch et al., 1989). However, more recent work has shown no consistent segmental pattern in stroke individuals in the acute and chronic phases, and that both proximal and distal joint impairments could contribute to reduced hand function and hence independence in performing ADLs (Beebe et al., 2008; Lang et al., 2007). This indicates the need for targeted training during the spontaneous recovery phase for multiple joints through the upper-extremity, to enhance plasticity in functionally meaningful directions (Hara, 2015).

Critical Periods for Rehabilitation

Interventions initiated early after stroke could enhance the effects of motor training on motor recovery, and may be more effective than those started later due to the heightened plasticity window of spontaneous recovery (Krakauer, 2020; Zeiler et al., 2013). However, the implementation of such experimental interventions in patients early post-stroke may be limited by several barriers, such as post-stroke fatigue, affecting up to 75% of post-stroke patients (Choi-Kwon et al., 2011), the presence of cognitive impairments, and overall reduced motivation and engagement. Moreover, in the early phase post-stroke, patients may be medically unstable and not able to sustain additional rehabilitation sessions on top of their usual treatment.

While it is known that starting motor rehabilitation early on can lead to better outcomes for stroke patients' recovery (Horn et al., 2005), very few motor rehabilitation trials are initiated in the

early post-stroke phase (Stinear et al., 2013). In fact, less than 12% of all RCTs targeting motor rehabilitation are initiated within 30 days post-stroke, and most interventions are pharmacological or variations of conventional therapy (Stinear et al., 2013), while only a few of these are trialling technology-based approaches. According to Stinear and colleagues, this discrepancy reflects the practical and clinical challenges of running early-phase rehabilitation studies: patients are often medically unstable, experience pronounced fatigue, and may be cognitively or physically unable to participate in structured motor training (Stinear et al., 2013). Moreover, implementing such protocols requires close collaboration with the acute care team, who are typically under high workload pressure and whose primary focus is often on medical stabilisation rather than rehabilitation research. For technology-assisted rehabilitation to be feasible in this setting, engineers and researchers must be embedded within the clinical environment. Finally, early post-stroke studies face the methodological difficulty of disentangling spontaneous neurological recovery from the effects of the intervention, complicating the interpretation of outcomes and limiting the conclusions that can be drawn about treatment efficacy. Despite the challenges, conducting motor rehabilitation trials in the early post-stroke phase remains essential, as this period may offer the greatest opportunity to influence recovery outcomes. Identifying effective therapies during this window could help accelerate functional gains, reduce long-term disability, and guide clinical practice towards evidence-based early rehabilitation strategies (Stinear et al., 2013).

Activity-Dependent Plasticity

Activity-dependent plasticity refers to the principle that specific patterns of activity can drive changes in neural connectivity, where synaptic efficacy can increase with repeated and persistent stimulation of a presynaptic cell to a postsynaptic cell, according to Hebbian theory (Hebb, 2005). This implies that repetitive, goal-directed, and feedback-rich practice can induce synaptic strengthening and cortical reorganisation, which are essential for functional recovery after stroke (Nudo, 2006; Murphy et al., 2009).

Related key principles underlying activity-dependent plasticity include “use it or lose it” (Hubel et al., 1965) which indicates that sensorimotor functions in the affected limbs could be further degraded if not used (Kleim et al., 2008). On the other hand, continuous movement practice could enhance function according to the principle “use it and improve it” (Kleim et al., 2008). Rehabilitation interventions that promote repetitive task practice with active engagement and that provide meaningful task-related feedback could be more effective in stimulating beneficial plastic changes (Lang et al., 2009; Blank et al., 2014).



Figure 2.1: Subacute stroke therapy at Charing Cross Hospital London. **A.** Physiotherapists with stroke patients practising walking. **B.** Occupational therapist with a stroke patient practising making tea in a kitchen.

2.2 Neurorehabilitation principles

Conventional upper-limb rehabilitation after stroke typically consists of one-on-one sessions with a physiotherapist or an occupational therapist, aiming at restoring motor function and promoting independence in daily activities through structured exercise-based interventions. This approach emphasises repetitive practice of functional movements, range-of-motion exercises, strengthening routines, and task-specific training, all tailored to the individual's needs and abilities. The underlying principles of neurorehabilitation are outlined in the following sections.

2.2.1 Motor learning in stroke rehabilitation

Motor learning refers to the process through which individuals acquire or modify movement skills through practice and experience (Schmidt et al., 2011), which may occur through the adaptation of an individual's internal dynamics model (Burdet et al., 2013). It is a key aspect of the motor rehabilitation process, as it aims to exploit these learning principles to drive functional improvement post-stroke, in addition to the spontaneous recovery mechanisms (Kleim et al., 2008; Winstein et al., 2014).

Several rehabilitation principles have been identified as key to promoting motor learning (Burdet et al., 2013; Winstein et al., 2014; Winstein et al., 2016), including: active participation, meaningful task-specific training towards patients' goals, high repetition and intensity, early intervention after stroke, variation in tasks to encourage generalisation, and the provision of feedback to retrain physiological movement patterns. Repetition is essential for reinforcing neural circuits through use-dependent plasticity, while task specificity ensures that training is relevant to everyday activities. Additionally, introducing variability in practice helps promote generalisation of skills and prevents overfitting to specific tasks. Feedback, whether intrinsic or extrinsic, plays a critical role in guiding movement correction and enhancing engagement. Training exercises that are actively engaging and

progressively with frequent adaptations to patients' individual capabilities can also support functional improvements.

2.2.2 Dose-Response in Neurorehabilitation

There is growing evidence supporting a dose-response relationship in stroke rehabilitation, where higher doses of training, in terms of intensity, frequency, and duration, are associated with better outcomes (Lang et al., 2015; Kwakkel et al., 2004; Ballester et al., 2022; Veerbeek et al., 2014; Clark et al., 2021). This higher-intensity training may indeed further reinforce the neural pathways responsible for the practised movements and enhance functional improvement, particularly when coupled with voluntary effort (Kleim et al., 2008). However, recent systematic evidence indicates that a small increase in time spent in rehabilitation yields little to no improvement in ADLs and upper-limb function, and that benefits may occur only when the total amount of therapy exceeds a certain threshold (approximately 1000 minutes), although the optimal therapy intensity and duration remain unclear (Kwakkel et al., 2004; Clark et al., 2021). Moreover, unlike pharmacological treatments, where dose, mechanism of action, and therapeutic window are well defined, rehabilitation dosing remains largely empirical and lacks standardised approach (Lang et al., 2015).

However, this must be balanced against fatigue and individual tolerance, especially in the subacute phase, where higher dose may not always be beneficial (Dromerick et al., 2009; Hunter et al., 2011) or feasible in real-world settings (Hunter et al., 2011).

Despite strong evidence for the importance of training dose, many patients receive relatively low-intensity therapy during typical clinical care, which may not be sufficient to enhance neural reorganisation and promote functional recovery post-stroke (Lang et al., 2009). This also indicates the need for scalable and feasible strategies and technologies that can increase training volume and intensity, and contribute to sustainable long-term care while reducing the socioeconomic impact of stroke.

2.2.3 Patient Engagement and Motivation

Patient engagement is a critical determinant of rehabilitation effectiveness. Engaged patients are more likely to participate actively in training, which supports learning and neuroplastic change (Blank et al., 2014; Winstein et al., 2016).

Motivation can be influenced by many factors, including task relevance, feedback, goal-setting, perceived self-efficacy, cognitive dysfunctions, hospital environment, and social support networks (Przewoźnik et al., 2015; Maclean et al., 2000a; Maclean et al., 2000b). Stroke survivors with higher levels of motivation tend to demonstrate better adherence and outcomes. Conversely, apathy, depression, and fatigue can negatively impact engagement and limit recovery potential (Choi-Kwon et al., 2011; Przewoźnik et al., 2015; Robinson et al., 2016).



Figure 2.2: Physiotherapist performing the Fugl-Meyer Upper-Extremity Assessment (FM-UE) with a stroke patient. **A.** Assessing patient's ability to perform shoulder flexion from 0° to 90° as part of the volitional movement mixing synergies test in the FM-UE (section A-II). **B.** Assessing patient's ability to perform shoulder flexion from 90° to 180° as part of the volitional movement with little or no synergy test in the FM-UE (section A-III). **C.** Assessing patient's ability to perform thumb adduction grasp as part of the hand test in the FM-UE (section C-b). **D.** Assessing patient's ability to perform cylinder grasp as part of the hand test in the FM-UE (section C-d).

One important factor for sustaining engagement in rehabilitation is maintaining an optimal level of task difficulty. Rehabilitation tasks that are too easy can become boring and demotivating, while those that are too difficult can cause frustration or disengagement. The psychological concept of *flow* describes a state in which individuals are fully immersed and motivated during task execution due to a well-balanced challenge-to-skill ratio (Csikszentmihalyi, 1990), which in turn can favour motor learning. In stroke rehabilitation, this concept is closely related to the challenge point theory (CPT) proposed by Guadagnoli and Lee (Guadagnoli et al., 2004), which defines optimal learning conditions in relation to the task difficulty, the learner's experience level, and the amount of available information (e.g., feedback). Learning is maximised when the functional difficulty matches the individual's capability, ensuring the challenge remains neither too high nor too low. A novice learner may benefit from simple tasks accompanied by high informational support, while more experienced individuals require increased task complexity and reduced guidance to continue progressing. This approach has been used in stroke rehabilitation, where, for example, the assistance parameters are updated based on the performance of the patient in previous trials (Krebs et al., 2003; Kahn et al., 2004).

Furthermore, assist-as-needed approaches in stroke rehabilitation have been widely used to increase patient involvement in the task, where the assistance only starts to kick in when the patient is unable to continue performing the movement until completion (Emken et al., 2005; Marchal-Crespo et al., 2009). Rehabilitation studies have shown that using such approaches instead of rigid guidance can be beneficial for patients' sensorimotor recovery (Krebs et al., 2003; Riener et al., 2010).



Figure 2.3: Physiotherapist performing the Action Research Arm Test (ARAT) with a stroke patient. **A.** Assessing patient's ability to grasp objects, here a 10 cm cube (top), and place them on top of a shelf (bottom). **B.** Assessing patient's ability to grip (top), here pouring water from glass to glass (bottom). **C.** Assessing patient's ability to pinch objects, here using the thumb and index to pinch a 6 mm ball bearing (top) and a 1.5 cm marble (bottom), and place them on top of a shelf.

2.2.4 Assessment in Stroke Rehabilitation

Effective assessment is essential for tracking patients' evolving capabilities throughout their recovery, as well as for tailoring interventions and evaluating treatment efficacy (Kwakkel, 2019). Various clinical scales have been developed to do so, focusing on assessing patients' motor recovery, e.g., Fugl-Meyer Assessment (FM-UE) (Fig. 2.2) (Duncan et al., 1983), or on the functional performance of their upper-extremity and their dexterity, with assessments using standardised objects mimicking those of daily living, e.g., the Action Research Arm Test (ARAT) (Fig. 2.3) (Lyle, 1981) and the Box and Block Test (BBT) (Mathiowetz et al., 1985). Other assessments, such as the Barthel Index (Mahoney et al., 1965), and the Functional Independence Measure (FIM) (Dodds et al., 1993), focus on evaluating functional independence in daily activities and disability level, through patients' self-report or clinician observation.

Although clinical scores provide valuable information on function and are easy to administer, therefore suitable for clinical environments, they are often subjective (Lincoln et al., 1991), have

limited reliability (Connell et al., 2012), and lack precision (Hillier et al., 2015). They may also be prone to floor and ceiling effects (Lincoln et al., 1991), making it difficult to detect small changes in performance in severely impaired individuals. As a complement, objective measures such as kinematic analysis, force production, and electromyographic (EMG) recordings could help identify earlier changes in motor strategies associated with goal-oriented tasks and distinguish behavioural restitution from compensation by objectively capturing quality of movement (De Los Reyes-Guzmán et al., 2014; Schwarz et al., 2019; Kwakkel, 2019).

Recent expert recommendations have highlighted the importance of integrating both clinical and quantitative assessments to comprehensively characterise upper-limb recovery after stroke. In particular, Kwakkel et al. (2019) (Kwakkel, 2019) and the CAULIN consensus (Prange-Lasonder et al., 2021) emphasise that combining validated clinical measures such as the FM-UE and ARAT with objective kinematic and sensor-based metrics could provide a better understanding of recovery trajectories and support evidence-based decision-making in neurorehabilitation.

2.2.5 Quality of evidence in neurorehabilitation research

While the literature on stroke rehabilitation provides valuable insights into motor learning, dose-response relationships, and technology-aided interventions, it is important to recognise that the overall quality of evidence in this field remains variable. According to the established hierarchy of evidence, systematic reviews and meta-analyses of randomised controlled trials (RCTs) represent the highest level of methodological rigour, followed by individual RCTs, cohort studies, and case reports (Devereaux et al., 2003). However, the inherent complexity of stroke-related disabilities, together with heterogeneous patient populations, varied intervention protocols, and the difficulty of recruiting large samples, often limits the feasibility of large, high-quality RCTs (Stinear et al., 2020). Consequently, many studies in neurorehabilitation are small-scale or exploratory, providing low- to moderate-certainty evidence (Winstein et al., 2016). This highlights the need for cautious interpretation of existing findings and continued efforts to strengthen the evidence base through multicentre collaborations, standardised outcome measures, and transparent reporting practices (Stinear et al., 2020).

2.3 Technology-Aided Rehabilitation

2.3.1 Robotic Systems for Upper-Limb Stroke Rehabilitation

Robotic technologies have become increasingly prominent in stroke upper-limb rehabilitation over the past decades, where various mechanical systems and controllers have been developed (Marchal-Crespo et al., 2009; Maciejasz et al., 2014; Basteris et al., 2014).

These systems can be grouped into four broad design categories. First, end-effector devices interact with the user at a single distal point, typically the hand or wrist, and guide the limb through spatial trajectories without directly controlling individual joints (Fig. 2.4 A). Second, exoskeleton robots comprise joint-aligned mechanical frames that attach along the arm to provide joint-specific actuation and support (Fig. 2.4 B). Third, soft exosuits and compliant robotic interfaces have emerged as lightweight alternatives, using textiles or flexible actuators to assist movement while conforming to the user's body (Fig. 2.4 C). Robotic rehabilitation devices are typically equipped with embedded sensors, such as encoders or force transducers, to monitor kinematics and dynamics, and with actuators to produce controlled movement. These devices typically aim to support the affected upper limb during pre-defined exercises, fully guiding the movement, providing gravitational compensation, or introducing various levels of assistance/resistance based on patients' abilities, which can promote active engagement.

A key advantage of robotic systems is their capacity to deliver high-repetition, high-intensity training (Kwakkel et al., 2008). This is particularly relevant in stroke rehabilitation, where neuroplastic changes depend on the volume and specificity of practice as mentioned previously (Kleim et al., 2008). Systematic reviews with meta-analysis have shown that robot-assisted arm training can lead to small but statistically significant improvements in upper-limb function and muscle strength (Mehrholz et al., 2018; Veerbeek et al., 2017; Bertani et al., 2017). These benefits are typically seen across acute, subacute, and chronic stroke stages, but effect sizes are slightly higher in early recovery (Mehrholz et al., 2018). However, motor improvements do not consistently generalise to real-world functional use, especially for more mildly impaired patients (Veerbeek et al., 2017); and severely impaired individuals, particularly those with limited voluntary movement, seem to benefit most from robotic therapy. This suggests that personalisation of robot-based training, where task difficulty and assistance level are tailored to each patient's abilities and progress, appears crucial for meaningful recovery outcomes. This is confirmed by a multi-centre randomised controlled trial (RCT) which showed that applying the same robot-assisted training programme to a heterogeneous patient group yields limited results in motor function improvements, when compared to usual care (Rodgers et al., 2019). However, when incorporated into a personalised rehabilitation programme, robotic training can contribute to increased motor and functional outcomes (Ward et al., 2019).



Figure 2.4: Example of robotic devices for upper-limb rehabilitation. **A.** End-effector device (MIT-Manus) (Krebs et al., 2004). **B.** Exoskeleton device (ArmeoSpring, Hocoma) **C.** Soft wearable exosuit (Lotti et al., 2020).

While many robotic systems target the shoulder and elbow due to their large range of motion and contribution to gross motor tasks, distal joints such as the wrist and fingers are often underrepresented in rehabilitation protocols (Squeri et al., 2014; Mazzoleni et al., 2018). Moreover, robot-assisted shoulder and elbow movements, such as during repetitive reaching tasks, result in statistically significant improvements at the trained joints, but not necessarily gains at the wrist or fingers, which are not directly exercised (Krebs et al., 2007; Mazzoleni et al., 2013). This suggests that motor recovery achieved through proximal training alone may not generalise distally, limiting its translation to functional activities that require coordinated hand use. In contrast, more recent work has shown that wrist-focused rehabilitation may induce improvements that extend beyond the trained joint, specifically leading to gains in motor control of the proximal parts of the upper-limb, as assessed by the FM-UE of the shoulder and elbow scores (Squeri et al., 2014; Takahashi et al., 2008; Krebs et al., 2007; Lambercy et al., 2011). Furthermore, when comparing improvements after shoulder-elbow training and wrist-only training after stroke, Mazzoleni and colleagues observed similar improvements on the proximal segments of the arm, reinforcing the potential of distal-focused therapy to drive more global upper-limb recovery (Mazzoleni et al., 2013; Mazzoleni et al., 2018). These findings are particularly important given that impairments at the wrist and fingers can greatly limit hand opening, object manipulation, and overall independence in daily life (Lambercy et al., 2007; Squeri et al., 2014).

While robotic rehabilitation often targets specific joints or motions, an open question remains whether training multiple joints simultaneously provides greater functional benefit than training joints in isolation. Milot and colleagues conducted a crossover trial in chronic stroke patients comparing single-joint versus multi-joint robotic training using a 6-DOF exoskeleton (Milot et al., 2013). Both

approaches led to clinically significant improvements in upper-limb outcomes, but no significant differences were found between the two training modes across primary and secondary outcome measures, including the BBT and FM-UE (Milot et al., 2013). Similarly, Fluet et al. compared integrated training of the hand and arm to isolated training of each joint using a haptically rendered virtual environment. While both training types improved performance, differences in retention and movement kinematics suggested that multi-joint training may offer more durable changes in some domains, though overall functional gains were comparable (Fluet et al., 2014). These results challenge the conventional assumption that complex, coordinated task training is superior. Instead, a flexible approach focusing on simpler movements and segment-specific training may result in similar recovery outcomes. This type of intervention may also be better suited to the clinical environment, where space, therapist time, and patient endurance are often limited. Single-joint training could reduce set-up and calibration times as well as patients' physical and cognitive demands, allowing rehabilitation to begin earlier post-stroke, hence leveraging the heightened plasticity of the early recovery window more effectively. Their relative simplicity makes these systems more suitable for financially constrained healthcare settings and easier and safer for both patients and therapists to use.

In summary, robotic systems can offer reproducible and intensive upper-limb training with quantifiable movement support and monitoring. Their versatility across impairment levels and compatibility with adaptive control strategies make them a useful tool in post-stroke motor rehabilitation. While robotic devices primarily deliver mechanical assistance, other technologies like functional electrical stimulation (FES) engage the neuromuscular system through the electrical activation of muscles, which can further support recovery.

2.3.2 Functional electrical stimulation (FES) for upper-limb rehabilitation

Electrical stimulation is a technology that delivers controlled electrical currents to peripheral nerves to evoke muscle contractions. In stroke rehabilitation, it is commonly used to restore upper-limb function by assisting voluntary movements such as grasping and walking (Lynch et al., 2008). These stimulation-induced contractions are typically achieved through surface electrodes and aim to enhance both task performance and neural recovery by engaging motor and sensory pathways, promoting neuroplasticity through orthodromic and antidromic signalling (Lynch et al., 2008). It may be applied passively or in conjunction with patient effort, often during repetitive and task-specific training to encourage motor relearning, where it is referred to as functional electrical stimulation (FES).

Numerous studies have demonstrated the efficacy of FES in improving upper-limb motor function after stroke. Systematic reviews with meta-analysis have shown that FES-based therapy leads to moderate improvements in motor performance compared to placebo or conventional therapy (Howlett

Table 2.1: Example of sensing, control inputs, and common types of controllers used in robotic, FES, and hybrid systems for upper-limb rehabilitation.

System Type	Sensing Modalities	Control Inputs	Actuation Type	Common Control Strategies
Robotic	Kinematics, torque, EMG	❖ Kinematic error ❖ Motor commands: torque, EMG-based (threshold, proportional)	Motors (actuators)	❖ Position control ❖ Impedance control ❖ Assist-as-needed ❖ EMG-modulated
FES	Kinematics, torque, EMG	❖ Kinematic error ❖ Motor commands: EMG-based (threshold, proportional) ❖ Fatigue: M-wave, FES-induced torque	Electrical stimulation	❖ EMG-triggered ❖ EMG-modulated ❖ Open-loop control ❖ Impedance control
Hybrid	Kinematics, torque, EMG	❖ Kinematic error ❖ Motor commands: torque, EMG-based ❖ Fatigue	Motors + stimulation	❖ Cooperative control ❖ Model predictive control ❖ Adaptive control ❖ Fatigue-compensation

et al., 2015; Eraifej et al., 2017). Specifically, Howlett and colleagues found that FES interventions after stroke led to statistically significant improvements in upper-limb activity (Howlett et al., 2015). However, the effects of FES on improvements in ADLs may be more beneficial when the intervention is applied within two months post-stroke (Eraifej et al., 2017). Similarly, when compared to a control group, motor recovery outcomes with FES-training led to significant and clinically important differences when initiated within two months post-stroke (Eraifej et al., 2017). FES is also effective in patients with severe hemiparesis who exhibit minimal or no voluntary movement. Alon et al. (Alon et al., 2008) showed that subacute individuals with severe upper-limb impairment achieved significant gains in the recovery of motor control (FM-UE score), after FES-assisted exercise compared to a group training without FES, but these are not necessarily transferred to functional improvements in severe patients (Alon et al., 2008; Shimodozono et al., 2014). Moreover, patients with severe hemiparesis may require longer training time to recover functional impairments in addition to motor control (Alon et al., 2008; Mangold et al., 2009). Indeed, another study investigating a more intensive FES programme (5 days a week, 12-16 weeks) for acute severe hemiplegic patients showed positive outcomes in both motor control recovery and ADLs compared to conventional therapy (Thrasher et al., 2008).

Additionally, national and international clinical guidelines increasingly support the use of FES for upper-limb stroke rehabilitation, particularly for reducing weakness and improving function (Salbach et al., 2022; Intercollegiate Stroke Working Party, 2023; Veterans Affairs/Department of Defense, 2024; Stroke Foundation, 2024). More specifically, the UK National Institute for Health and Care Excellence (NICE) (Intercollegiate Stroke Working Party, 2023), the Canadian Stroke Best Practice Guidelines (Salbach et al., 2022) and the Dutch KNGF guidelines (Royal Dutch Society for Physical Therapy, 2014) recommend its use in forearm muscles, to improve wrist and finger extension movements and increase strength. These recommendations are backed by clinical trial data showing meaningful improvements when FES is applied early after stroke and within functionally relevant training paradigms.

Despite its benefits, FES therapy is associated with several challenges. One major limitation is

muscle fatigue, which can arise rapidly due to the non-physiological recruitment of motor units during stimulation, unlike the naturally varying recruitment pattern seen in voluntary movements (Gorgey et al., 2009; Maffiuletti, 2010; Bickel et al., 2011; Miura et al., 2016; Zhang et al., 2011). Indeed, there are different types of motor units, where some are slow-twitch and resistant to fatigue, while others are fast-twitch and fast-fatigable (Merletti et al., 2004). For sustained small contraction levels, the nervous system tends to first activate slow-type motor units. However, during FES all types of motor units are likely to be activated, including those which are fast-fatigable (Lynch et al., 2008). This leads to increased fatigue at a similar contraction level compared to voluntarily-sustained contraction.

This limitation is recognised and has been well-studied in assisting devices and athletic contexts, especially for individuals with spinal cord injury (Ibitoye et al., 2016), such as during the Cybathlon FES cycling race (Riener et al., 2014). However, there is a lack of evidence on whether and how this mechanism could arise during stroke rehabilitation. Although in these contexts, FES is often applied intermittently and in conjunction with voluntary effort, which can help reduce fatigue and improve comfort (Eraifej et al., 2017), studying the effect of FES-induced contractions in such scenarios could help confirm whether these are sufficient for preventing the rise of fatigue. Indeed, the underlying neural conditions after stroke and a spinal cord injury differ markedly. In individuals with spinal cord injury, motor pathways are completely disrupted, preventing voluntary neural signals from reaching the muscles and resulting in full reliance on externally induced contractions, where fatigue may develop more rapidly. In contrast, post-stroke patients typically retain partially intact descending pathways and can still send motor commands (although weak) to contract muscles, where the contraction can be increased using FES. Additionally, discomfort and skin irritation from surface stimulation can limit its use, although this can sometimes be mitigated by using larger electrodes to distribute current over a larger area.

To mitigate these issues, various control algorithms have been developed for adjusting stimulation parameters and electrode activation to mimic natural recruitment. For instance, rotating pulses between multiple stimulating electrodes has been tested as a way to mitigate fatigue and has shown some positive results (Maffiuletti et al., 2014; Wiest et al., 2019; Laubacher et al., 2019; Barss et al., 2021), although it is sometimes associated with increased discomfort, likely due to the smaller electrodes inducing a larger current density (Wiest et al., 2019; Barss et al., 2021).

In parallel, research has focused on detecting muscle fatigue through physiological signals such as EMG and torque outputs. Frequency-domain features such as mean or median frequency, have been used to assess muscle fatigue (Stulen et al., 1981; Arendt-Nielsen et al., 1989). On the other hand, the muscle's response to electrical stimulation can be used to estimate muscle fatigue. This so-called M-wave represents the total electrical activity of all motor units depolarised within the stimulation electrodes' range (Rodriguez-Falces et al., 2018), where its amplitude, duration, and area can be used as fatigue measures (Chesler et al., 1997; Tepavac et al., 1997; Badier et al., 1999; Rodriguez-Falces

et al., 2018). However, the literature presents discrepancies regarding which M-wave parameters best quantify muscle fatigue, as the underlying mechanisms are not fully understood. Some studies report a decrease in M-wave peak-to-peak amplitude with fatigue (Tepavac et al., 1997; Chesler et al., 1997; Mizrahi et al., 1994), and the extent of this change may be influenced by stimulation parameters and muscle type (Badier et al., 1999; Vromans et al., 2018). Conversely, other research highlights an increase in M-wave duration (or a decrease in frequency) or area with fatigue (Dimitrova et al., 2005; Chesler et al., 1997; Heasman et al., 2000; Hayashibe et al., 2011). In light of these inconsistent findings, some researchers have focused on the biphasic characteristic of the M-wave, extracting parameters from each of the two phases separately. It is believed that these phases are differently affected by the physiological processes of fatigue (Lateva et al., 1996; Heasman et al., 2000; Rodriguez-Falces et al., 2017; Rodriguez-Falces et al., 2018). Studies suggest that the second phase of the M-wave may be influenced by changes in muscle architecture, such as shortening muscle length or relative positional changes between the muscle and recording electrodes, making it less suitable for fatigue analysis (Lateva et al., 1996; Rodriguez-Falces et al., 2018). However, recent findings indicate that the first phase of the M-wave may remain unaffected by such structural changes and may reflect more accurately fatigue-related mechanisms (Rodriguez-Falces et al., 2017). Thus, separate analysis of the two M-wave phases is recommended (Rodriguez-Falces et al., 2018).

These features are increasingly being incorporated into closed-loop control algorithms to modulate FES intensity or timing based on real-time feedback. For instance, Li and colleagues used a muscle model to characterise the response of stimulation parameters to the evoked muscle activity (Li et al., 2018). This closed-loop FES control system could allow the tracking of desired muscle activation patterns of spinal cord injury patients, while limiting fatigue (Li et al., 2018). Similarly, evoked-EMG was also used to predict the torque output even in the presence of muscle fatigue, and could be implemented in a closed-loop controller (Qiu et al., 2016). The change in FES-induced torque was also used as a metric to trigger a change in the stimulation frequency, hence maximising the generated torque output (Dudley-Javoroski et al., 2011).

Other control algorithms utilising user intention or movement as an input are also investigated, where stimulation is triggered or modulated based on EMG activity, torque, or movement performance so that patient engagement can be enhanced. EMG-triggered FES protocols typically deliver stimulation when a predefined threshold of voluntary EMG activity is detected in the target muscle, thus reinforcing patients' own effort and potentially facilitating learning and recovery (Kroon et al., 2005; Bolton et al., 2004). EMG-modulated systems go one step further by continuously adjusting the intensity of stimulation in real time, proportionally to the amplitude of voluntary muscle activity (Fujiwara et al., 2009; Shindo et al., 2011; Ambrosini et al., 2014). These strategies help maintain synchrony between voluntary effort and the FES-induced contraction, potentially enhancing motor learning and user engagement (Ambrosini et al., 2014). Shindo and colleagues compared subacute stroke patients

wearing a splint and an EMG-controlled FES system for finger extension with a control group wearing a splint alone, both groups wearing the systems daily but without specific additional therapy (Shindo et al., 2011). They found that the group with the EMG-controlled FES system showed greater gains in distal motor recovery and in upper-limb functions (Shindo et al., 2011). Similar results were obtained in chronic patients wearing the EMG-controlled FES system and the splint daily (Fujiwara et al., 2009). Furthermore, more subacute stroke patients receiving task-oriented therapy with assistance of EMG-controlled FES compared to the conventional therapy control group improved in terms of upper-limb impairment and functions, although the expected effect size was not reached (Jonsdottir et al., 2017).

Nonetheless, a major challenge in implementing these systems is the electromechanical delay between electrical stimulation and the resulting muscle contraction (e.g. 10140 ms (Lynch et al., 2008; Downey et al., 2017). This delay complicates the synchronisation of FES with robotic actuators or voluntary movements and can lead to suboptimal assistance or unintended counterforces. Studies have shown that when combined with robotic assistance, it can induce higher muscular effort, likely due to misaligned actuation timing (Hu et al., 2011). Predictive models of the muscle response to electrical stimulation have been proposed to compensate for this delay (Riener et al., 1996; Ferrarin et al., 2000; Gollee et al., 2001; Gwo-Ching Chang et al., 1997), and advanced controllers have been developed to align stimulation timing with motion trajectories (del-Ama et al., 2014; Qiu et al., 2016). However, most of these approaches are designed for repetitive, cyclic tasks, do not account for the time-varying nature of electromechanical delay (Downey et al., 2017), and are typically applied to cyclic gait motion or to the tracking of pre-determined trajectories, which can limit their application in dynamic or goal-directed rehabilitation scenarios.

In summary, FES is a flexible and well-supported intervention that can restore upper-limb motor control after stroke, even in severely impaired individuals. Its ability to engage physiological mechanisms of neuroplasticity and its compatibility with other rehabilitation technologies make it a critical tool for maximising recovery, though fatigue and discomfort remain important challenges to address.

2.3.3 Hybrid Robotic and Functional Electrical Stimulation Systems

The individual limitations of robotic and FES-based rehabilitation systems have motivated researchers to explore hybrid approaches that combine both technologies. While FES provides sensory feedback and elicits muscle contraction, robotic systems assist users in performing desired tasks by acting on joint torques, resulting in smooth limb motion (Resquin et al., 2016). Such hybrid systems may be beneficial as they can provide users with a more complete sensorimotor experience, which could enhance therapeutic effects (Lee et al., 2015; Hu et al., 2015), while reducing stimulation amplitude

which may cause fatigue or discomfort over time (Gorgey et al., 2009; Maffiuletti, 2010; Miura et al., 2016; Zhang et al., 2011). Robotic assistance can complement FES by providing the powerful and smooth motion that electrical stimulation alone cannot achieve, while FES contributes to the neuroplastic benefits of muscle activation that passive robotic assistance lacks (Resquin et al., 2016).

A recent systematic review by Höhler et al. (2024) comprehensively evaluated the efficacy of hybrid neuroprostheses for upper limb rehabilitation after stroke, with a meta-analysis of seven RCTs that compared hybrid robot-FES systems to control interventions (Höhler et al., 2024). The meta-analysis demonstrated that hybrid neuroprostheses have a positive effect on upper limb recovery after stroke both in the subacute and chronic stages, with effects persisting at least three months after the intervention.

The collective evidence from these RCTs also indicates that treatment duration can be a critical factor in the effectiveness of hybrid systems (Höhler et al., 2024). Improvements in clinical outcomes of the hybrid intervention compared to the control group (either conventional or robot-only therapy) increase with therapy duration (from 2 weeks for short protocols to 4-9 weeks for longer protocols). The location of robotic assistance (distal versus proximal) seems less important than the combined approach itself, as both configurations demonstrated similar therapeutic benefits. However, systems providing simultaneous hybrid support to both distal and proximal joints consistently induced recovery of both distal and proximal functions immediately after intervention and at 3-month follow-up (Qian et al., 2019). In contrast, devices focusing on distal support initially produced improvements exclusively in proximal functions, with distal improvements becoming apparent only at follow-up assessments (Huang et al., 2020; Hu et al., 2015). This pattern suggests that proximal functions recover first, with distal improvements manifesting after a delay, which may be attributable to proximal compensatory movements during distal limb tasks (Hu et al., 2015). These findings indicate that hybrid devices providing combined distal and proximal support may be particularly effective in counteracting the typically asynchronous recovery pattern of upper limb functions after stroke. Additionally, the method of FES activation (EMG-driven (Hu et al., 2015; Qian et al., 2017; Huang et al., 2020; Ambrosini et al., 2021) versus externally controlled (Miyasaka et al., 2016; Lee et al., 2015; Grigoras et al., 2016)) did not appear to significantly influence outcomes (Höhler et al., 2024). This may also be due to therapists encouraging patients to actively imagine the motion and/or contract their muscles to increase engagement, which may have a similar effect as an EMG-triggered system. However, the heterogeneity in intervention protocols, patient populations, and outcome measures across studies highlights the ongoing need for standardised approaches to optimise hybrid rehabilitation systems (Höhler et al., 2024).

Despite these promising clinical outcomes, current hybrid systems suffer from several limitations that restrict their therapeutic potential. Most previous work on hybrid systems for upper-limb stroke rehabilitation has opted for designs where FES and robotic devices do not directly act on the same

joint motion (Resquin et al., 2016). More specifically, the majority of existing systems rely on FES as the primary means of assistance while using robotic devices only to promote stability and gravitational support (Ambrosini et al., 2017; Alon et al., 2003; Ring et al., 2005; Fujiwara et al., 2009; Barker et al., 2008; Wu et al., 2011; Meadmore et al., 2012; Westerveld et al., 2014; Resquín et al., 2016), or to contribute to different joint movements than those supported by FES (Alon et al., 2003; Ring et al., 2005; Meadmore et al., 2012; Resquín et al., 2016). For instance, the RETRAINER system combines a passive exoskeleton that provides arm weight anti-gravity support with EMG-controlled FES placed on the arm muscles depending on patients' needs (Ambrosini et al., 2017; Ambrosini et al., 2021). Furthermore, many of these hybrid devices do not provide continuous, adaptive assistance as FES is often triggered manually by therapists via button presses (Alon et al., 2003; Ring et al., 2005), which restricts the continuity of movement execution and may diminish patient engagement in the rehabilitation process (Kroon et al., 2005; Rushton, 2003; Kahn et al., 2006; Blank et al., 2014). Other systems rely on electromyographic signals (EMG) to trigger FES assistance (Fujiwara et al., 2009; Barker et al., 2008; Ambrosini et al., 2021), which can be problematic given that EMG signals are often impaired in stroke patients (Roh et al., 2015; Raghavan, 2015; Roh et al., 2013). Using EMG as the sole control input may therefore limit the system's applicability to users with reliable muscle contraction (Resquin et al., 2016).

More recently, researchers have begun developing systems that combine FES and robotic assistance on the same joint motion. These approaches aim to leverage the complementary advantages of both technologies while mitigating their individual limitations (Resquin et al., 2016). However, the technical complexity of coordinating two active devices in a stroke rehabilitation scenario presents significant challenges. The integration requires sophisticated control algorithms to appropriately distribute assistance between the two modalities, manage potential conflicts between robotic and FES-induced forces, and ensure safe operation. Additionally, the non-linear and time-varying nature of FES-induced muscle responses, combined with the need to account for muscle fatigue and individual patient characteristics, makes the development of effective hybrid controllers particularly challenging (Resquin et al., 2016).

Recent research has begun to address these limitations through the development of more sophisticated hybrid control strategies. Advanced controllers using model predictive control have been proposed to optimally distribute actuation between FES and robotic systems (Dunkelberger et al., 2023), while adaptive cooperative control approaches that consider FES-induced muscle fatigue in the control loop have been developed (Burchielli et al., 2022; Bardi et al., 2021; del-Ama et al., 2014). These advanced control strategies show promise for delaying the onset of fatigue (Burchielli et al., 2022; Bardi et al., 2021), and reducing power requirements (Wolf et al., 2017; Bardi et al., 2021; Dunkelberger et al., 2022) compared to FES or robotic assistance alone. However, most of these developments have been tested primarily in unimpaired participants or simulation environments, and focus mainly on assistance rather than rehabilitation (Dunkelberger et al., 2022; Burchielli et al., 2022;

Bardi et al., 2021). Additionally, the challenge of compensating the delay between the stimulation onset and the resulting torque generation has also been tackled in recent works (del-Ama et al., 2014; Qiu et al., 2016), which could lead to better alignment of the motion resulting from the two actuation systems. However, these approaches for delay compensation do not consider the time-varying nature of the electromechanical delay (Downey et al., 2017), and are typically applied to cyclic gait motion or to the tracking of predetermined trajectories, making them less suitable for rehabilitation tasks.

The translation of these advanced controllers to clinical practice faces several challenges. The complexity of parameter identification for patient-specific models, the need for extensive calibration procedures, and the requirement for sophisticated sensing and control hardware, may all limit their immediate applicability to clinical environments. Additionally, ensuring that these advanced systems maintain the principle of promoting patient engagement rather than replacing patient effort remains a critical consideration in their development (Winstein et al., 2018). Indeed, an important distinction in hybrid system design is the difference between assistive and rehabilitative use. In rehabilitation, the goal is not simply to complete the task but to engage the patient in active participation to drive neuroplastic changes. Systems that overly compensate for the user or automate the task may reduce patient effort and limit the therapeutic effect, a phenomenon sometimes described as "slacking" (Kahn et al., 2006; Rushton, 2003; Blank et al., 2014). Currently, most of these advanced systems are designed with the goal of assisting and providing optimal tracking performance in a specific task, e.g., for use at home by individuals with spinal cord injury. These approaches may not be suitable for rehabilitation of stroke patients, where it is crucial for the patient to remain actively involved in the movement, using appropriate levels of assistance, which challenge the patient while ensuring task completion, with the goal of enhancing recovery outcomes. The deployment of hybrid robot-FES systems, sharing the actuation load between the two modalities, while incorporating fatigue and delay compensation mechanisms where required, and specifically designed for stroke rehabilitation is still needed. Maintaining patient engagement while preventing over-assistance and lengthy calibration procedures are key aspects in making these systems suitable for clinical implementation in stroke rehabilitation settings.

Chapter 3

Experimental system and analyses

3.1 Hybrid robot-FES system

3.1.1 Wrist robotic interface

The HRX-1 robot shown in Figure 3.1 is a one-DOF interface for wrist flexion/extension (Human-RobotiX, UK). It is compact and light and can be quickly installed by mounting it to a table with clamps. The hand is attached to an ergonomic handle while the forearm is strapped to an adjustable arm support to ensure joint alignment and comfortable natural movements for various arm and hand sizes. It is actuated by a brushless low-friction motor, which delivers up to 4 Nm of torque and is controlled by the Epos4 70/15 motor controller (Maxon Motors, Switzerland). Torque measurement is provided by the embedded torque sensor (with 0.014 Nm resolution) and the user's wrist angle is recorded using the embedded optical encoder (0.01° resolution). The robot is programmed in Matlab and run through serial communication at a frequency of approximately 100 Hz. Redundant safety measures have been implemented in this device through mechanical, electrical and software limits. A physical safety stop is in place to turn off the power input to the robot.



Figure 3.1: HRX-1 robotic device for wrist flexion/extension, featuring an ergonomic handle and an adjustable forearm support with straps to secure the hand and forearm, in its compact casing.

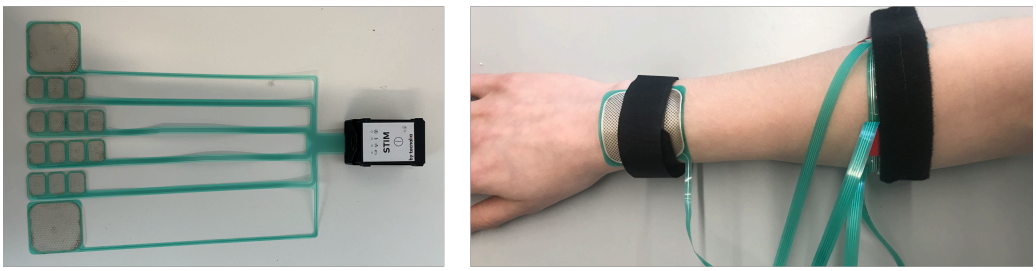


Figure 3.2: FES device with the stimulation module and the 16-electrode array with the anode electrode positioned on the dorsal and ventral side of the wrist near the ulnar head and the cathode array positioned around the arm in line with the belly of the wrist flexor and extensor muscles.

3.1.2 Functional electrical stimulation (FES) device

The FES device shown in Figure 3.2 comprises a stimulation module, a 16-electrode array, and a socket case connected to the multi-field electrode array via pressure connectors (Tecnalia Research & Innovation, Spain). The wireless stimulation module is responsible for generating symmetrical biphasic electrical pulses that will then be transmitted to the skin by the electrodes. A hydrogel layer is placed on the electrodes to improve the conductivity of the array with the skin and additional Velcro straps are positioned around the electrodes to tighten the array around the forearm. The anode electrode is positioned on the dorsal side of the wrist near the ulnar head and the cathode array is positioned around the arm in line with the belly of the wrist flexor and extensor muscles for comfortable and effective stimulation (Fig. 3.2). The frequency of the stimulation is fixed at 35 Hz and the pulse width at 300 μs as these values are used clinically (Kapadia et al., 2013). The amplitude of the stimulation can be varied up from 0.1 - 90 mA (with 0.1 mA resolution). The system is designed to be controlled remotely by Matlab via Bluetooth communication. Redundant safety measures have been implemented in this device through firmware and software limits. A physical safety stop is in place to turn off the power input to the stimulator.

After positioning the electrodes on the wrist flexor and extensor muscles, an FES calibration is performed. Two cathode electrodes within the cathode array are selected to generate the flexion movements and two other cathode electrodes for the extension movements. The electrode location and corresponding maximum stimulation are selected individually for the flexion and extension side, such that the stimulation is comfortable and the generated movement covers as much of the participant's range of motion as possible. The FES amplitude is capped at the maximum comfortable stimulation determined by the user for the flexion and extension movements. The minimum FES amplitude is defined as the participant's sensory threshold through self-report or as the motor threshold (defined as the amplitude at which an average torque of 0.2 Nm is generated during a 3-second stimulation). This is done individually for the flexor stimulation and the extensor stimulation. The torque generated by each of these stimulation amplitudes while the participant is relaxed is then recorded to obtain a mapping between torque and stimulation amplitude for flexion and extension, respectively.



Figure 3.3: Hybrid system combining FES with electrodes placed on the wrist flexor and extensor muscles and the wrist HRX-1 robot providing torque to the wrist. The hybrid robot-FES system is used to assist participants in tracking a randomly moving target on-screen using wrist flexion/extension movements.

3.2 Tracking task

The task used throughout this work is a continuous tracking task, in which individuals track a moving target placed in front of them using wrist flexion/extension movements, while being assisted by a robot or FES as shown in Figure 3.3. This task requires continuous motor control and hand-eye coordination, which are essential in many real-world actions. When robot-FES assistance is applied, multimodal feedback is provided, with visual, proprioceptive, sensory, and muscle stimulations, which can further reinforce motor learning mechanisms (Lang et al., 2009; Blank et al., 2014). Additionally, the dynamic nature of the task enables a high number of repetitions, which are beneficial in rehabilitation post-stroke to drive neuroplastic changes (Nudo, 2006; Murphy et al., 2009). This task is also modular enough to be adapted to different levels of impairments, where the speed of the target and its range can be modified to personalise rehabilitation training. This 1-DOF device and task can thus be used to train wrist flexion–extension as an isolated joint movement to enhance motor control and coordination in the distal part of the upper-limb, crucial to perform many ADLs. Using a single DOF also limits the cognitive load required to complete the task and makes it accessible and suitable for individuals in the subacute stage of stroke.

The Matlab App graphical user interface is used to display two circles on a screen, representing the user's wrist angular position and the target angle. The target trajectory is defined as the product of two sinusoids, which has been extensively used in human-robot interaction with unimpaired participants (Ivanova et al., 2020; Ivanova et al., 2022; Börner et al., 2023):

$$q^*(t) = q^*_{mid} + q^*_{max} \sin\left(\omega_1 t^+\right) \sin\left(\omega_2 t^+\right) \tag{3.1}$$

where $t^+ = t + t_0$, t is the elapsed time and t_0 is the starting time. t_0 is selected to vary across trials to prevent consistent prediction of the target trajectory by the participants. q^* is the target angle. q^*_{mid} is the middle point of the target range and the amplitude from that point to the maximum range is q^*_{max}. In experiments with unimpaired participants $q^*_{mid} = 0°$ and $q^*_{max} = 38.6°$. For stroke patients q^*_{max} and q^*_{mid} are set based on each patient's active and passive range of motion. ω_1 and ω_2 determine the frequency of the target sinusoids and are set to $\omega_1 = 2.0308\,\text{Hz}$ and $\omega_2 = 1.0927\,\text{Hz}$ for unimpaired participants and to $\omega_1 = 0.2586\,\text{Hz}$ and $\omega_2 = 0.1860\,\text{Hz}$ in stroke patients, with variations when the difficulty of the task is adapted.

The target is programmed and updated in Matlab. Participants are instructed to track the target as accurately as possible and told that they may feel haptic interaction from the robot and/or electrical stimulation.

3.3 Metrics

A set of metrics based on kinematic data and muscle activity data from EMG recordings has been defined to characterise performance and physiological features during training, such as tracking error, motion smoothness, effort, and fatigue. These metrics can be evaluated during assisted trials to observe the assistive effects of the robot and/or FES, and during unassisted trials where participants perform the task alone. Additionally, these metrics can provide information on changes over time, allowing the monitoring of training effects.

3.3.1 Kinematic metrics

Task performance is quantified by multiple metrics based on kinematic data. The *root mean square error* (RMSE) in degrees between the participant trajectory $q(t)$ and the target trajectory $q^*(t)$

$$\left(\frac{1}{T}\int_0^T e(t)^2\,dt\right)^{1/2}, \qquad e(t) = q(t) - q^*(t) \tag{3.2}$$

with T the trial duration, is used to analyse the tracking performance. The RMSE has been used previously to characterise the sensorimotor control strategies of stroke patients during target tracking tasks (Ao et al., 2015) and has been shown to reflect their motor recovery (Hu et al., 2009). The *Spearman's correlation* between the target and participant's trajectory was also used as a metric to quantify tracking performance.

We also investigated metrics in the frequency domain to characterise how well participants were tracking the pattern of the target and whether their trajectory contains high-frequency components, which would indicate jerky motion. The *spectral correlation* (Spearman's correlation) between the

frequency spectra of the target and participant's trajectories characterises how well participants are tracking the target and its pattern. This metric was introduced for this task specifically, to observe whether patients were able to move in a synchronous way with the target, as most patients had severe impairments preventing them from tracking the target without assistance. Furthermore, it could capture the presence of high frequency components, which are not observed in the target's spectrum. This way, this metric can also quantify the motion smoothness of the patient, where evidence has shown that it could be linked with motor recovery (Rohrer et al., 2002; Saes et al., 2021). It could also capture the relative magnitude of the patient's movement compared to the target, as represented by the power of the spectrum around the target frequencies.

SPARC (Spectral Arc Length), which is a marker of the quality of sensorimotor control (Balasubramanian et al., 2015), is also explored in this work to quantify motion smoothness (but it does not indicate how well the target itself was tracked). However, many stroke patients could not move at all during the tracking task, especially at the start, hence the SPARC metric was not always suitable and could not capture the amount of movement performed by the patient and whether this was task-meaningful.

3.3.2 Muscle activity metrics

EMG pre-processing

Muscle activity metrics are extracted from pre-processed EMG recordings of the wrist flexor carpi radialis (FCR) and extensor carpi radialis longus (ECRL) muscles. EMG pre-processing consists of a Notch filter at the mains noise frequency of 50 Hz, followed by a high-pass and low-pass second order Butterworth filters (with cut-off frequencies $f_c = 10$ Hz and $f_c = 500$ Hz, respectively). This signal is then referred to as the filtered EMG. To obtain the envelope of the EMG, the filtered EMG is rectified and filtered with low-pass second order Butterworth filter with cut-off frequency $f_c = 5$ Hz.

The EMG envelope is then either converted to torque, or normalised by the maximum EMG envelope throughout the trials or obtained during maximum voluntary contraction. For the former, the torque-EMG relationship is obtained by linearly regressing the envelope of the rectified EMG during the EMG calibration procedure with the corresponding torque. During this EMG calibration participants are asked to resist different torque levels in flexion and extension while their EMG is recorded.

The EMG metrics of interest can be divided into two categories: time-domain and frequency-domain metrics. Time-domain metrics, typically used to characterise effort, are obtained from the envelope of the EMG while frequency-domain metrics, often used to estimate fatigue, are calculated from the filtered EMG. When FES is applied at a constant amplitude, the evoked FES response, named the M-wave, can be characterised with different metrics to investigate FES-induced fatigue.

Time-domain metrics

For the time-domain metrics, the *amplitude of the EMG envelope* for the flexor EMG_{flex} and extensor EMG_{ext} averaged over a trial can be used to characterise effort. *Cocontraction* is calculated from: $CC = min(EMG_{flex}, EMG_{ext})$, and is typically associated with learning (Thoroughman et al., 1999; Franklin et al., 2003) and reciprocal activation from: $RA = max(EMG_{flex}, EMG_{ext}) - min(EMG_{flex}, EMG_{ext})$, which is a measure of the net effort contributing to the motion.

In FES-assisted trials, the EMG signal is corrupted and contains: (i) the FES artefact, (ii) the evoked M-wave which is not a voluntary contribution but still leads to recruitment of motor units, and (iii) the human voluntary contribution. The FES artifact can be filtered using a Hampel filter, where outliers 1.5 standard deviations away from the median of 30 surrounding samples are replaced by that median, filtering the FES artefacts. The envelope of this rectified signal containing both the M-wave and the volitional activity can be used to compute the muscular effort metric since both are contributing to the activation of motor units and thus affect the characteristics of the muscles (Rodriguez-Falces et al., 2018). On the other hand, adaptive filters can be used to filter both the FES artifact and the M-wave contribution, to extract only the volitional contribution. Here, an adaptive filter designed and validated in the same setup for EMG-based torque estimation under stimulation of wrist flexor and extensor (Kavianirad et al., 2022) is used for this purpose. The filter operates by predicting the stimulation-related artifacts, and M-wave components, based on a linear combination of several preceding EMG window frames. The filter thus continuously estimates and subtracts these predictable components from the current EMG window frame, in order to extract the residual voluntary EMG.

Frequency-domain metrics

To compute metrics in the frequency domain the filtered EMG is used. Fatigue can be estimated by computing the *median frequency* of the filtered EMG signal, from its Fourier transform (Stulen et al., 1981; Arendt-Nielsen et al., 1989). A decrease in EMG median frequency corresponds to an increase in fatigue. The *Choi-Williams time-frequency distribution* (Choi et al., 1989) can also be used to extract the instantaneous mean frequency of the time-dependent power spectrum, with the mean and variance as fatigue metrics specifically during dynamic contractions (Karlsson et al., 2000; Bonato et al., 2001; González-Izal et al., 2010). The mean and variance metrics were computed across the instantaneous mean frequencies obtained within one trial duration, where the Choi-Williams time-frequency distribution was computed at each time point within the 10-500 Hz band. The *Dimitrov Spectral Index*, defined as the ratio of the signal spectral moment of order (-1) and the spectral moment of order five is also relevant for detecting muscle fatigue (Dimitrov et al., 2006).

FES-specific M-wave metrics

The *M-wave*, which is the response of the muscle evoked by an electrical stimulation, can be isolated from the EMG signal and used to estimate muscle fatigue induced by FES. Features from the M-wave can be extracted such as its amplitude, duration and area and used as measures of fatigue (Chesler et al., 1997; Tepavac et al., 1997; Badier et al., 1999; Rodriguez-Falces et al., 2018). The M-wave typically contains two phases which can have different responses. The aforementioned metrics can thus be computed for each phase separately or for the entire M-wave. The Dimitrov Spectral Index aforementioned has also been used as a measure of muscle fatigue during FES-evoked muscle contractions (Dimitrova et al., 2005).

3.4 Clinical scores

To quantify patients' motor recovery and the severity of their upper-limb impairments, we used the Fugl-Meyer Assessment (FM-UE) (Duncan et al., 1983). It is one of the most widely used quantitative measures of motor impairment and has been extensively validated (Gladstone et al., 2002).

The Action Research Arm Test (ARAT) was used to assess functional performance of patients' upper-extremity and their dexterity. This test uses standardised objects mimicking those used in daily living and has been validated for use in upper-extremity rehabilitation trials (Lyle, 1981; Lang et al., 2006).

FUGL-MEYER ASSESSMENT UPPER EXTREMITY (FMA-UE) Assessment of sensorimotor function

ID:
Date:
Examiner:

Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S: The post-stroke hemiplegic patient. A method for evaluation of physical performance. Scand J Rehabil Med 1975, 7:13-31.

A. UPPER EXTREMITY, sitting position

I. Reflex activity	none	can be elicited
Flexors: biceps and finger flexors (at least one)	0	2
Extensors: triceps	0	2
Subtotal I (max 4)		

II. Volitional movement within synergies, without gravitational help			none	partial	full
Flexor synergy: Hand from contralateral knee to ipsilateral ear. From extensor synergy (shoulder adduction/ internal rotation, elbow extension, forearm pronation) to flexor synergy (shoulder abduction/ external rotation, elbow flexion, forearm supination). **Extensor synergy:** Hand from ipsilateral ear to the contralateral knee	Shoulder	retraction	0	1	2
		elevation	0	1	2
		abduction (90°)	0	1	2
		external rotation	0	1	2
	Elbow	flexion	0	1	2
	Forearm	supination	0	1	2
	Shoulder	adduction/internal rotation	0	1	2
	Elbow	extension	0	1	2
	Forearm	pronation	0	1	2
Subtotal II (max 18)					

III. Volitional movement mixing synergies, without compensation		none	partial	full
Hand to lumbar spine hand on lap	cannot perform or hand in front of ant-sup iliac spine	0		
	hand behind ant-sup iliac spine (without compensation)		1	
	hand to lumbar spine (without compensation)			2
Shoulder flexion 0°- 90° elbow at 0° pronation-supination 0°	immediate abduction or elbow flexion	0		
	abduction or elbow flexion during movement		1	
	flexion 90°, no shoulder abduction or elbow flexion			2
Pronation-supination elbow at 90° shoulder at 0°	no pronation/supination, starting position impossible	0		
	limited pronation/supination, maintains starting position		1	
	full pronation/supination, maintains starting position			2
Subtotal III (max 6)				

IV. Volitional movement with little or no synergy		none	partial	full
Shoulder abduction 0 - 90° elbow at 0° forearm neutral	immediate supination or elbow flexion	0		
	supination or elbow flexion during movement		1	
	abduction 90°, maintains extension and pronation			2
Shoulder flexion 90° - 180° elbow at 0° pronation-supination 0°	immediate abduction or elbow flexion	0		
	abduction or elbow flexion during movement		1	
	flexion 180°, no shoulder abduction or elbow flexion			2
Pronation/supination elbow at 0° shoulder at about 30° flexion	no pronation/supination, starting position impossible	0		
	limited pronation/supination, maintains start position		1	
	full pronation/supination, maintains starting position			2
Subtotal IV (max 6)				

V. Normal reflex activity assessed only if full score of 6 points is achieved in part IV; compare with the unaffected side		hyper	lively	normal
Biceps, triceps, finger flexors	2 of 3 reflexes markedly hyperactive	0		
	1 reflex markedly hyperactive or at least 2 reflexes lively		1	
	maximum of 1 reflex lively, none hyperactive			2
Subtotal V (max 2)				
Total A (max 36)				

GÖTEBORGS UNIVERSITET

B. WRIST support may be provided at the elbow to take or hold the starting position, no support at wrist, check the passive range of motion prior testing		**none**	**partial**	**full**
Stability at 15° dorsiflexion elbow at 90°, forearm pronated shoulder at 0°	less than 15° active dorsiflexion dorsiflexion 15°, no resistance tolerated maintains dorsiflexion against resistance	0	1	2
Repeated dorsifexion / volar flexion elbow at 90°, forearm pronated shoulder at 0°, slight finger flexion	cannot perform volitionally limited active range of motion full active range of motion, smoothly	0	1	2
Stability at 15° dorsiflexion elbow at 0°, forearm pronated slight shoulder flexion/abduction	less than 15° active dorsiflexion dorsiflexion 15°, no resistance tolerated maintains dorsiflexion against resistance	0	1	2
Repeated dorsifexion / volar flexion elbow at 0°, forearm pronated slight shoulder flexion/abduction	cannot perform volitionally limited active range of motion full active range of motion, smoothly	0	1	2
Circumduction elbow at 90°, forearm pronated shoulder at 0°	cannot perform volitionally jerky movement or incomplete complete and smooth circumduction	0	1	2
	Total B (max 10)			

C. HAND support may be provided at the elbow to keep 90° flexion, no support at the wrist, compare with unaffected hand, the objects are interposed, active grasp		**none**	**partial**	**full**
Mass flexion from full active or passive extension		0	1	2
Mass extension from full active or passive flexion		0	1	2
GRASP				
a. Hook grasp flexion in PIP and DIP (digits II-V), extension in MCP II-V	cannot be performed can hold position but weak maintains position against resistance	0	1	2
b. Thumb adduction 1-st CMC, MCP, IP at 0°, scrap of paper between thumb and 2-nd MCP joint	cannot be performed can hold paper but not against tug can hold paper against a tug	0	1	2
c. Pincer grasp, opposition pulpa of the thumb against the pulpa of 2-nd finger, pencil, tug upward	cannot be performed can hold pencil but not against tug can hold pencil against a tug	0	1	2
d. Cylinder grasp cylinder shaped object (small can) tug upward, opposition of thumb and fingers	cannot be performed can hold cylinder but not against tug can hold cylinder against a tug	0	1	2
e. Spherical grasp fingers in abduction/flexion, thumb opposed, tennis ball, tug away	cannot be performed can hold ball but not against tug can hold ball against a tug	0	1	2
	Total C (max 14)			

D. COORDINATION/SPEED, sitting, after one trial with both arms, eyes closed, tip of the index finger from knee to nose, 5 times as fast as possible		**marked**	**slight**	**none**
Tremor		0	1	2
Dysmetria	pronounced or unsystematic slight and systematic no dysmetria	0	1	2
		≥ 6s	**2 - 5s**	**< 2s**
Time start and end with the hand on the knee	6 or more seconds slower than unaffected side 2-5 seconds slower than unaffected side less than 2 seconds difference	0	1	2
	Total D (max 6)			

TOTAL A-D (max 66)	

GÖTEBORGS UNIVERSITET

H. SENSATION, upper extremity eyes closed, compared with the unaffected side		**anesthesia**	**hypoesthesia or dysesthesia**	**normal**
Light touch	upper arm, forearm palmary surface of the hand	0 0	1 1	2 2
		less than 3/4 correct or absence	**3/4 correct or considerable difference**	**correct 100%, little or no difference**
Position small alterations in the position	shoulder elbow wrist thumb (IP-joint)	0 0 0 0	1 1 1 1	2 2 2 2
			Total H (max12)	

I. PASSIVE JOINT MOTION, upper extremity, sitting position, compare with the unaffected side				**J. JOINT PAIN** during passive motion, upper extremity		
	only few degrees (less than 10° in shoulder)	decreased	normal	pronounced pain during movement or very marked pain at the end of the movement	some pain	no pain
Shoulder						
Flexion (0° - 180°)	0	1	2	0	1	2
Abduction (0°-90°)	0	1	2	0	1	2
External rotation	0	1	2	0	1	2
Internal rotation	0	1	2	0	1	2
Elbow						
Flexion	0	1	2	0	1	2
Extension	0	1	2	0	1	2
Forearm						
Pronation	0	1	2	0	1	2
Supination	0	1	2	0	1	2
Wrist						
Flexion	0	1	2	0	1	2
Extension	0	1	2	0	1	2
Fingers						
Flexion	0	1	2	0	1	2
Extension	0	1	2	0	1	2
Total (max 24)				**Total** (max 24)		

GÖTEBORGS UNIVERSITET

A. UPPER EXTREMITY	/36
B. WRIST	/10
C. HAND	/14
D. COORDINATION / SPEED	/ 6
TOTAL A-D (motor function)	/66

H. SENSATION	/12
I. PASSIVE JOINT MOTION	/24
J. JOINT PAIN	/24

Action Research Arm Test

Patient Name: _____ **Date:** _____

Rater's Name: _____

Score Legend:

3	Finished the task quickly with the appropriate body position and normal hand/arm movements
2	Can finish the task but takes abnormally long, has great difficulty, or has improper body posture/hand/arm movements
1	Can finish the task partially regardless of position/movements
0	Unable to finish the task

Grasp

		Left	Right
1	Block (wood), 10 cm. cube		
2	Block (wood), 2.5 cm. cube		
3	Block (wood), 5 cm. cube		
4	Block (wood), 7.5 cm. cube		
5	Cricket ball		
6	Sharpening stone		
	Subtotal		

Grip

		Left	Right
1	Pour water from one glass to another		
2	Transfer a 2.25 cm tube from one side to the other		
3	Transfer a 1 cm. Tube from one side to the other		
4	Place the washer over the bolt		
	Subtotal		

Pinch

		Left	Right
1	Ball Bearing between thumb and ring finger (3rd finger)		
2	Marble between thumb and index finger (1st finger)		
3	Ball bearing between thumb and middle finger (2nd finger)		
4	Ball bearing between thumb and index finger (1st finger)		
5	Marble between the thumb and ring finger (3rd finger)		
6	Marble between the thumb and middle finger (2nd finger)		
	Subtotal		

Reference: Internet Stroke Center

Gross Movement

		Left	Right
1	Hand behind the head		
2	Hand on top of the head		
3	Hand to mouth		
	Subtotal		

Total		

Notes:

Reference: Internet Stroke Center

Chapter 4

Proof of concept of hybrid robot- and FES-assisted training in unimpaired participants

The previous chapters have outlined the rationale for developing a hybrid neurorehabilitation system that combines robotic assistance and FES to enhance upper-limb recovery after stroke. As discussed in Chapter 2, robot- and FES-based technologies each provide unique advantages: robotic devices offer well-controlled assistance and enable high-intensity training, while FES engages peripheral nerves and muscles to promote neuroplasticity. However, limitations such as muscle fatigue with FES and slacking with robotic systems highlight the potential for complementary use. Furthermore, most hybrid systems described in the literature rely on FES as the main actuator and use robots primarily for support, without both modalities acting on the same joint, limiting their synergy and impact on sensorimotor recovery (Resquin et al., 2016).

To explore the clinical potential of more integrated hybrid control strategies, I have co-developed a simple, portable one-DOF robot-FES system targeting wrist flexion/extension that is designed for use in clinical environments and allows controlled, joint-specific hybrid assistance. Before applying it to stroke patients, it is critical to understand how such assistance modulates motor performance, user engagement, physiological load, and perceived fatigue in unimpaired individuals. These insights can inform both controller design and experimental protocols for subsequent clinical testing.

This chapter presents a proof-of-concept study that addresses research question QA: *How does robotic and/or FES assistance affect unimpaired individuals' behavioural and physiological features?* Unimpaired participants were asked to perform a continuous wrist tracking task under four different assistance conditions: no assistance, robotic assistance alone, FES assistance alone, and hybrid robot-FES assistance. The impact of each assistance mode on performance, smoothness, effort, fatigue, and user experience is analysed to characterise behavioural and neuromechanical responses. Here, we

hypothesised that robotic assistance could lead to reduced fatigue and tracking error but also lower effort than FES, as previously observed in the literature and described in Chapter 2, Section 2.3. We also hypothesised that the combination of these two modalities would improve tracking performance, although the addition of FES to robotic assistance could lead to less smooth motion. This study aims to understand whether this device can be safe to use, as well as to establish a baseline and guide the implementation of hybrid assistance strategies in clinical populations, which is the focus of the next chapter.

This study is described in the following publication: Cazenave, L., Einenkel, M., Yurkewich, A., Endo, S., Hirche, S., & Burdet, E. (2023). Hybrid robotic and electrical stimulation assistance can enhance performance and reduce mental demand. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 31,* 4063-4072. A verbatim copy of this paper is also included in Appendix A. Part of this work was carried out by M. Einenkel as part of his MSc thesis, under the supervision of A. Yurkewich, S. Endo and myself. Specifically, M. Einenkel was involved in the programming of the experimental task, collected the data, and performed some preliminary analyses. A. Yurkewich assisted in the programming of the experimental task. All collaborators were involved in the definition of the experimental protocol and interpretation of the results. I contributed to conceiving and designing the research, developing and implementing the experimental protocol, performing the data analysis, creating the figures in this chapter, and interpreting the results.

4.1 Methods

4.1.1 Participants

This study was approved by the Research Ethics Committee of Imperial College London (approval number: 21IC6935). 15 unimpaired participants (6 female) aged 27.8 ± 3.41 years old were recruited for this study. The participants signed an informed consent form and filled out a demographic questionnaire prior to participating in the experiment. 13 participants were right handed and two were left handed, as assessed using the Edinburgh Handedness Inventory (Oldfield, 1971).

4.1.2 Hybrid robot-FES system

The hybrid robot-FES system is composed of the HRX-1 one DOF wrist robotic interface (HumanRobotiX, UK) and the CLASS V1.0 FES device 16-electrode array (Tecnalia Research & Innovation, Spain). These systems were introduced in Chapter 3, Section 3.1, where further details and pictures can be found.

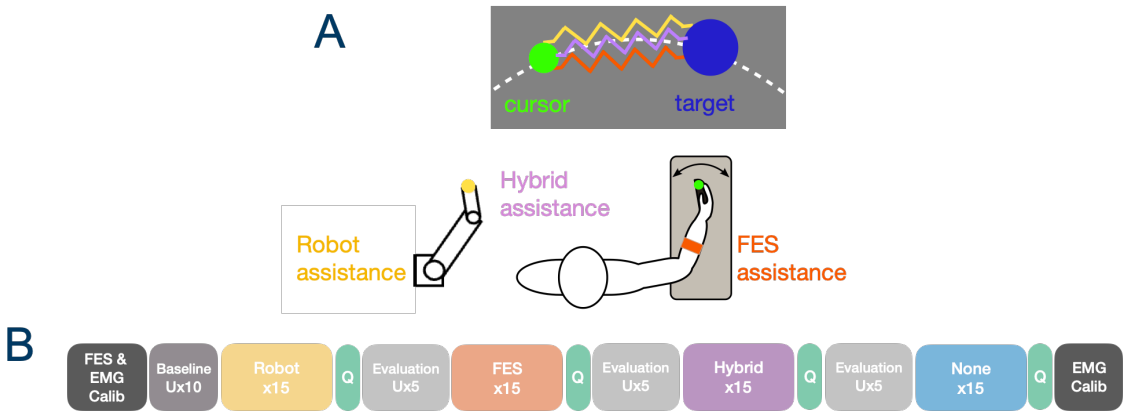


Figure 4.1: Experiment description. **A.** Participants track a randomly moving target on-screen with wrist flexion/extension and receive four different assistance conditions: no assistance, robot-only assistance, FES-only assistance and hybrid (robot + FES) assistance. **B.** Overview of experimental protocol, where four assistance conditions were presented randomly to each participant: no assistance, FES-only assistance, robot-only assistance and hybrid assistance. Each block represents one trial of the target tracking task.

4.1.3 EMG recording

Muscle activity is recorded using two 32-channel EMG electrode arrays (GR10MM0804, OT Bioelettronica, Italy) with a Sessantaquattro amplifier (OT Bioelettronica, Italy). We used two electrode arrays that covered the forearm proximally to the FES electrodes, which recorded the activity in muscles such as the extensor carpi radialis longus, the extensor digitorum, the flexor carpi radialis, and the flexor digitorum superficialis. The EMG data was sampled at a frequency of 2000 Hz. Further details and pictures can be found in Chapter 3, Section 3.1.

4.1.4 Experiment task

The participants tracked a moving target on a computer monitor placed in front of them using wrist flexion/extension movements of the right hand while being assisted by a robot or FES (Fig. 4.1 A). As indicated in Chapter 3, Section 3.2, the target trajectory was defined as:

$$q^*(t) = 38.6\,^\circ \sin\Big[2.0308(t^+)\Big] \sin\Big[1.0927(t^+)\Big] \tag{4.1}$$

where $t^+ = t + t_0$, t is the elapsed time and t_0 is the starting time. q^* is the target angle. The target was programmed and updated in Matlab and $t_0 \in \{0, 3.094, 14.375\}$ s was randomly selected every trial to prevent consistent prediction of the target trajectory by the participants. Participants were instructed to track the target as accurately as possible and told that they may feel haptic interaction from the robot and/or electrical stimulation.

4.1.5 FES and EMG Calibration

An *FES calibration* was performed at the start of the experiment, as detailed in Chapter 3, Section 3.1.2, where the electrode location, comfortable maximum stimulation (s_f^{max} for the wrist flexion, and s_e^{max} for the wrist extension) and sensory threshold (s_f^{min} and s_e^{min}), for the wrist flexion and extension movements, were identified. The torque generated by each of these stimulation amplitudes while the participant is relaxed was also recorded as τ_f^{max} and τ_e^{max}. We assume a linear mapping between the stimulation amplitude s_f and s_e and the produced torque τ_f and τ_e for amplitudes above s_f^{min} and s_e^{min} for the flexion and extension movements respectively (Kavianirad et al., 2022) such that:

$$\tau_f(t) = \alpha_s \, s_f(t) \qquad \tau_e(t) = \alpha_s \, s_e(t) \tag{4.2}$$

with the linear coefficient α_s defined as:

$$\alpha_s = \frac{s_f^{max} - s_f^{min}}{\tau_f^{max}} \tag{4.3}$$

An *EMG calibration* was then performed to obtain a measure of effort, by linearly regressing muscle activity with torque produced during isometric contraction. During this calibration, participants were asked to resist each of the four increasing torque levels: $\{0.4, 0.8, 1.2, 1.7\}$ Nm during 2.5 s in flexion and extension at the fixed angle $q = 30\,°$. This was repeated four times with a 3 s rest in between to prevent fatigue.

4.1.6 Control of robot-FES system

The task considered in this study is a continuous target tracking task with a pseudo-random trajectory, requiring continuous assistive feedback. Therefore, the torque exerted on the wrist flexion/extension by the robot is described as:

$$u_r(t) = K_r \, e(t) \qquad e(t) = q(t) - q^*(t) \tag{4.4}$$

where $e(t)$ is the tracking error between the participant trajectory q and the target trajectory q^*. The robot control stiffness $K_r = 0.56$ Nm/rad corresponds to a soft-middle interaction stiffness (Ivanova et al., 2020). It was selected after preliminary tests in order to observe tracking improvement with assistance, while preventing slacking.

The stimulation amplitude provided to the wrist flexor or extensor is described as:

$$s(t) = \begin{cases} s_e(t) = -K_s \, e(t) \, + \, s_e^{min} & e(t) < 0 \\ s_f(t) = K_s \, e(t) \, + \, s_f^{min} & e(t) > 0 \end{cases} \tag{4.5}$$

where $s_e(t)$ refers to an extensor muscle stimulation and $s_f(t)$ a flexor muscle stimulation. K_s (in mA/°) is the FES control stiffness and is the same for the extensor and flexor stimulation in order to match the robot assistance behaviour. It is defined from the linear mapping α_s between the FES amplitude and torque ranges of the flexor as it was found to be more comfortable during preliminary tests:

$$K_s = \alpha_s K_r \tag{4.6}$$

The four assistance conditions of the experiment are defined as follows: {hybrid, robot ($s_e \equiv 0, s_f \equiv 0$), FES ($u_r \equiv 0$), no assistance ($s_e \equiv 0, s_f \equiv 0$ and $u_r \equiv 0$)}. In the hybrid condition, participants receive the same robot assistance as in the robot condition as well as the same FES assistance as in the FES condition.

4.1.7 Protocol

The experimental protocol is outlined in Fig. 4.1 B. The experiment started with an FES and EMG calibration as detailed in Section 4.1.5. This EMG calibration was also carried out at the end of the experiment to examine potential changes in muscle activity due to fatigue. The participants first completed ten trials of the target tracking task without assistance. They then completed four blocks of the target tracking task, each block using one of the four assistance conditions: {hybrid, robot, FES and no assistance}. The conditions were presented in random order, with each block containing 15 trials consisting of 15 s of target tracking and a 3 s rest. Each block was followed by a questionnaire that evaluated the workload using the NASA-TLX ten-point ordinal Likert Scale (Hart et al., 1988) and the comfort and usefulness of the stimulation and robot torques using five-point ordinal Likert Scale questions (Allen et al., 2007). Subsequently, a block of five target tracking trials with no assistance was performed, including a first washout trial and four evaluation trials.

4.1.8 Performance analyses

Task performance was quantified by the Root Mean Square Error (RMSE), the time delay [s], tracking error due to a temporal shift between the target and participant trajectories, and motion smoothness (SPARC) (Balasubramanian et al., 2015). These were introduced in Chapter 3, Section 3.3.1.

4.1.9 Effort and fatigue

Fatigue and effort during the task were estimated using recorded EMG signals of the flexor and extensor muscles from the participants. The EMG pre-processing pipeline used has been described in Chapter 3, Section 3.3.2. Since high-density EMG grids were used here, the channels on the extensor and flexor arrays with the highest envelope amplitude during the EMG calibration were used for

the following analyses. For both time-domain effort metrics, the torque-normalised EMG signal was used. It was obtained by linearly regressing the envelope of the fully-rectified EMG during the EMG calibration procedure with the corresponding torque, as described in Chapter 3, Section 3.3.2.

Fatigue was characterised by the median frequency of the filtered EMG signal (Tu et al., 2016) (more details in Chapter 3, Section 3.3.2), where a decrease in EMG median frequency corresponds to an increase in fatigue. The EMG frequency during the EMG calibration at the start and end of the experiment, and across conditions was compared. For the latter, the median frequency was averaged for the last four trials of the previous and following evaluation blocks and their difference was taken to quantify fatigue changes.

For the muscular effort metric, the EMG envelope signal containing both the FES-induced muscle activity, i.e. the evoked M-wave, and the volitional activity was considered. Although the evoked M-wave is not a voluntary contribution, it results in the recruitment of motor units leading to muscle contraction, as with volition. The envelope of the EMG was obtained and the total effort was evaluated from the mean amplitude of the envelope of the torque-normalised EMG signal, averaged across trials. Muscular effort levels during the EMG calibration at the start and end of the experiment were compared as well as during each training condition.

The volitional contribution was also considered, where the M-wave was filtered using an adaptive filter (Kavianirad et al., 2022), as described in Chapter 3, Section 3.3.2. The torque-normalised EMG was obtained from the envelope of this signal, and averaged across trials.

4.1.10 Questionnaire

Participants answered the following set of questions after each block. Their perceived workload was assessed with the NASA-TLX ten-point ordinal Likert Scale (Hart et al., 1988) and the comfort and usefulness of the stimulation and robot torques were assessed using five-point ordinal Likert Scale questions (Allen et al., 2007).

- How mentally demanding was the task?
  (1 = very low; 10 = very high)
- How physically demanding was the task?
  (1 = very low; 10 = very high)
- How hurried or rushed was the pace of the task?
  (1 = very low; 10 = very high)
- How successful were you in accomplishing what you were asked to do?
  (1 = very bad; 10 = very good)

- How hard did you have to work to accomplish your level of performance?
  (1 = very low; 10 = very high)
- How insecure, discouraged, irritated, stressed, and annoyed were you?
  (1 = very low; 10 = very high)
- The forces were comfortable.
  (from 'strongly disagree' to 'strongly agree')
- The forces improved my performance.
  (from 'strongly disagree' to 'strongly agree')
- The electrical stimulation was comfortable.
  (from 'strongly disagree' to 'strongly agree')
- The electrical stimulation improved my performance.
  (from 'strongly disagree' to 'strongly agree')

4.1.11 Statistical analysis

For the comparison of performance metrics, effort, fatigue levels and questionnaire answers between the conditions, we used a one-way repeated measures ANOVA or a non-parametric Friedman test when the data was not normally distributed. A one-sample Shapiro-Wilk test was used to test the null hypothesis that the data came from a normal distribution. Post-hoc paired sample t-tests or paired Wilcoxon sign-rank tests were used for pairwise comparisons of performance metrics, effort and fatigue levels and questionnaire answers between each condition, controlling for the family-wise error rate with Bonferroni-Holm correction. For the comparison of the fatigue level before and after the experiment, a paired Wilcoxon sign-rank test was used since the data was not normally distributed. Similarly, for questions comparing the FES and hybrid conditions, and the hybrid and robot conditions, paired Wilcoxon sign-rank tests were used. For the statistical analysis of performance, effort and fatigue metrics, the average across trials in one condition was calculated for each participant. In the box plot figures, the whisker lines above and below the box indicate the 1.5 interquartile range. Outliers are displayed by a red + sign. Comparisons not shown are not significant. The significance level was set at $\alpha = 0.05$ for all tests.

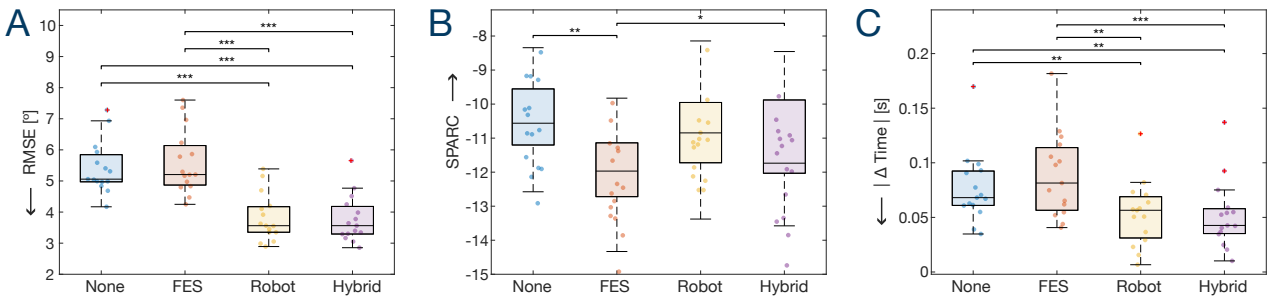


Figure 4.2: Performance, motor adaptation and quality of motion metrics during the tracking task with four different assistance conditions. (**A**) Tracking performance indicated by the Root Mean Square Error (RMSE). (**B**) Tracking performance improvement indicates the difference in participant's tracking performance before and after training; a positive result indicates that they are performing better after training. (**C**) Time Delay indicates the temporal shift between the target and participant trajectories. (**D**) Smoothness of participant's trajectory, evaluated using Spectral Arc Length (SPARC) (Balasubramanian et al., 2015). A SPARC value closer to zero corresponds to a smoother motion. $* : p < 0.05, ** : p < 0.01, *** : p < 0.001$. Comparisons not shown are not significant.

4.2 Results

4.2.1 Performance results

The assistance condition affects participants' tracking performance ($F(3, 56) = 20.38$, $p < 0.001$). RMSE is smaller with hybrid or robot assistance relative to the no assistance and FES conditions (all $p < 0.001$) (Fig. 4.2 A). There is no significant difference between hybrid assistance and robot assistance ($p = 0.74$). The effect of assistance condition on smoothness was also investigated ($F(3, 56) = 3.82$, $p = 0.015$) and results indicate that FES assistance leads to decreased smoothness compared to the hybrid condition ($p < 0.05$) but other differences are not significant (all $p > 0.075$) (Fig. 4.2 B). The hybrid and robot assistance also reduce time delays compared to no assistance and FES conditions (all $p < 0.01$) and there is no statistical difference between the hybrid and the robot conditions ($p = 0.93$) (Fig. 4.2 C). When investigating performance improvement on evaluation trials before and after each assistance condition, we do not find statistical differences ($F(3, 56) = 0.37, p = 0.77$) (Additional Figure 4.6).

4.2.2 Effort and Fatigue

The EMG recording for one participant was corrupted and thus EMG-based metrics are reported as $N = 14$. When comparing the total level of muscle activity in the flexor muscles during the assisted tracking task ($\chi^2(3) = 37.46$, $p < 0.001$) (Fig. 4.3 C), we find that it is lower with robot assistance compared to all other assistance conditions ($p < 0.001$ with FES and hybrid and $p < 0.05$ with no assistance). Higher muscular effort is observed in the FES and hybrid assistance compared to no assistance, with higher muscle activity in the hybrid condition ($p < 0.05$ with FES). Similar trends are found for the extensor muscles ($\chi^2(3) = 24.26$, $p < 0.001$) (Fig. 4.3 D), although there is no statistical

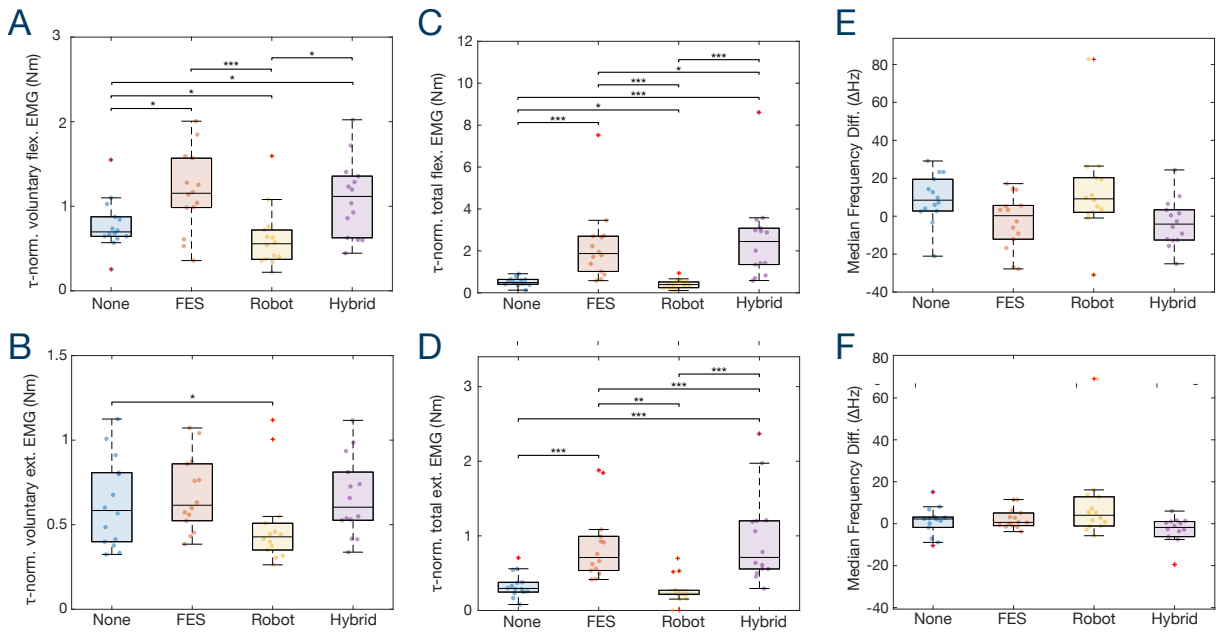


Figure 4.3: Voluntary effort (A,B), muscular effort (C,D) and changes in muscle fatigue (E,F) during the tracking task assisted with four different assistance conditions. The effort metrics are estimated as the mean envelope amplitude of the torque-normalised EMG signal. Fatigue is obtained from the median frequency of the EMG signal, a decrease in frequency indicates increased fatigue. (**A**) Voluntary effort in the flexor muscles. (**B**) Voluntary effort in the extensor muscles. (**C**) Total muscular effort in the flexor muscles (including M-wave contribution). (**D**) Total muscular effort in the extensor muscles (including M-wave contribution). (**E**) Fatigue changes in the flexor muscles. (**F**) Fatigue changes in the extensor muscles. $* : p < 0.05, ** : p < 0.01, *** : p < 0.001$. Comparisons not shown are not significant.

difference between the robot and no assistance conditions ($p = 0.90$) and total muscle activity is highest in the hybrid condition ($p < 0.001$ with FES).

Regarding the voluntary effort (Fig. 4.3 A, B), similar trends are found in the flexor muscle ($\chi^2(3) = 25.00$, $p < 0.001$), where higher volition is observed in the FES and hybrid assistance conditions, while these differences are not present in the extensor muscle ($\chi^2(3) = 16.54$, $p < 0.001$). The voluntary contribution is similar in the FES and hybrid conditions for both flexor ($p = 0.46$) and extensor muscles ($p = 0.53$). In the robot condition, the volitional contraction is lowest ($p < 0.05$ with no assisatnce in flexor and extensor muscles).

Regarding fatigue, we observe that the median frequency of the flexor muscle activity increases in the no assistance and robot conditions, suggesting muscle recovery and does not change after the FES and hybrid condition when looking at the mean (Fig. 4.3 E). These differences are not as clear in the extensor muscles (Fig. 4.3 F). The comparison of the change in muscle fatigue between conditions is not statistically different for the flexor ($\chi^2(3) = 5.40$, $p = 0.15$) or the extensor ($\chi^2(3) = 7.71$, $p = 0.052$). No statistical differences are found when comparing muscle fatigue before and after the experiment during the EMG calibration (Additional Figure 4.7).

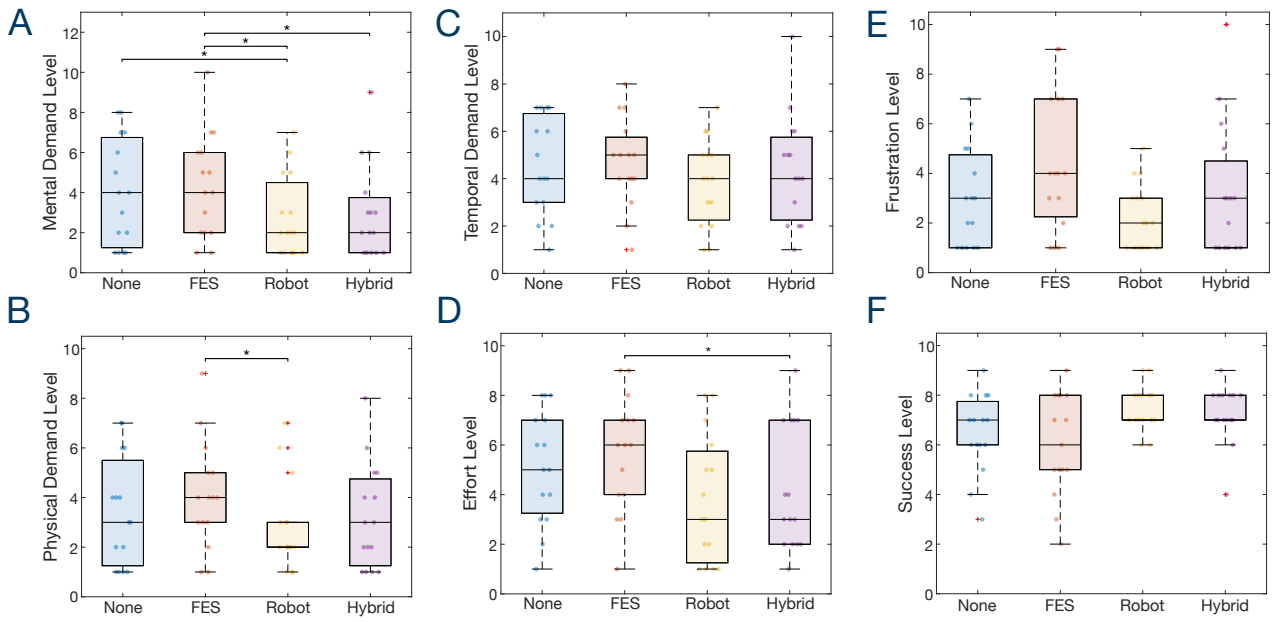


Figure 4.4: Answers to the 10-point NASA-TLX questionnaires on perceived workload after the trajectory tracking task with four different assistance conditions, with answers from very low (1) to very high (10). $*: p < 0.05$. Comparisons not shown are not significant.

4.2.3 Questionnaire Answers

The answers to the NASA-TLX questions are shown in Fig. 4.4. The assistance type affected participants' mental demand ($\chi^2(3) = 16.18$, $p = 0.001$) (Fig. 4.4 A). It is lower in the robot and the hybrid conditions in comparison with the no assistance and FES assistance conditions ($p < 0.05$). Participants also perceived the lowest physical demand in the robot condition, but this difference is statistically significant only with respect to the FES condition ($p < 0.05$) (Fig. 4.4 B). Moreover, participants indicated that their effort was lowest in the robot and hybrid conditions and the latter is significantly different from the FES condition ($p < 0.05$) (Fig. 4.4 D). Their frustration level during the assisted task was lower in the hybrid and robot assistance conditions than in the FES condition but differences are not statistically significant ($\chi^2(3) = 7.68$, $p = 0.053$) (Fig. 4.4 E). The responses to the statement "The electrical stimulation was comfortable" are similar in the hybrid and FES conditions ($p = 0.94$) but participants thought that their performance increased thanks to the stimulation with the hybrid assistance but not with FES only, although this difference is not statistically significant ($p = 0.57$) (Fig. 4.5). The robotic forces were rated as comfortable and useful in both the hybrid and robot conditions.

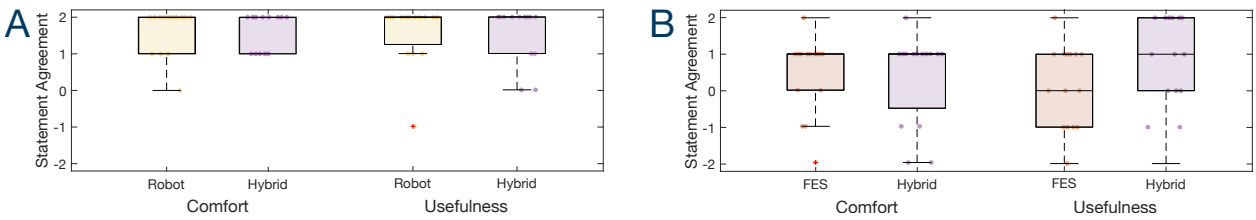


Figure 4.5: Answers from a 5-point ordinal Likert scale questionnaire on comfort (**A** and **C**) and usefulness (**B** and **D**) of robotic force (top row) and electrical stimulation (bottom row) after trajectory tracking with four different assistance conditions. Agreement level from 'Strongly Agree' (2) to 'Strongly Disagree' (-2) was provided for each statement.

4.3 Discussion

Literature suggests that adding FES to robotic assistance could improve motor recovery during stroke rehabilitation. However, there is a need to understand how FES and robotic assistance alter performance, physiological measures and subjective experience, such that the benefits of these modalities can be fully exploited for clinical applications. This work thus used a simple wrist flexion/extension interface to explore these aspects in unimpaired participants in a target tracking task, requiring continuous assistance FES and robot assistance proportional to the tracking error.

Performance and quality of motion increases when robotic assistance is present. Tracking performance is higher when participants receive hybrid and robot assistance compared to no assistance or FES assistance. Hybrid assistance does not improve tracking performance more than robot assistance. We find that the assistance modes improve tracking performance except the FES assistance alone. However, the added stimulation is not disturbing participants' performance, even though we used a simple controller. On the other hand, we expected that the combination of FES and robotic assistance would further improve performance, even though the goal of the hybrid controller was not focused on improving tracking performance but rather made simple to investigate the effects of assistance. The stimulation thus does not seem to contribute to performance improvement in the hybrid condition. These observations could be extended to the use of more advanced strategies, where the goal is to optimise for control objectives such as tracking performance or learning. However, few studies have tested other strategies to assist users in ADLs, such as shared control approaches, where the action of one modality has knowledge of the other, and similarly they did not always find performance improvements in the hybrid compared to the robot-only condition (Dunkelberger et al., 2023; Burchielli et al., 2022).

In this chapter, we additionally investigated the effect of each modality and their combination on various quality of motion metrics. We found that participants' movements are smoother with the hybrid assistance than with the FES assistance and there is no significant difference in movement smoothness in the hybrid, robot and no assistance conditions. We see similar trends for other objective

metrics, such as time delay and under/overshoot. Adding FES to a robotic-based assistive device thus does not impede motion quality in our experiment, even though the controller used is simple and does not account for the delay between the trigger of the stimulation and the resulting muscle contraction (e.g. $10-140\,ms$ (Lynch et al., 2008; Downey et al., 2017)). It is useful to understand how smoothness is affected by different assistive modalities as it captures motor control abilities which are affected in stroke population, and is linked with functional recovery (Rohrer et al., 2002; Saes et al., 2021). Furthermore, this analysis can then be used as a reference to later interpret data from stroke patients performing similar tasks with these assistance modes. In the hybrid context, it can also be used to inform on the assisted motion quality and as an indicator of possible counteracting effects between the stimulation and robot torque (Dunkelberger et al., 2020). As no difference was found in participants' smoothness during the no-assistance and hybrid conditions, it seems that the electromechanical delay did not affect participants' motion.

Total muscular effort is higher when stimulation is applied while it does not induce more fatigue, and voluntary effort is lowest in the robot-only condition. The amount of muscular effort, quantified by the total level of muscle activity, both from the stimulation-induced M-wave and the voluntary contribution, is generally higher in the conditions with electrical stimulation (FES and hybrid) compared to the other two conditions; this is due to the M-wave contribution of the stimulation. Although it is common to disregard the M-wave and only investigate the voluntary contribution, we chose to also explore the total EMG activity as FES also leads to the activation of motor units and thus affects the characteristics of the muscles (Rodriguez-Falces et al., 2018).

We also observe that voluntary effort is lowest in the robot condition. This suggests the potential value of integrating FES assistance into robotic-based therapy as it leads to increased total muscle contraction but also higher voluntary contribution, thus enhancing user engagement which could potentially promote recovery in stroke patients. Additionally it could prevent slacking that seems to occur here when robot-only assistance is provided. On the other hand, we find that the total muscular effort is higher in the hybrid than in the FES condition. This could be due to the electromechanical delay between the stimulation and the resulting muscle contraction, which is not present when a robotic torque is applied to the handle. In some cases the stimulation could lead to overshooting of the trajectory although the target is already moving towards the other direction. Although we do not see a difference in performance and smoothness between the robot and hybrid conditions, it might be that the two assisting systems are counteracting each other, which could cause increased muscle activity level for the user to drive the handle in the desired direction. Similarly, the higher voluntary contribution of the flexor muscles in the hybrid and FES conditions could be a consequence of a counteraction between the user's intention and the delayed contraction resulting from the stimulation. These trends were observed in another hybrid training study with stroke patients where EMG activa-

tion levels in the flexors and extensors were lower with FES compared to hybrid assistance (Hu et al., 2011). Models of the muscle response to electrical stimulation are available and could be incorporated as a feedforward element to the existing controller to ensure muscle contraction resulting from FES occurs in a similar time range as the robotic torque assistance for the motion to be produced (Riener et al., 1996; Ferrarin et al., 2000; Gollee et al., 2001; Gwo-Ching Chang et al., 1997). Recent works have also targeted the development of controllers to reduce the effect of the electromechanical delay of the stimulation (del-Ama et al., 2014; Qiu et al., 2016), which would lead to a better alignment of the motion resulting from the two actuation systems. However, these approaches for delay compensation are not considering the time-varying nature of the electromechanical delay (Downey et al., 2017), and are applied to cyclic gait motion or to the tracking of pre-determined trajectories, hence they would not be suitable for this pseudo-random tracking task.

Regarding fatigue, there are no significant changes before and after the experiment in the flexor and extensor muscles. We also do not observe that the FES and hybrid conditions lead to higher fatigue than the other conditions when investigating fatigue changes for each condition individually. Although FES is commonly described as fatiguing, we do not find such trends in these unimpaired participants who performed a task that is not physically demanding – average rating below 4 for all conditions in the 10-point NASA-TLX questionnaire. This could be in part due to the dynamic nature of the task, which did not require sustained stimulation, as well as the relatively short duration of each trial and training block. FES is also mostly in clinical settings, and the response to stimulation amplitudes and duration might be different in unimpaired participants who already have the capacity to move and stroke patients who may have weakness and lack the ability to contract their muscles as intended.

Mental demand is rated as lowest in the hybrid and robot conditions. The NASA-TLX questionnaire answers also indicate that in this study, participants did not feel more frustrated when training with FES or hybrid assistance compared to robot or no assistance. The electrical stimulation was rated as comfortable on average but participants perceived that the stimulation in the hybrid assistance was more useful in improving their performance than in the FES condition. This finding resonates with the tracking error results, where performance in the hybrid condition is higher than in the FES condition, although this increase might not be due to the stimulation directly. Robot-assisted training is perceived as the least physically demanding, but is only significantly different to FES-assisted training, whereas the effort is perceived significantly lower in hybrid than FES conditions. Indeed, the effort rating could be considered by users as a compound of mental and physical demand (Akizuki et al., 2015), and here mental demand is rated lower in the hybrid and robot conditions.

These answers only partly translate to the physiological differences on voluntary effort that we observe, where in the flexor muscles, we do find differences between most conditions. Although

previous studies have found relationships between task difficulty, NASA-TLX ratings and muscle activity amplitude, these were investigated in more demanding and tiring tasks such as repairing a pump gearbox (Alhaag et al., 2022), controlling traffic density (Fallahi et al., 2016), and performing surgical procedures (Caldiroli et al., 2014). For instance in the repair task, the complex task resulted in significantly higher physical demand ratings and EMG levels compared to the simple task, with a significant correlation between these two metrics (Alhaag et al., 2022). The average physical demand rating of this task was higher than 6, whereas our target tracking task was rated below 4 on average in all conditions. The absence of consistent findings between physical demand ratings and EMG levels in our work could be explained by the low demand of the target tracking task we investigated. The results from the subjective workload assessment motivate the use of hybrid assistance for motor training: although total muscle activity level is higher than with FES assistance, perceived effort is lower, which could lead to longer and more enjoyable training. On the other hand, hybrid and robot assistance are rated as less mentally demanding than FES and they are not significantly different from each other. The trends observed in these answers seem to follow those of the tracking performance, which suggests that they could be related. This is in agreement with previous motor task studies investigating the relationship between mental load and motor performance (Hu et al., 2016; Shuggi et al., 2017). This indicates that using hybrid assistance could reduce mental demand, thus enhancing user experience.

The hybrid robot and FES system and the tracking task are not necessarily applicable to a stroke population. Testing the hybrid system in unimpaired participants provided a valuable first step toward validating the device and its control strategy before clinical application. This approach allowed us to confirm that the system operated safely and as intended under controlled conditions, that the robot and FES can assist individuals in completing a target tracking task without disturbing them, and that it could be used comfortably and without adverse effects. Such preliminary evaluation is essential both from an ethical and a methodological perspectives, ensuring that subsequent studies involving stroke patients are justified and minimise potential risk. However, while the results obtained in unimpaired participants demonstrate that the system functions as expected in terms of kinematic performance, muscle activation, and perceived workload, these findings cannot be directly extrapolated to clinical populations. Stroke patients often exhibit altered motor control, muscle weakness, and spasticity, which may influence how they respond torobotic and FES assistance (Balasubramanian, 2015). Therefore, further investigation in post-stroke individuals is necessary to determine whether the same hybrid control principles remain effective, and to assess the system's rehabilitative potential in a clinical context.

4.4 Conclusion

This proof-of-concept study demonstrated how robotic and FES assistance, applied individually or in combination, influence motor behaviour, physiological effort, and perceived workload in unimpaired individuals performing a wrist target tracking task. The results provide valuable insights into how such hybrid systems may operate in rehabilitation settings and inform their deployment in stroke patients, which will be investigated in the following chapter (Chapter 5).

Hybrid assistance and robot-only assistance significantly improved tracking performance and reduced time delay compared to no assistance or FES-only conditions. However, hybrid assistance did not yield superior performance relative to robot assistance alone, suggesting that FES did not provide additional benefits in this experimental setup, although it did not disrupt participants' motor control, which can be characterised by motion smoothness.

Regarding physiological measures, robotic assistance significantly reduced total muscular and voluntary effort, consistent with previous observations of slacking behaviour. In contrast, FES and hybrid assistance elicited higher muscle activation and voluntary contribution, suggesting increased user engagement. The hybrid condition thus appears to balance improved performance with sustained muscular activation, supporting its potential therapeutic value, where active participation drives neuroplasticity.

Notably, none of the conditions led to significant increases in muscle fatigue, as measured by EMG frequency metrics. This is likely due to the moderate task demands and relatively short training duration. However, these results support the feasibility of using hybrid assistance for longer sessions without inducing fatigue in unimpaired users. Chapter 6 will further explore whether these findings translate to stroke populations, where fatigue susceptibility may be higher and effort generation is more limited.

Subjective experience, as captured by the NASA-TLX and Likert scale questionnaires, further supports the value of hybrid assistance. Participants rated hybrid and robotic assistance as less mentally and physically demanding than FES alone, and reported lower effort and frustration, suggesting an enhanced user experience, which may contribute to improving patient engagement and adherence in rehabilitation contexts.

Although these results validate the safe use of the developed hybrid system for assisting upper-limb movement in unimpaired participants, they cannot be directly extrapolated to clinical populations. Stroke patients exhibit distinct motor impairments, which may affect their response to robotic and FES assistance. Nonetheless, conducting this preliminary evaluation in unimpaired individuals was an essential and ethical step to ensure the system's safety and functionality prior to clinical translation. These findings therefore justify and inform its subsequent evaluation in subacute stroke patients.

The next chapter (Chapter 5) builds on these findings by assessing the feasibility of using the

system in subacute stroke patients, investigating both its potential as a rehabilitation tool and as an assessment platform for estimating motor impairment severity.

4.5 Additional figures

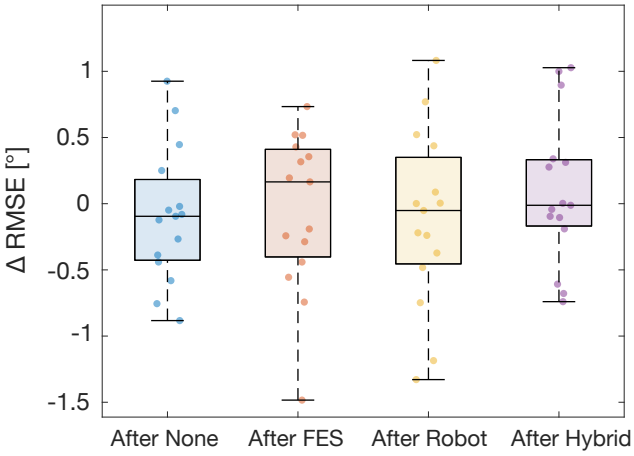


Figure 4.6: Motor adaptation during the tracking task with four different assistance conditions. Tracking performance improvement indicates the difference in participant's tracking performance before and after training; a positive result indicates that they are performing better after training.

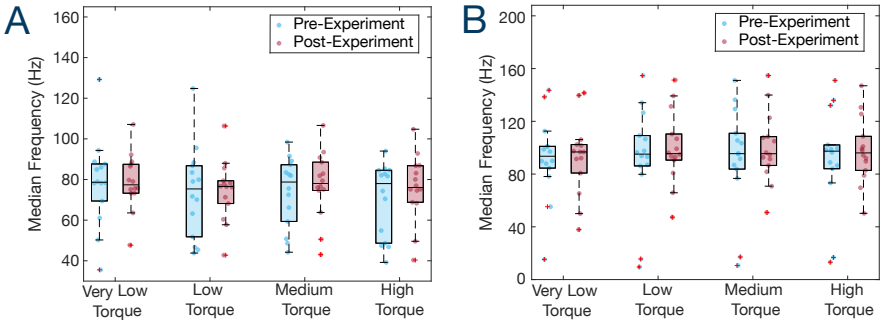


Figure 4.7: Muscle fatigue was evaluated during the EMG calibration at the start and end of the experiment, where participants had to track four different levels of torque. Fatigue is calculated as the median frequency of the EMG signal, a decrease in frequency indicates an increased fatigue. Level of fatigue for (**A**) the flexor muscles and (**B**) the extensor muscles.

Chapter 5

Feasibility of hybrid robot-FES system with subacute stroke patients in a clinical setting

The previous chapter investigated the effects of hybrid robot-FES assistance on motor performance, neuromuscular effort, and user experience in unimpaired individuals. These results established the technical feasibility and safety of the system and informed the selection of suitable control and task design for use with stroke patients. Findings indicated that hybrid assistance, combining robotic support with FES, could enhance tracking performance and increase voluntary muscle engagement in unimpaired participants, while remaining well tolerated and not inducing fatigue. These insights laid the groundwork for assessing the clinical applicability of this hybrid strategy in stroke rehabilitation.

This chapter thus addresses the next step of this thesis's translational effort by exploring the feasibility of using the developed hybrid system in subacute stroke patients. As discussed in Chapter 2, upper-limb recovery after stroke is mediated by activity-dependent neuroplasticity, and active patient participation plays a central role in promoting functional gains. Robotic devices can facilitate repetitive training with precise control, whereas FES can enhance the activation of weakened muscles by supplementing impaired voluntary drive and engaging residual neuromuscular pathways. Yet, their individual limitations, such as reduced engagement in robot-only therapy or early fatigue in FES-only training, highlight the need for combined approaches.

While previous clinical studies have explored hybrid rehabilitation paradigms (Resquin et al., 2016; Höhler et al., 2024), many employed asynchronous or modality-specific control strategies (Alon et al., 2003; Ring et al., 2005), or relied on passive robotic components that limited the synergy between modalities (Ambrosini et al., 2017; Alon et al., 2003; Ring et al., 2005; Fujiwara et al., 2009; Barker et al., 2008; Wu et al., 2011; Meadmore et al., 2014; Westerveld et al., 2014; Resquín et al., 2016). Moreover, few studies have reported objective performance and physiological metrics alongside

user feedback, which is essential to assess both neuromechanical and user-centered aspects such as comfort and motivation. This work aims to address these gaps by using the hybrid system assisting stroke patients to perform the continuous target tracking task validated in unimpaired participants (in Chapter 4).

Specifically, this chapter investigates research question QB: *Can a hybrid robot-FES system be used to aid the rehabilitation and assessment of sensorimotor functions in stroke individuals?* and explores the effect of robotic and/or FES assistance on behavioural and physiological features in subacute stroke patients. To this end, we evaluate (i) how hybrid, robotic-only, or FES-only assistance impacts patients' task performance and quality of motion during a wrist tracking task, (ii) how they affect muscular and voluntary effort, (iii) whether short-term training with each modality improves unassisted performance across sessions, and (iv) patients' subjective experience of each assistance mode. Additionally, we explore whether metrics derived from task kinematics and EMG activity can be used to predict patients' impairment severity, laying the foundation for developing objective assessment tools in future work.

Through this feasibility study, we aim to determine whether the hybrid system can be safely and effectively deployed in a clinical setting, and whether it holds potential as both a rehabilitation device and an assessment platform for upper-limb recovery post-stroke. The findings presented here will also inform the design of future intervention studies with the hybrid device, as described in Chapter 7.

This study was partly described in the following publication: Cazenave, L., Yurkewich, A., Höhler, C., Keller, T., Krewer, C., Jahn, K., Hirche, S., Endo, S. & Burdet, E., (2023). Hybrid Functional Electrical Stimulation and Robotic Assistance for Wrist Motion Training After Stroke: Preliminary Results. *IEEE International Conference on Rehabilitation Robotics.* A verbatim copy of this paper is also included in Appendix A. The work presented in this chapter and this publication was carried out in collaboration with the Technical University of Munich (TUM), the Schön Klinik Bad Aibling, and Tecnalia. Specifically, all collaborators were involved in the definition of the experimental protocol. C. Höhler, C. Krewer, K. Jahn and their colleagues from Schön Klinik Bad Aibling recruited the participants in this study and collected subsequent data, after I set up the device in the clinic and trained them to conduct the experiment. I contributed to conceiving and designing the research, developing the experimental protocol and programming the experimental task, performing the data analysis and created the figures in this chapter, and interpreting the results.



Figure 5.1: Experiment description. **A.** A patient tracks a randomly moving target on-screen with wrist flexion/extension. **B.** Overview of experimental protocol, where a patient performs a series of calibration and assessment steps followed by unassisted trials (U), where no stimulation or robotic assistance are provided, and assisted training trials (A), where patients receive hybrid assistance. 'x10' refers to the number of trials for each block, here ten. 'Q' refers to the questionnaire step.

5.1 Methods

5.1.1 Participants

The study was run at the Schön Klinik Bad Aibling and was approved by the Ethics Committee of the Ludwig-Maximilians University (LMU) Munich, Germany (number: 22-0297, DRKS registration: 00030586). All participants or their legal representatives signed an informed consent form prior to participating in the experiment. The participants in this study are subacute stroke patients staying at the inpatient rehabilitation hospital after an ischaemic or haemorrhagic infarction.

The inclusion criteria are as follows: age >18 years old, cognitively able to follow instructions, with functional impairments in the wrist or fingers as assessed by the Medical Research Council score (MRC ≤ 3) and low level or no pain in the wrist or fingers (Numeric Rating Scale <4). Exclusion criteria can be divided in robot-related and FES-related exclusion criteria. Robot-related exclusion criteria are: severe contractures or muscle tone resulting in the operator's inability to position the patient's arm in the device and flex or extend the wrist more than 20°. FES-related exclusion criteria are: pregnancy, presence of implantable devices or other metal implants in the stimulated area, no motion or muscle contraction resulting from FES, patients with severe epilepsy and cancer or wounds in the stimulated area. Patients are also excluded if they had a severe psychiatric disorder or had no function as well as no deep sensitivity in the fingers or wrists.

5.1.2 Protocol

The experimental protocol is outlined in Fig. 5.1 B. Once recruited, patients are randomised into one of three intervention groups: Robot, FES or Hybrid (Robot+FES), which determines the assistance mode that they would receive during the assisted training over the three intervention sessions. Prior to the three intervention sessions, an initial calibration session is scheduled for the patients to familiarise

themselves with the system and to perform the first FES calibration as detailed below. Following this, the patients participated in three intervention sessions of around one hour each, separated by at least one break day. Each session is identical, starting with the FES calibration, followed by a ROM calibration and the experimental task.

FES calibration

As further detailed already in Chapter 3, Section 3.1.2, the electrode location, comfortable maximum stimulation (s_f^{max} for the wrist flexion, and s_e^{max} for the wrist extension) and sensory threshold (s_f^{min} and s_e^{min}), for the wrist flexion and extension movements, are identified. In the initial calibration session prior to the three main sessions, the electrode locations are marked on the patient's skin if there are no dermatological counter-indications, so that the electrodes can be placed in a similar location in the three sessions. The stimulation parameters are also noted down for the same purpose.

Subsequently, the patient is asked to relax while the stimulation amplitude is applied for 2 seconds and increased from s_{min} to s_{max}, with a resolution of 1 mA while the generated torque is recorded. There is a 2-second rest between each stimulation. This is done to empirically identify the coefficients of the mapping between the stimulation amplitudes s_f and s_e and the produced torques τ_f and τ_e (Eq. 5.1) in each session, avoiding the assumption of a linear mapping between the minimum and maximum calibrated stimulation amplitudes. The linear mapping was previously used in unimpaired participants, but may not be valid in stroke populations where the muscular response to FES may be more variable. Preliminary testing indicated that the relationship between stimulation amplitude and torque could be approximated by a second order exponential for the flexion and extension movements respectively, such that:

$$\begin{aligned} s_f &= f(\tau_f = \alpha_f\, e^{\beta_f\, \tau_f} + \delta_f\, e^{\gamma_f\, \tau_f(t)} \\ s_e &= f(\tau_e = \alpha_e\, e^{\beta_e\, \tau_e} + \delta_e\, e^{\gamma_e\, \tau_e} \end{aligned} \tag{5.1}$$

with α, β, γ, $\delta \in R$ are coefficients of the exponential terms. This mapping is used to determine the required FES amplitude when the patients are assisted by the hybrid system, and ensure that the FES and robot assistance provide similar torque levels.

ROM calibration

The ROM calibration is performed as an assessment of patient's progress but also to adjust the target trajectory amplitude to each patient, so that it does not go beyond the patient's passive ROM but still challenges them beyond their active motion abilities. It starts with a passive calibration, where the experimenter moves the handle of the robot in the flexion direction until they feel a resistance or a discomfort reported by the patient. This is also done in the extension direction and the cycle is repeated three times, the maximum flexion and extension angles are kept and define the patient's

PROM. After that, an active calibration is repeated three times, where the patient is asked to actively move their wrist as far as they can in flexion and then extension. Similarly as for the passive one, the maximum flexion and extension angles reached by the patient are used to define the patient's AROM. This sequence is followed so that the patient becomes familiar with this task and the visuals on-screen during the passive ROM and can then reproduce it in an active manner during the active ROM.

Experimental task

In the remaining parts of the session, the patient performs a target tracking task with the wrist flexion/extension movements of their impaired hand, either unassisted (baseline and evaluation trials in Fig. 5.1 B) where no FES or robotic assistance is provided, or assisted by the system (two training blocks), where the patient received FES and/or robotic assistance, depending on the group they are assigned to upon recruitment. Ten unassisted trials are first completed by the patient as a baseline. The first training block consists of 30 assisted trials, and is followed by five unassisted trials as intermediate evaluation. If time allows and the patient still feels comfortable and able to maintain concentration, a second training block of 30 assisted trials is performed and followed by the final evaluation block of ten unassisted trials. If the second training is not performed, five additional unassisted trials are completed so that the session ends in a similar way, with 10 unassisted trials, considered as the final evaluation block.

Each trial lasts 12 seconds with a 3 second break. The rest time can be prolonged as desired by the patient. After the first training block and the first evaluation block, patients answer a set of questions on the comfort of the system, the perception and usefulness of the assistance, as well as two questions taken from the enjoyment section of the Intrinsic Motivation Index.

In each trial, the patient tracks a moving target on a computer monitor placed in front of them. The target trajectory is defined similarly as the one previously used in unimpaired participants (in Chapter 4), but here the frequencies have been adapted to the stroke population, following preliminary testings with clinicians and patients, for the target to be slower. We used:

$$q^*(t) = q^*_{mid} + q^*_{max} \sin\Big(0.2586\, t^+\Big) \sin\Big(0.1860\, t^+\Big) \tag{5.2}$$

where q^* is the target angle, $t^+ = t + t_0$, with t the elapsed time and t_0 selected to ensure that the target would start at the position of the user and to prevent consistent prediction of the target trajectory by the user. q^*_{mid} is the middle point of the target range and the amplitude from that point to the maximum range is q^*_{max}. These are determined from the maximum target amplitude in flexion q_f^{max} and in extension q_e^{max}, where the target is defined to go up to 30% beyond the active ROM of

the patient but capped by their passive ROM:

$$q^*_{max} = \frac{|q_f^{max} - q_e^{max}|}{2}, \qquad q^*_{mid} = \frac{q_f^{max} + q_e^{max}}{2}. \tag{5.3}$$

Patients are instructed to track the target as accurately as possible and told that they may feel haptic interaction from the robotic device and/or electrical stimulation.

5.1.3 Hybrid Robot-FES system

The electrical stimulation and robotic devices used have been described in Chapter 3, Section 1. Muscle activity of the wrist flexor (flexor carpi radialis) and wrist extensor (extensor carpi radialis longus) is recorded at a frequency of 1500 Hz using bipolar EMG electrodes (Noraxon, USA). The system was cleaned before and after each use. The pulse frequency of the stimulation is set to 35 Hz and the pulse width to 300 μs as these values have been used clinically (Kapadia et al., 2013), and as tested with unimpaired participants (Chapter 4). The amplitude of the stimulation varies (with 0.1 mA resolution) during the experiment. The control of the hybrid system used is the same as in the study with unimpaired participants (Chapter 4), where the amount of robotic assistance (robot torque: u_r) and FES assistance (stimulation in the flexor s_f and extensor s_e muscles) is proportional to the tracking error and the connection stiffness is $K = 0.42$ Nm/rad corresponding to a soft-medium interaction stiffness (Ivanova et al., 2020). It has been selected after preliminary testings with clinicians and patients to assist them in the task while preventing slacking.

The control of the hybrid robot-FES system depends on the intervention group that the patient was assigned to: {hybrid, robot ($s_e \equiv 0, s_f \equiv 0$), FES ($u_r \equiv 0$)}. In the hybrid group, patients receive the same robot assistance as patients in the robot group as well as the same FES assistance as those in the FES group.

5.1.4 Data analysis

We collected both quantitative and qualitative data to compare the separate and combined use of robotic and FES assistance on performance and effort changes in the task under the three assistance modalities, as well as on patients' perceptions of the system's comfort, the usefulness of the assistance and their enjoyment of the task.

As previously presented in Chapter 3, Section 3.3.1 and used in Chapter 4, performance was measured using the RMSE between the patient and target trajectories, normalised by the target range, which was calibrated to each patient's ROM. The Spearman's correlation between the frequency spectra of the target and the patient's trajectory was also used to quantify how well participants followed the target as well as whether their movement was jerky. Muscle activity was characterised

using cocontraction (CC) and reciprocal activation (RA) indices derived from surface EMG recordings as described in Chapter 3, Section 3.3.2, when these were available (EMG was not recorded for ten patient-session pairs due to technical issues). Both metrics were normalised by the maximum contraction obtained during the EMG calibration phase. For subsequent analyses, the channel on the extensor and flexor arrays with the highest envelope amplitude during the EMG calibration was selected. All metrics were calculated for each trial during the ten baseline trials and the 30 trials of the first training block, which are the two phases of the experiment (unassisted, assisted). The average across the baseline trials and the training trials were obtained and used for the analysis.

Subjective feedback was obtained via the following questionnaire administered at the end of each unassisted and assisted phase. The NASA-TLX was used to assess their perceived workload (Hart et al., 1988). They also answered questions about the comfort and usefulness of the assistance and of two questions taken from the enjoyment section of the Intrinsic Motivation Index. Average scores across sessions (for the unassisted and assisted phases separately) were used for analysis.

- How mentally demanding was the task?
  (1 = very low; 10 = very high)
- How physically demanding was the task?
  (1 = very low; 10 = very high)
- How hurried or rushed was the pace of the task?
  (1 = very low; 10 = very high)
- How successful were you in accomplishing what you were asked to do?
  (1 = very bad; 10 = very good)
- How hard did you have to work to accomplish your level of performance?
  (1 = very low; 10 = very high)
- How insecure, discouraged, irritated, stressed, and annoyed were you?
  (1 = very low; 10 = very high)
- The device was comfortable.
  (from 'strongly disagree' to 'strongly agree')
- During the experiment, I felt some assistance.
  (from 'strongly disagree' to 'strongly agree')
- The device improved my performance.
  (from 'strongly disagree' to 'strongly agree')

- I enjoyed this activity very much.
  (from 'strongly disagree' to 'strongly agree')

- I would like to use this device in my therapy.
  (from 'strongly disagree' to 'strongly agree')

5.1.5 Statistical analysis

To assess the effects of assistance, training, and impairment on task performance and muscle activation, linear mixed-effects models (LMEs) with restricted maximum likelihood estimation were fitted. The dependent variables were the four primary outcomes: normalised RMSE, spectral correlation, normalised cocontraction, and normalised reciprocal activation. The statistical analyses were performed in R (version 2024.4.2) using the `lmerTest` and `emmeans` packages. The significance level was set at $\alpha = 0.05$ for all tests.

Fixed effects included Phase (unassisted vs. assisted), Session (numeric predictor for sessions 1, 2, 3), Group (FES, Robot, Hybrid), and baseline motor impairment FM-UE (centered FM-UE score). Two-way interactions between FM-UE and Phase or Session were included to test whether the assistance effects or the metrics trends over time changed with patients' the impairment level. Patients' IDs were included as a random intercept to account for repeated measures within participants.

When main effects or interactions were significant, planned contrasts were estimated with estimated marginal means: (i) Phase contrasts (assisted vs. unassisted) globally and/or within groups, (ii) Session slopes (training trends) within groups and/or phases, (iii) Comparisons of FM-UE slopes between the two phases. P-values for multiple contrasts were adjusted with Bonferroni-Holm's method.

For the questionnaire answers, Kruskal–Wallis rank sum test (between-subject: group) was used to investigate potential effect of the intervention group on questionnaire answers, due to ordinal data and non-normal distributions.

All analyses followed an intention-to-treat principle, whereby all available data were included even when some sessions were missing, except for longitudinal analyses, which required complete data across all sessions.

5.1.6 Estimating FM-UE scores from extracted metrics

We developed regression models to estimate upper-limb motor impairment, quantified by FM-UE, from metrics extracted from kinematics and EMG data in the first five trials of the unassisted baseline. This was to determine whether impairment severity could be monitored while patients performed their rehabilitation training.

Cross-validation scheme Model training and evaluation followed a nested cross-validation procedure. At the outer level, five folds were used to partition the dataset into independent training and testing sets. For each outer training set, an additional five-fold inner cross-validation was performed to optimise feature selection and model hyperparameters.

To avoid information leakage between folds, cross-validation was carried out at the participant level. In both outer (train/test) and inner (train/validation) partitions, participants were uniquely assigned to a single split. This design ensured that all trials from a given participant were either included in training or in validation/testing, but never both.

Extracted features To characterise motor performance, a wide range of kinematic- and EMG-based metrics was extracted from the tracking and muscle activity data. These features were then used as input for regression models estimating FM-UE scores. Three datasets were considered: (i) a kinematic dataset containing only movement-derived features, (ii) an EMG dataset containing only muscle-activity-derived features, and (iii) a combined dataset merging both kinematic and EMG features.

For the kinematic data, we computed a broad set of metrics capturing various aspects of participants' movements. These included:

- **Accuracy and error metrics:** root mean square error (RMSE and normalised RMSE), mean absolute error (MAE and normalised MAE), dynamic time warping distance between the participant and target trajectories, and absolute differences between peaks of participant and target trajectories, as well as the cross-correlation between the participant and target trajectories and their Spearman's correlation.
- **Smoothness metrics:** spectral arc length (SPARC) (Balasubramanian et al., 2015) and jerk-based indices (number of zero-crossings of jerk, log-dimensionless jerk, log-normalised jerk, dimensionless jerk) (Hogan et al., 2009; Balasubramanian et al., 2012).
- **Range-of-motion (ROM) metrics:** maximum and minimum joint angles, trajectory ROM, and differences or ratios relative to the target.
- **Variability metrics:** trajectory standard deviation and its ratio with the target standard deviation, and path length ratios.
- **Velocity-based features:** mean, peak, and standard deviation of velocity, peak velocity ratio, velocity error and ratio relative to the target.
- **Frequency-domain metrics:** dominant frequency errors, ratios, and phase lags, as well as the RMSE, MAE, integral error, and correlation between the spectra of the participant and target trajectories, both across the full spectrum and restricted to the low-frequency range (< 20

Hz). The coefficient of determination (R^2) from a four-sine fit was used to quantify how well participant trajectories could be represented as a sum of sinusoidal components.

For the EMG data, we extracted envelope- and frequency-based features:

- **Envelope metrics:** mean, peak, and RMS values of flexor and extensor activity, total activation, and derived indices such as cocontraction and reciprocal activation, with normalisation to maximum voluntary contraction where applicable. Trial-level moving-window estimates of these measures were also included.

- **Spectral EMG features:** median and mean frequencies, maximum frequency components, and spectral descriptors such as the Dimitrov index (Dimitrov et al., 2006), the mean and variance of the instantaneous mean and median frequency of Choi-Williams time-frequency distribution (Choi et al., 1989; Karlsson et al., 2000).

- **Motion-specific metrics:** all features above were computed for the full movement as well as separately during identified flexion- and extension-only periods, to capture motion-specific behaviour.

Feature preprocessing and selection Within each outer fold, training and test features were z-normalised (zero mean, unit variance) using parameters computed from the training set. Several feature selection strategies were compared within the inner cross-validation, including correlation-based thresholds (0.7, 0.8, 0.9), principal component analysis (PCA, retaining 95% of variance), LASSO regression, recursive feature elimination (RFE), ReliefF, χ^2 tests, and Kruskal–Wallis tests, alongside the use of all features. The feature selection method yielding the lowest average mean absolute error (MAE) across inner folds was chosen and subsequently applied to the outer test set to obtain the model performance.

Regression models We evaluated a diverse set of machine learning algorithms:

- Linear models (ordinary least squares, robust linear regression),

- Support vector regression (SVR) with hyperparameter optimisation,

- Ensemble methods, including random forests (with and without surrogate splits, the latter providing robustness to missing values), boosted trees (with and without surrogate splits), and fully optimised ensembles,

- Bayesian-optimised neural networks with varying layer sizes and activation functions.

Hyperparameters for SVR, ensemble methods, boosted trees, random forests, and neural networks were optimised using Bayesian optimisation (expected-improvement acquisition, maximum 200 evaluations).

We also included a baseline "mean" model that predicts for each subject the mean FM-UE score of the training set. This provides a simple reference for model comparison and represents the minimal performance expected from any regression approach.

Performance analysis Model performance was evaluated on outer test sets using the mean absolute error (MAE), as it directly reflects the average magnitude of error in FM-UE estimation.

For each dataset (kinematics, EMG, combined), we statistically compared model performance using non-parametric Friedman tests. All models, including the baseline mean predictor, were included in these comparisons. Where significant main effects were found, pairwise Wilcoxon signed-rank tests were conducted between the best-performing model (lowest mean MAE) and (i) the baseline mean model, and (ii) the linear regression model. This was performed for each dataset individually. The best models for each dataset were then compared against each other using a Friedman test again and pairwise comparisons when the result was significant.

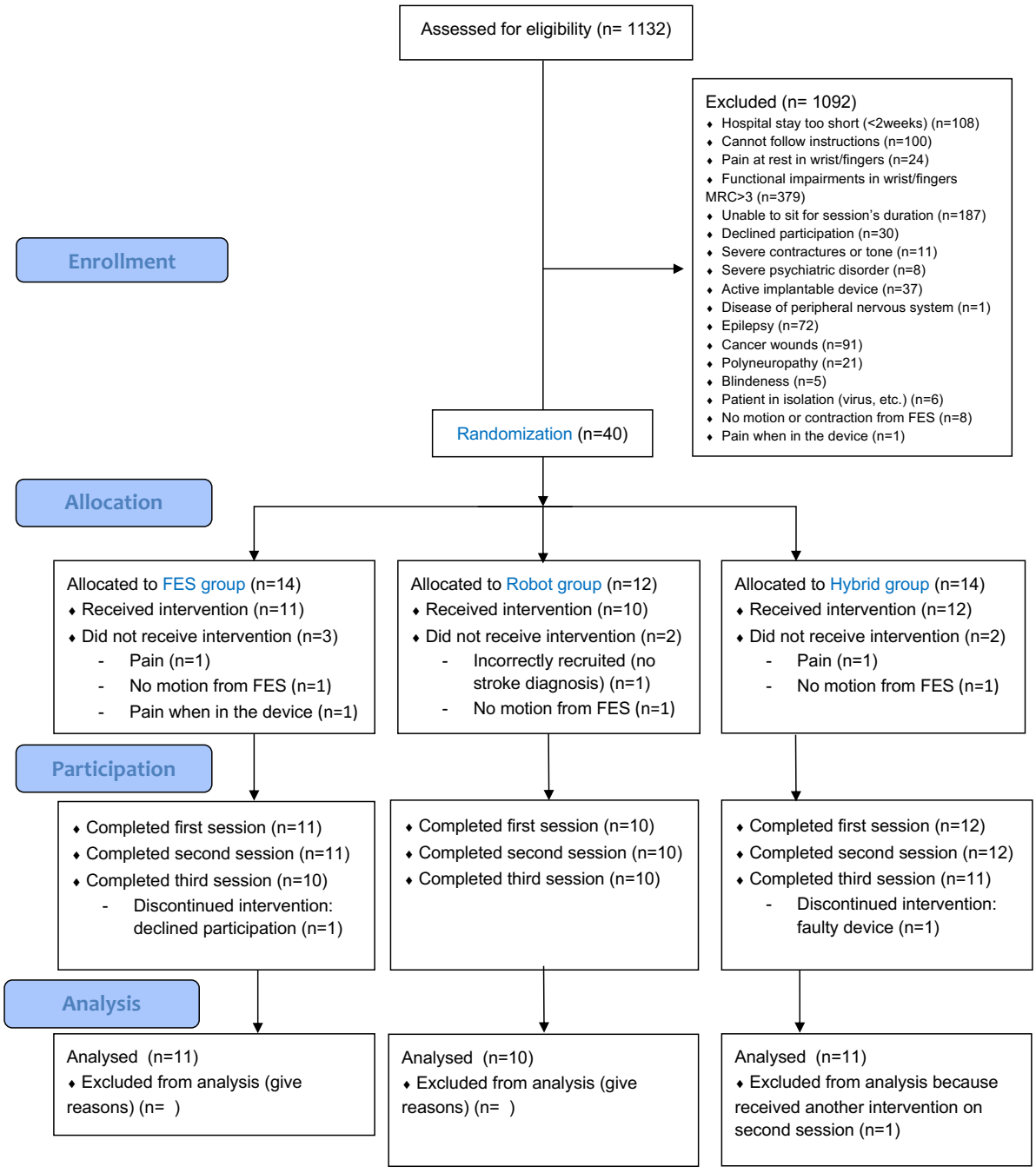


Figure 5.2: Consolidated Standards of Reporting Trials (CONSORT) diagram, showing participants screening, group allocation, participation and data analysis.

Table 5.1: Patient demographics

Group	Sex (M | F)	Age, years, mean (sd)	Side of paresis (R | L)	Time since stroke, weeks, mean (sd)	FM-UE mean (sd)
Total	22 | 10	66 (14)	15 | 17	11 (7)	19 (14)
FES	9 | 2	61 (18)	5 | 6	15 (8)	15 (11)
Robot	7 | 3	69 (11)	7 | 3	9 (6)	23 (15)
Hybrid	6 | 5	68 (11)	3 | 8	9 (4)	20 (17)

FM-UE: Fugl-Meyer Upper-Extremity score, maximum score: 66.

5.2 Results

5.2.1 Participants

2032 patients were screened from October 25 2022 date to June 6 2025 (Fig. 5.2). 40 patients were recruited and 30 completed the full three-session intervention (Table 5.1) (two patients did not complete the third session but were included for the analysis on the assistance effect). Twenty-two patients were severely impaired (Fugl-Meyer Upper-Extremity score (FM-UE≤25), four moderately impaired (25≤FM-UE≤40) and four mildly impaired (FM-UE>40) (Woytowicz et al., 2017). The FM-UE score is missing for two patients. Additionally, the FM-UE baseline scores did not differ significantly across intervention groups ($F(2, 27) = 0.60, p = 0.556$), indicating that the baseline impairment level of participants was similar across groups. The time since stroke was also not significantly different across groups ($\chi^2(2) = 4.83, p = 0.089$).

5.2.2 Assistance

We report the effect of assistance from the robot, FES, or both, on the performance and EMG metrics. The Phase factor (unassisted U1/assisted A1) was considered to assess whether the assistance provided to patients during the target-tracking task improved their performance and whether differences were observed between assistive modalities. Plots of the mean metric values across sessions in the unassisted and assisted trials for each group are displayed in Fig. 5.3.

The LME revealed a strong main effect of Phase ($F(1, 132.8) = 13.70$, $p < 0.001$) on the normalised RMSE between the patient and target trajectories (Fig. 5.3 A). A significantly lower RMSE was observed during assisted trials compared to unassisted trials (U1–A1 difference $= 0.134 \pm 0.013$, $t(133) = 10.35$, $p < 0.0001$). This indicates, as expected, that providing patients with assistance to perform the task increases their performance. However, the assistance modality does not affect this improvement (Group effect: $F(1, 81.4) = 0.4392$, $p = 0.6460$). Additionally, a significant Phase × FM-UE interaction was also observed ($F(1, 132.8) = 9.24$, $p = 0.0028$), where pairwise contrasts indi-

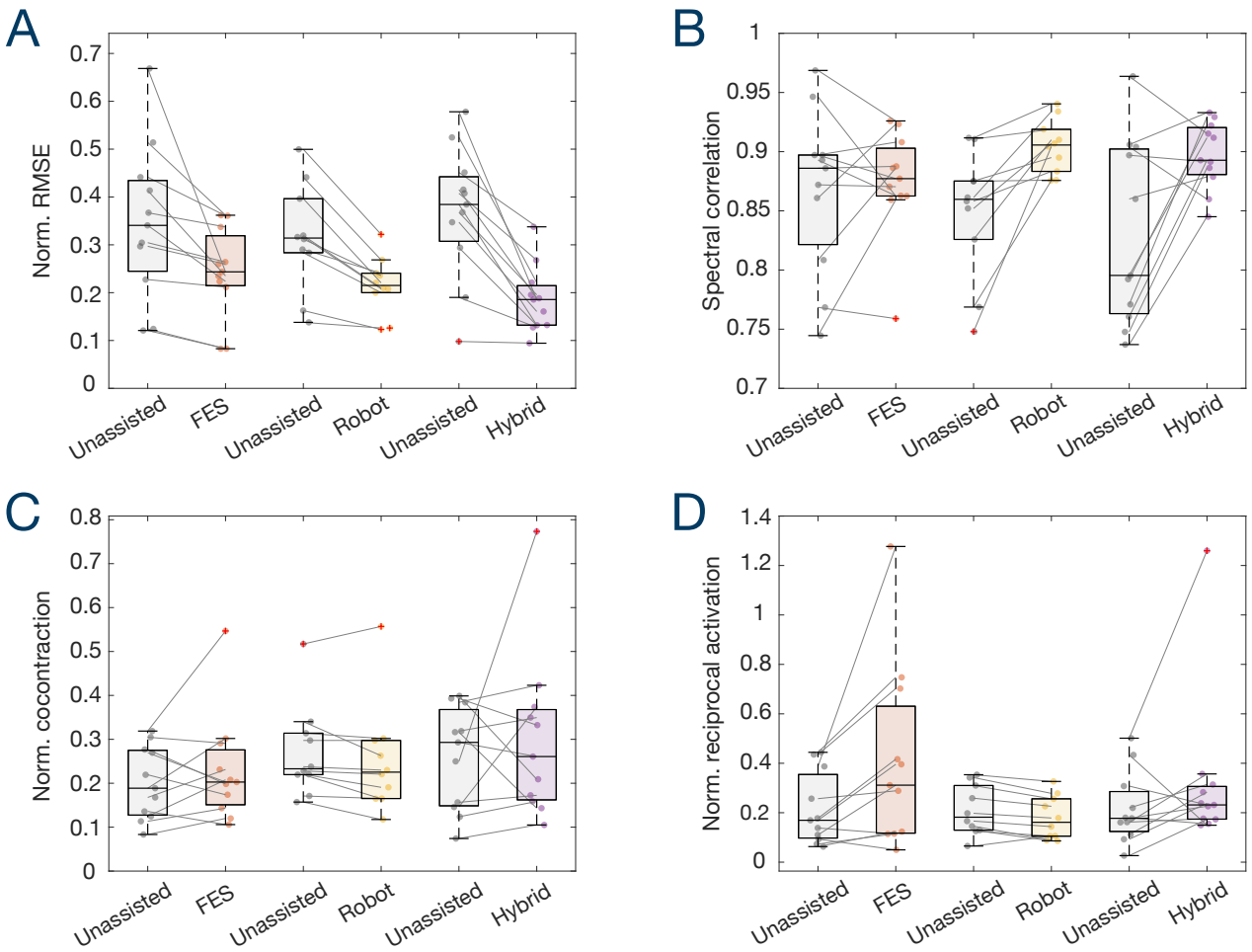


Figure 5.3: Assistive effect of the FES and robot during the target-tracking task. **A.** Effect of the assistance on the normalised RMSE between the patient and target trajectories. **B.** Effect of the assistance on the correlation between the frequency spectra of the patient and target trajectories. **C.** Effect of the assistance on the cocontraction of the wrist flexor and extensor muscles. **D.** Effect of the assistance on the reciprocal activation of the wrist flexor and extensor muscles.

cated that the reduction in RMSE with assistance was larger in more impaired patients (Additional Figure 5.7 A). The FM-UE slope differed significantly between U1 and A1 (U1–A1 slope difference $= -0.00295 \pm 0.00097$, $t(133) = -3.04$, $p = 0.0028$). This indicates that the benefit of assistance is especially strong for more impaired patients (lower FM-UE), who typically cannot perform very well in the unassisted trials due to the lack of volitional movement. No main effect of Group or other interactions reached significance ($p > 0.06$).

For the correlation between the frequency spectra of the patient and the target trajectories, the main effect of Phase was not significant ($F(1, 132.1) = 3.33$, $p = 0.070$) (Fig. 5.3 B), but a Phase × FM-UE interaction was detected ($F(1, 132.1) = 19.64$, $p < 0.0001$). Follow-up contrasts confirmed that FM-UE strongly predicted performance improvement with assistance (U1–A1 slope difference $= 0.00254 \pm 0.00057$, $t(132) = 4.43$, $p < 0.0001$). Similarly as with the normalised RMSE, the patients with higher impairment gained proportionally more from the assistance in terms of spectral correlation (Additional Figure 5.7 B). No other main effects or interactions were significant ($p > 0.07$).

For the cocontraction, no main effects of Phase, Group, or FM-UE were observed (all $p > 0.11$) but a three-way Phase × Session × Group interaction ($F(2, 116.78) = 3.23, p = 0.043$) was found. The cocontraction levels in the unassisted and assisted trials in each group can be seen in Fig. 5.3 C. Follow-up analyses revealed group-specific patterns. When comparing assisted and unassisted trials within each group across sessions, patients in the FES groups showed significantly lower cocontraction in unassisted than assisted trials at the average session (U1–A1 slope difference = $-0.182 \pm 0.064, t(117) = -2.85, p = 0.005$). By contrast, no such phase differences were found in the Robot group ($p = 0.88$), and patients in the Hybrid group showed a trend towards increased cocontraction with assistance (U1–A1 slope difference = $-0.135 \pm 0.068, t(117) = -1.97, p = 0.051$). Additionally, a significant Phase × FM-UE interaction was observed ($F(1, 116.8) = 6.85$, $p = 0.01003$). Planned contrasts showed significant differences between phases (U1–A1 slope difference = 0.00704 ± 0.00269, $t(117) = 2.617$, $p = 0.0100$), indicating that impairment level modulated the degree to which assistance altered antagonist muscle coactivation. Patients with higher FM-UE thus tended to show larger reductions in cocontraction in the assisted phase (Additional Figure 5.7 C).

For reciprocal activation (RA), the model revealed no main effect of Phase ($F(1, 115.82) = 0.07, p = 0.793$) or Group ($F(2, 115.25) = 2.68, p = 0.073$) (Fig. 5.3 D). There was also a significant main effect of FM-UE ($F(1, 115.63) = 8.00, p = 0.006$), and this effect interacted with Phase (Phase × FM-UE, $F(1, 115.82) = 7.20, p = 0.008$). However, follow-up analyses did not reveal a significant increase in RA with higher FM-UE when investigating each phase separately ($p > 0.19$) (Additional Figure 5.7 D).

5.2.3 Training

With the LMEs, we also investigated the temporal effect of training with the robot, FES or both over three sessions and examined any potential changes, specifically in the unassisted performance and muscle activity metrics of patients, which may indicate some task learning. Plots of the metric values over sessions in the unassisted and assisted trials for each group are displayed in Fig. 5.4.

For the normalised RMSE between the patient and target trajectories, no significant main effect of Session ($F(1, 134.1) = 0.352$, $p = 0.5541$) or Session × Group interaction ($F(1, 132.8) = 0.066$, $p = 0.063$) was found, indicating no systematic improvement in unassisted performance across sessions. The unassisted normalised RMSE over the three sessions is displayed in Fig. 5.4 A.

Similarly for the spectral correlation, there was no significant main effect of Session ($F(1, 134.3) = 1.24$, $p = 0.27$) or Session × Group interaction ($F(1, 134.51) = 1.625$, $p = 0.201$), indicating that the tracking performance did not improve consistently across repeated sessions. The evolution of the spectral correlation over unassisted trials is displayed in Fig. 5.4 B. This suggests that the main gains in performance occur during assisted trials within sessions, rather than cumulatively across repeated

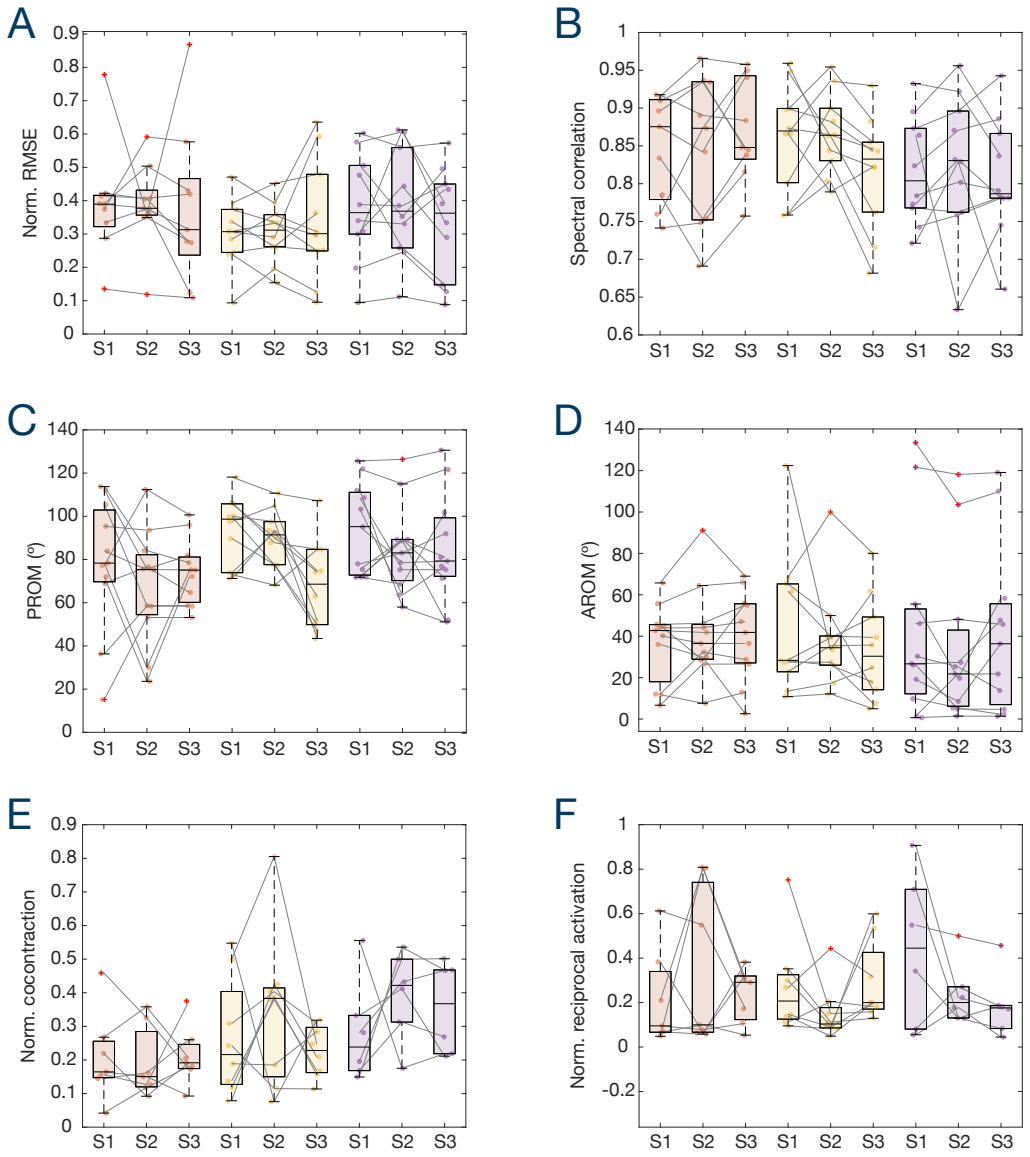


Figure 5.4: Temporal evolution of the unassisted performance and muscle activity during the target-tracking task. **A.** Effect of the training on the normalised RMSE between the patient and target trajectories. **B.** Effect of the training on the correlation between the frequency spectra of the patient and target trajectories. **C.** Effect of the training on the cocontraction of the wrist flexor and extensor muscles. **D.** Effect of the training on the reciprocal activation of the wrist flexor and extensor muscles.

exposure. The expected training or learning effect of the task through this repeated assistive training was not observed here in any of the groups. Furthermore, the variability across all sessions in both tracking metrics remains quite high, hinting at heterogeneous adaptation patterns or the lack thereof, although patients' FM-UE scores did not have a significant interaction effect with Session ($p = 0.946$) (Additional Figure 5.8 B).

Regarding cocontraction, a significant Phase × Session × Group interaction was detected ($F(2, 118.6) = 5.17$, $p = 0.0432$). However, further exploration of group-wise trends within phases indicated that in the unassisted condition, session trends were small and non-significant across groups (all $p > 0.09$) (Fig. 5.4 E). As with the performance metrics, these results suggest that training did not systematically reduce CC within groups over the three sessions and that it is likely that learning did not occur

here, potentially due to this short training period. Additionally, there was a significant interaction between Session and FM-UE score ($F(1, 118) = 5.17, p = 0.025$). Post-hoc analyses revealed that session-related trends differed by impairment severity (Additional Figure 5.8 C): mildly impaired patients (FM-UE > 40) showed a significant reduction in CC across sessions (slope $= -0.115 \pm 0.055$, $p = 0.0367$), whereas no consistent changes were observed in moderate or severely impaired groups ($p > 0.057$). Pairwise comparisons indicated that session slopes differed significantly between mild and severe patients ($p = 0.037$).

For reciprocal activation, the model revealed significant main effects of Session ($F(1, 123.2) = 4.85$, $p = 0.030$) and a Session $\times$ Group ($F(2, 122.8) = 8.05$, $p = 0.0005$) interaction. However, the interaction between Phase and Session was not significant ($p = 0.500$) (Fig. 5.4 F), as both assisted and unassisted trials are grouped in post-hoc tests. Group-wise analyses indicated that RA increased significantly over sessions in the Hybrid group (sessions slope $= 0.118 \pm 0.028$, $p < 0.001$), whereas FES and Robot groups showed no significant trends ($p > 0.3$). Similarly as for the cocontraction, we found a significant interaction between Session and FM-UE score ($F(1, 118) = 12.76, p = 0.0005$). When analysing session-related trends by impairment severity (Additional Figure 5.8 D), we also observed a significant reduction in RA over session in mildly impaired patients (slope $= -0.0773 \pm 0.0335$, $p = 0.0225$), but no changes in the moderate and severely impaired groups ($p > 0.1$). Pairwise comparisons between the severity groups also indicated that session slopes differed significantly between all severity groups (all $p = 0.0015$).

We also investigated the evolution in the passive and active ROM (Fig 5.4 C,D) over sessions, which was recorded at the start of each session during the ROM calibration. There we investigated the effect of Session, Group and FM-UE score on each metric. For the PROM, we found a significant effect of Session ($F(1, 51.66) = 6.27$, $p = 0.1546$), Group ($F(2, 77.98) = 3.980$, $p = 0.2260$), and Session $\times$ Group effect ($F(2, 51.79) = 5.846$, $p = 0.192$). When further investigating the group-wise difference in the PROM slopes over sessions, we found a significant decrease in PROM only for patients in the Robot group (session slope $= -14.23 \pm 3.62$, $p = 0.0003$) and no significant changes were observed in the FES and Hybrid groups ($p > 0.6$). When investigating the slope differences between groups, no significant differences were found (FES-Robot and Hybrid-Robot: $p > 0.0503$, Hybrid-FES: $p = 0.884$). For the AROM, we found a significant effect of FM-UE ($F(1, 68.8) = 17.62$, $p < 0.0001$), but no other significant effect (all $p > 0.3$). As expected this indicates that patients with more severe impairments had a smaller active ROM.

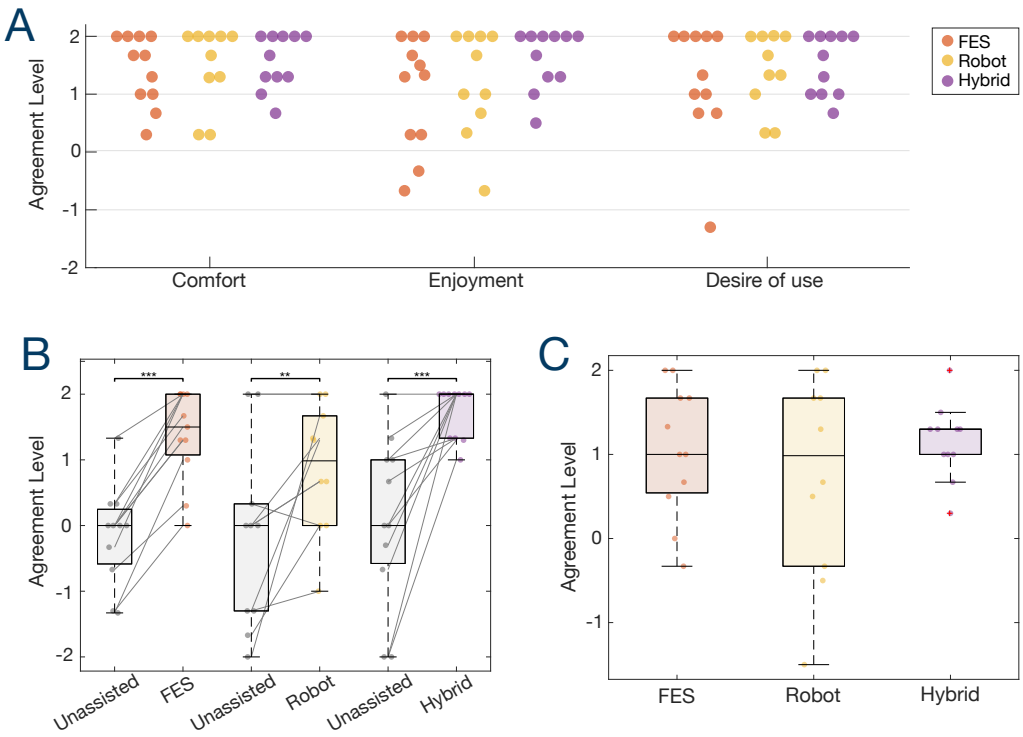


Figure 5.5: Subjective perception of the unassisted and assisted target-tracking task for each intervention group, reported by patients through a 5-point Likert Scale questionnaire, from 'Strongly disagree' (-2) to 'Strongly agree' (2). **A.** Answers to the questions (figure from left to right): 'The use of the device was comfortable', 'I enjoyed doing this activity very much', 'I would like to use this system for my upper-limb therapy in the clinic'. **B.** Answers to the questions 'During the experiment, I felt assistance' after the unassisted and assisted trial. **C.** Answers to the questions 'The use of the device improved my performance'.

5.2.4 User experience

After the assisted training block, we asked patients about the comfort using the device, whether they enjoyed the activity, and whether they would use this system for their upper-limb therapy in the clinic. The Kruskal–Wallis tests find no significant group differences in the reported comfort ($\chi^2(2) = 0.36698$, $p = 0.8324$), enjoyment ($\chi^2(2) = 2.3377$, $p = 0.3107$), or desire of use ($\chi^2(2) = 0.4166$, $p = 0.812$). Across all metrics, ratings were generally high, indicating a positive reception of the training regardless of the intervention modality. Comfort ratings were consistently positive across participants, with minimal variance, suggesting that none of the assistance modes introduced notable physical discomfort, even when electrical stimulation was applied. Enjoyment scores were high as well, reflecting good engagement with the task, while desire of use ratings indicated a general willingness to continue using the device, regardless of modality. Although the statistics do not support significant between-group effects, the distribution of the data suggests slightly more clustered high ratings in the Hybrid group for the answers regarding patients' enjoyment and desire to further use the device, potentially due to the perceived benefit of dual-modal assistance or the generally higher assistance level.

We also investigated whether patients perceived the provided assistance and their perception of the assistance. We asked them whether they felt any assistance during the task both after the assisted

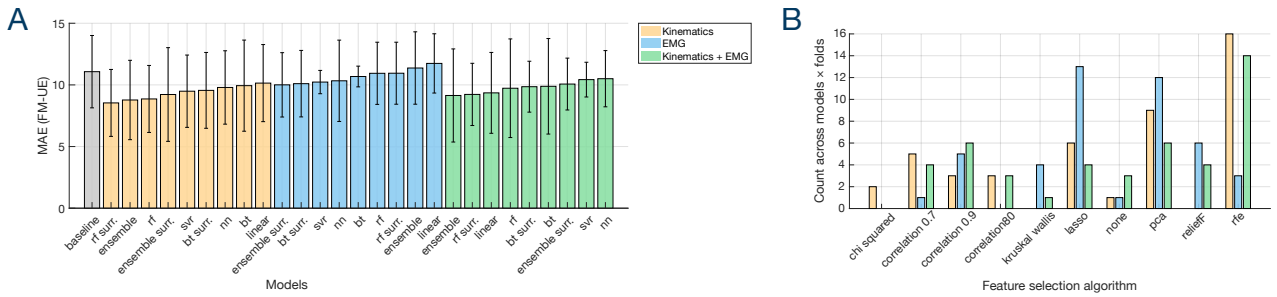


Figure 5.6: Estimating FM-UE scores of patients using kinematic and EMG data collected in the first five unassisted baseline trials of the first session. **(A)** Models performance (mean absolute error) across the three datasets. Models compared include: baseline mean predictor (base), random forest with surrogate splits (rf surr.), linear regression (linear), random forest (rf), boosted trees with surrogate splits (bt surr.), support vector regression (svr), ensemble of learners (ensemble), boosted trees (bt), ensemble with surrogate splits (ensemble surr.), and neural networks (nn) **(B)** Frequency of feature selection algorithms applied across regression models and outer folds, for the three datasets. Feature selection methods included: no feature selection (none), recursive feature elimination (RFE), principal component analysis (PCA), least absolute shrinkage and selection operator (LASSO), correlation-based selection with thresholds of 0.9 (Corr. 0.9) or 0.7 (Corr. 0.7), principal component analysis (PCA), reliefF, chi-squared test–based feature selection, and Kruskal–Wallis test–based selection.

trials and after the unassisted trials (Fig. 5.5 B). The 2×3 mixed ANOVA (Phase vs. Group) indicated a significant main effect of assistance type ($F(1, 29) = 56.2901$, $p < 0.0001$), but no significant main effect of group ($F(2, 29) = 1.1410$, $p = 0.3334$) or interaction ($F(2, 29) = 0.9664$, $p = 0.3923$). Post-hoc comparisons indeed reveal that patients perceived the increase in assistance between the unassisted and assisted trials in all groups (FES: $p = 0.0001$; Robot: $p = 0.004$; Hybrid: $p < 0.0001$). Visual inspection of the figure indicates that the FES and Hybrid groups displayed slightly higher median ratings, possibly reflecting the more tangible or noticeable nature of electrical stimulation compared to purely mechanical guidance, especially with this compliant controller. The ceiling effect of this questionnaire could also limit the effect of the Group on the answer.

Furthermore, we asked patients after the assisted training block how useful the assistance was (Fig. 5.5 C). Although the Kruskal–Wallis test does not reveal a significant effect of group (FES, Robot, Hybrid) on perceived usefulness of the assistance ($\chi^2(2) = 2.237$, $p = 0.3268$), it can be observed that the variance of the answers in the Hybrid group was smaller with all patients considering the assistance useful. On the other hand, the variance in the Robot group was larger with some patients finding the assistance not useful to perform the task.

5.2.5 Assessment

The performance of the regression models trained on the kinematics, EMG and kinematics+EMG features to estimate patients' FM-UE scores is displayed in Fig. 5.6 A. Data from 28 patients were considered as for some patients, EMG was not recorded in the first session and hence EMG metrics were not available. The performance of the models in each dataset separately was not significantly different from each other (Kinematics: $\chi^2(9) = 5.27$, $p = 0.81$; EMG: $\chi^2(9) = 3.30$, $p = 0.95$; Kinematics+EMG:

$\chi^2(9) = 5.25$, $p = 0.81$), with a baseline model average MAE of 11.1 ± 2.9 points in the FM-UE scale, where scores are from 0 to 66. The best performing model is the random forest model using the kinematic dataset with an MAE of 8.5 ± 2.7 points.

Moreover, on average, models overestimated the score of severely impaired patients (FM-UE ≤ 25) by 5 points while they underestimated other the patients' scores by 14 points. This is likely due to the unbalanced distribution of FM-UE scores in the population, where 20/28 patients were severely impaired, and only four moderately and four mildly impaired. Upon observing this trend, the regression models were then trained and tested only on severely impaired patients and their performance can be seen in Additional Figure 5.9 A. Here, the baseline model using the mean FM-UE score of the training data to estimate the FM-UE score of the test data was better than all other models, irrespective of the dataset used, with an average MAE of 4.6 ± 1.8 points in the FM-UE scale. The model with the lowest MAE after the baseline was the neural network trained on the EMG data (MAE: 5.23 ± 1.0).

Further investigation of the selected features revealed that, for the kinematic dataset, the most frequently chosen metrics were cross-correlation (30 counts out of 50 possible counts, i.e. 5 outer folds × 10 models), cross-correlation lag (32), velocity error (29), and R^2 from sinusoidal fits (25). For the EMG dataset, the most selected features included cocontraction (31), normalised cocontraction (29), and normalised reciprocal activation (29). In the combined dataset, the most frequently selected features were R^2 from sinusoidal fits (30), normalised reciprocal activation (29), and velocity error (26). Regarding the feature selection algorithm (Fig. 5.6 B), the most frequent one was recursive feature elimination (RFE), which iteratively removes the least important features based on model performance until the optimal subset is reached. Principal component analysis (PCA), which reduces dimensionality by combining correlated features into orthogonal components, was also often used.

5.3 Discussion

This study investigated the feasibility of using a simple hybrid robot-FES system in a clinical environment with subacute stroke patients, as this device had previously been found to be usable and safe to use in unimpaired participants. The goal here was to characterise the impact of robotic, FES, and combined hybrid assistance on motor performance, muscle activity, and user experience to further inform the design of a rehabilitation study using hybrid training.

Immediate assistance improves tracking error in the time-domain but not consistently in the frequency-domain. The results from the mixed-effects analyses in this study indicate that, in general, assistance improved tracking error compared to unassisted trials, irrespectively of the assistance modalities (Fig. 5.3 A,B). This indicates that the Hybrid assistance was not

associated with greater gains in tracking performance even though patients received the combination of robotic and FES assistance, and it did not outperform the Robot assistance. This is in line with our observations in unimpaired participants (Cazenave et al., 2023) and results from other studies (Dunkelberger et al., 2023; Burchielli et al., 2022). Additionally, this result suggests that FES alone improved tracking performance, which is in agreement with previous work in the literature indicating that at a slow target speed ($10°/s$), there is no significant difference in RMSE with various combinations of robot and FES assistance (Hu et al., 2011). However, this is not the case for other studies (Rong et al., 2015). The Group effect in this study may also not have been detected due to the use of an LME with various other factors.

Furthermore, the interaction between Phase and FM-UE was significant, indicating that patients with greater impairment showed larger reductions in RMSE with assistance. On the other hand, different results were obtained with the spectral correlation where we did not see a significant global Phase effect, although a significant FM-UE $\times$ Phase interaction was found, similarly as in the RMSE. Although there was no interaction with Group, when further inspecting the boxplots of the normalised RMSE and spectral correlation (Fig. 5.3 A,B), one can clearly see that all patients in the FES group improved their tracking error with assistance and this was not the case for the spectral correlation, while in the Robot group all patients improved in both metric. This suggests that stimulation can reduce positional error but is less effective in shaping temporal accuracy, likely due to the electromechanical delay, i.e. the delay between the stimulation onset and the induced motion (Lynch et al., 2008). The variability in individual performance improvements may reflect a more heterogeneous response to stimulation compared to the robotic assistance. To further investigate this trend, the correlation between the FM-UE score and the assistance effect (difference in spectral correlation between the unassisted and assisted trials) was computed (Fig. 5.7). We found negative correlations for patients in the Robot ($\rho = -0.22$) and Hybrid ($\rho = -0.51$) groups, indicating that patients with stronger impairment (lower FM-UE) benefit more from the assistance, which was also observed in the LME results. However, in the FES group, this correlation is positive ($\rho = 0.20$), hence showing that patients with low motion abilities did not necessarily improve their performance with FES assistance. This provides further evidence that FES may not be useful in improving accuracy in the frequency domain. In addition to the electromechanical delay, this may also be due in part to the fact that the comfortable stimulation amplitude range in some patients was limited and could not generate strong torque, although it could contract muscles.

Muscle activity patterns reveal differences in recruitment strategies between the assistance modalities. We found that cocontraction levels increased significantly from the unassisted to the assisted trials for patients in the FES group, but there was no significant changes in the Robot group and a slight trend for patients in the Hybrid group. The elevated muscle activity when

stimulation is applied is expected as this adds to the natural contraction induced during volitional activation in the unassisted trials. Such observations are consistent with our study in impaired participants (Cazenave et al., 2023) and with the literature (Hu et al., 2011; Rong et al., 2015). The larger cocontraction in the FES and Hybrid groups may also indicate some level of counteraction between the user's intention and the delayed stimulation, or between the robotic torque and the torque induced by the FES, delayed with respect to the robotic one. The interaction between the FM-UE score and the Phase further indicated that patients with higher impairments tended to show a larger reduction in cocontraction in the assisted phase. This may be in part due to the electromechanical delay where patients who are able to perform the task without assistance may find the FES assistance counteracting their motion. This could also be associated with a reduced volitional effort in patients with severe impairments once this assistance is provided.

Training over three sessions did not induce consistent improvements in unassisted tracking performance and physiological measures. Although task-related improvements were expected in this study due to the training effect over the three sessions, there were no significant changes in unassisted performance over time (Fig. 5.4 A,B). Similarly, group-wise reductions in cocontraction during the unassisted trials, which typically indicate motor learning, were not significant, although a significant interaction between Phase, Session and Group was found. This confirms the observation from the tracking metrics. This is likely due to the short intervention periods, where three days spread across a week are not sufficient to drive measurable motor learning, even though only improvements in the trained sensorimotor task were expected. Similarly for the ROM metrics, we did not find a significant change over time except for the passive ROM for patients in the Robot group only.

Furthermore, we found that the FM-UE scores had an effect on the changes in cocontraction and reciprocal activation over sessions, where mildly impaired patients (FM-UE > 40) showed significant reductions in physiological measures, indicating learning, while this was not the case in the more impaired patients (Additional Fig. 5.8 C,D). This may reflect that patients with milder impairments could already benefit from this short training while patients with lower motor capabilities need longer training before physiological adaptations can be observed. However, as mentioned, the FM-UE had an effect on the assistance effect, suggesting that patients of all severity levels could potentially benefit from such training. Indeed patients with very severe upper-limb impairments, including eight patients with FM-UE scores lower than ten could participate in the study and could improve their tracking performance with the assistance, while enjoying the training. This indicates that this system and protocol is suitable for a wide range of impairments, even with this standard assistance level across patients. Moreover, the FM-UE scores were balanced across groups but differences in baseline performance and EMG levels suggest potential group-specific biases and participants may benefit from

stronger assistance or a more challenging task to drive their individual improvements, specifically those with more severe impairments. This approach would however reduce the standardisation of the protocol, potentially complicating the interpretation of the results, especially when the primary aim is not to conclude on the clinical efficacy of an intervention. In addition, the sample size within each intervention group remained modest, and this heterogeneous baseline impairment levels likely contributed to the observed variability in performance and muscle activity patterns.

User experience is consistently positive for the robot, FES and combined hybrid modalities. Patients across all groups rated the system as comfortable, enjoyable to use, and desirable for continued use, with hybrid assistance showing slightly more clustered positive responses (Fig. 5.5 A).

While most previous evaluations of hybrid systems have focused on performance outcomes, only a few have examined usability from the patient's perspective (Meadmore et al., 2014; Ambrosini et al., 2021). For example, when electrical stimulation was combined with a passive robotic device, patients reported the stimulation as comfortable and the training as enjoyable (Meadmore et al., 2014). In contrast, training with another passive exoskeleton paired with FES was rated only moderately usable (Ambrosini et al., 2021). In this context, our qualitative findings extend existing evidence by showing that the proposed system is both well tolerated in the clinic and perceived as engaging by stroke patients.

Interestingly, although patients consistently perceived assistance across all modalities, their ratings of its usefulness were mixed (Fig. 5.5 B,C). This suggests that the assistance did not always align with patients' intended motion, as it was controlled to follow the target rather than their volitional effort. Similar observations have been reported in robot rehabilitation, where patients described the robot as resisting their movement (Park et al., 2020). In the present study, the variability was most evident in the robot group, likely due to the relatively low torque levels chosen to avoid slacking, which may not have always been perceived. In contrast, electrical stimulation was more noticeable and often rated as useful, despite its less consistent influence on performance metrics. Moreover, the assistance in the Hybrid group was the combined assistance form the FES and the Robot group, which could explain a consistently higher rating.

The short training duration, heterogeneous cohort, and simple control strategy constrain the interpretation of these findings. The intervention period was limited to only three sessions, which could inform about the feasibility of using such system in a rehabilitation setting, but was insufficient to induce consistent improvements in unassisted performance. Moreover, the sample size within each intervention group remained modest, and heterogeneous baseline impairment levels likely contributed to the observed variability in performance and muscle activity patterns. Finally, a

simple impedance controller was used, which may have not stimulated the targeted muscles in a timely manner. Patient-specific stimulation strategies that consider the dynamics of FES may mitigate these effects in future implementations. Although the electromechanical delay between the stimulation onset and resulting contraction could have been explicitly considered within the proportional controller used here, this approach presents some drawbacks. As the stimulation encompasses both a sensory and a motor component, explicitly including the delay could lead to the sensory feedback being perceived ahead of the corresponding error; while in this case, the FES provides sensory feedback in the same way the robot provides haptic feedback, as well as added motion benefit. Furthermore, the electromechanical delay typically varies across individuals and over time (Downey et al., 2017), hence including a fixed delay term in a proportional controller may also lead to delayed assistance and counteract the robot-induced motion as observed here.

The extracted kinematic and physiological features from the unassisted trials could not be used to estimate patients' FM-UE scores with good accuracy. Although several regression models were evaluated across kinematic, EMG, and combined feature sets, the accuracy in estimating patients' impairment severity remained limited, with mean absolute errors (MAE) in the range of 8–12 FM-UE points. This is above the MCID for FM-UE (6.6 points), indicating that such models are not suitable for reliable patient-level estimation in their current state. One likely reason is the strong imbalance in the dataset, with the majority of patients being severely impaired. This skew in FM-UE distribution was associated with systematic overestimation of scores in more impaired patients and underestimation in those with moderate or mild impairment. However, when models were retrained using only the severely impaired subgroup, performance improved but the simple baseline predictor (mean FM-UE of the training set) outperformed all feature-based models.

Most previous work estimating FM-UE or related clinical outcomes has primarily relied on demographic variables and clinical assessments collected at earlier time points to predict recovery trajectories at three or six months post-stroke (Nijland et al., 2010; Stinear et al., 2017; Van Der Vliet et al., 2020; Kwah et al., 2013; Gandolfi et al., 2023). These approaches have demonstrated predictive value but depend on repeated assessments that can be time-consuming and not routinely performed in many clinical environments. A few studies have explored the use of wearable or robot-derived kinematic and physiological data to predict clinical scores (Camardella et al., 2023; Lee et al., 2021; Bo et al., 2022). These studies typically applied similar modelling approaches to those used here, such as random forests, but achieved higher predictive accuracy, likely because they leveraged data collected at multiple time points to forecast future outcomes, thereby benefitting from richer longitudinal information. This could also be because they generally combined sensor-derived features with baseline clinical and demographic data, rather than relying solely on device outputs. Demographic factors such as age often emerged as dominant predictors, and in some instances, adding sensor-based features did

not improve performance (Camardella et al., 2023; Bo et al., 2022). By contrast, the present work focused on whether robot- and EMG-derived features collected exclusively during rehabilitation training could capture sufficient information to infer motor impairment severity in subacute stroke patients. This was not the case, suggesting that the available sample size was too limited to accurately estimate clinical scores or to reliably distinguish impairment levels. Indeed, even when adding demographics information from the patients (i.e. age and time since stroke) to the training set and using the best performing model (RF with surrogate splits trained on kinematic features), the performance did not improve (MAE: 9.8 $\pm$ 2.9, compared to MAE: 8.5 $\pm$ 2.7 without demographics).

5.4 Conclusion

This chapter assessed the feasibility and short-term effects of robotic, FES, and hybrid assistance during a wrist tracking task in individuals with subacute stroke staying at an inpatient rehabilitation clinic. All modalities significantly improved task performance within sessions, but no consistent training-related gains were observed across the three-session intervention. Robotic assistance reduced cocontraction and reciprocal activation, reflecting decreased effort in the task, while FES and hybrid assistance increased overall muscle activity, aligning with their role in promoting active engagement, although the electromechanical delay may have also induced undesired cocontraction. Importantly, patient-reported outcomes confirmed that all modalities were well tolerated, enjoyable, and perceived as useful, with hybrid assistance in particular receiving consistently positive feedback. On the other hand, the use of the kinematic and EMG metrics, extracted from the unassisted target-tracking task, to estimate patients' FM-UE scores did not yield satisfying outcomes, with errors above 12% of the full score. This limits the potential use of this device as a tool to assess upper-limb recovery.

Taken together, these findings suggest that while robotic assistance provides reliable improvements in movement accuracy, FES and hybrid approaches offer complementary benefits by engaging muscle activity and supporting patient-perceived usefulness, which may enhance overall patient experience. However, the short training duration and the standard assistance and task difficulty across patients limited the ability to detect cumulative learning and consistent improvements. The next chapter extends this work in a longitudinal hospital-based study, where patients underwent three weeks of FES–robot assisted training, with optimised patient-specific shared control between the two actuating modalities and task difficulty adaptation. This enables the evaluation of motor adaptation during repeated practice and the potential clinical efficacy of this hybrid rehabilitation approach.

5.5 Additional figures

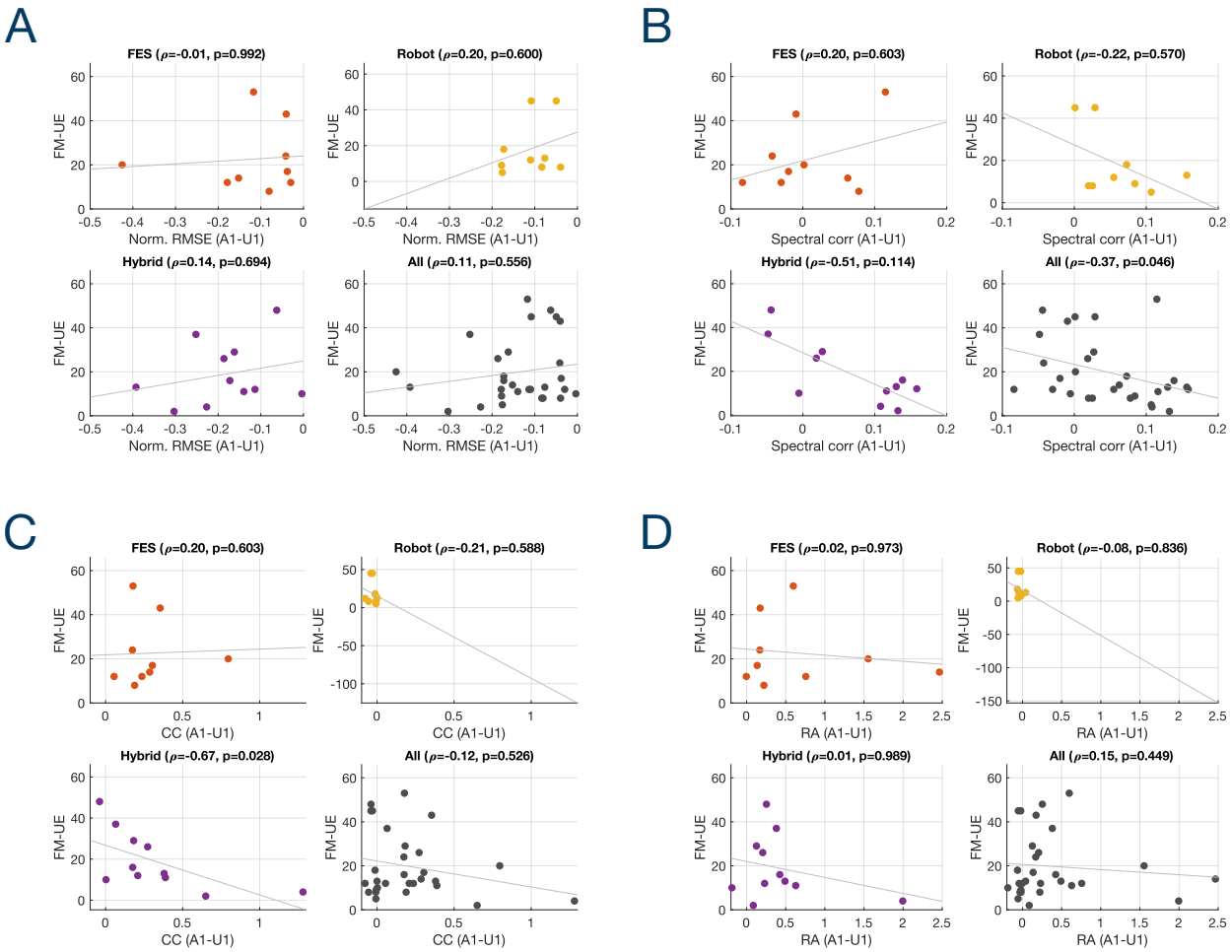


Figure 5.7: Correlation between FM-UE scores and assistance effect (assisted performance – unassisted performance) on various metrics: normalised RMSE **(A)**, spectral correlation **(B)**, cocontraction **(C)**, and reciprocal activation **(D)**, for each group individually and the whole population. A performance improvement is indicated by a negative RMSE difference and a positive spectral correlation difference. A negative cocontraction or reciprocal activation indicates a reduction in physiological measures with assistance.

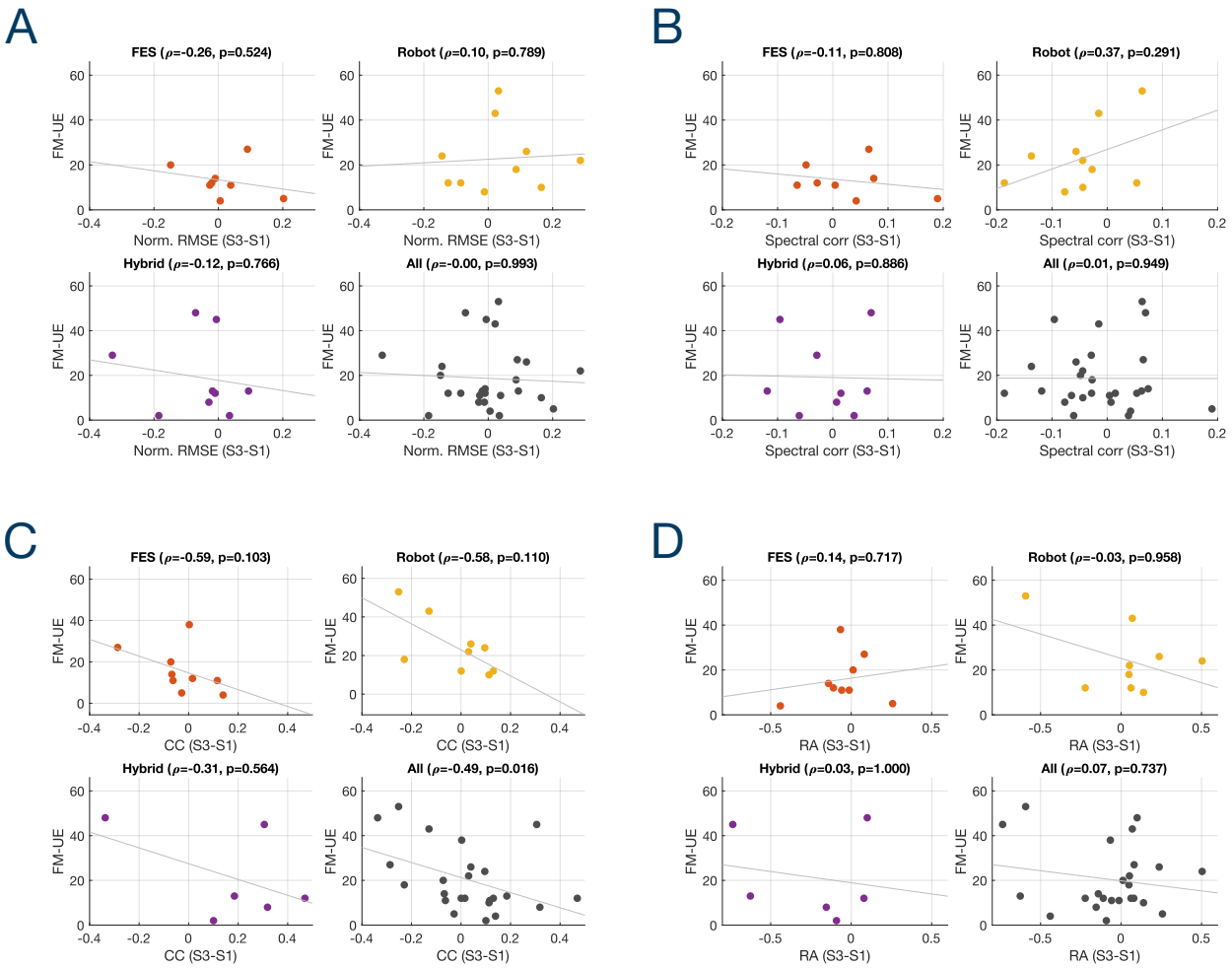


Figure 5.8: Correlation between FM-UE scores and improvement in unassisted trials over sessions (S3 – S1) on various metrics: normalised RMSE **(A)**, spectral correlation **(B)**, cocontraction **(C)**, and reciprocal activation **(D)**, for each group individually and the whole population. A performance improvement is indicated by a negative RMSE difference and a positive spectral correlation difference. A negative cocontraction or reciprocal activation indicates a reduction in physiological measures from Session 1 to 3.

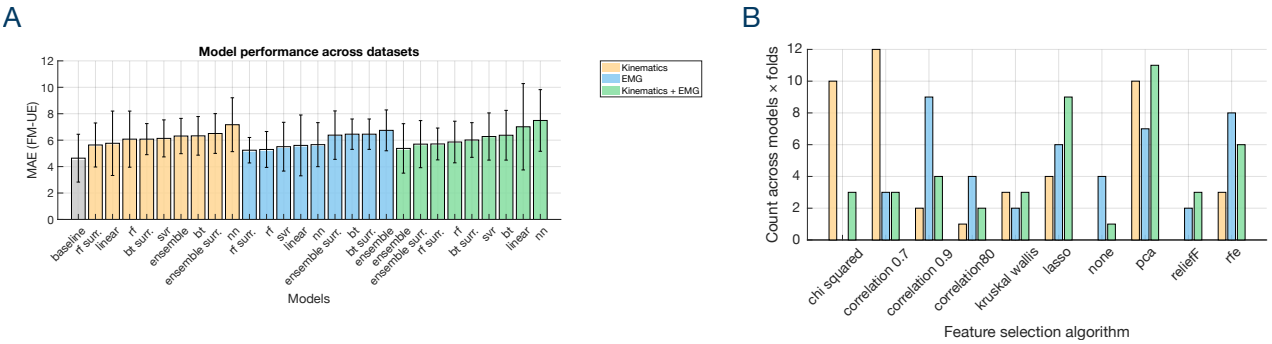


Figure 5.9: Estimating FM-UE scores of severely impaired patients (FM-UE $\leq$ 25) using kinematic and EMG data collected in the first five unassisted baseline trials of the first session. **(A)** Models performance (mean absolute error) across the three datasets. Models compared include: baseline mean predictor (base), random forest with surrogate splits (rf surr.), linear regression (linear), random forest (rf), boosted trees with surrogate splits (bt surr.), support vector regression (svr), ensemble of learners (ensemble), boosted trees (bt), ensemble with surrogate splits (ensemble surr.), and neural networks (nn) **(B)** Frequency of feature selection algorithms applied across regression models and outer folds, for the three datasets. Feature selection methods included: no feature selection (none), recursive feature elimination (RFE), principal component analysis (PCA), least absolute shrinkage and selection operator (LASSO), correlation-based selection with thresholds of 0.9 (Corr. 0.9) or 0.7 (Corr. 0.7), principal component analysis (PCA), reliefF, chi-squared test–based feature selection, and Kruskal–Wallis test–based selection.

Chapter 6

Fatigue induced by FES and voluntary movements in unimpaired and stroke participants

The previous chapters established the potential of a hybrid robot-FES system for improving upper-limb motor performance in unimpaired individuals (Chapter 4) and stroke patients (Chapter 5). These studies showed that combining robotic and FES assistance can enhance tracking accuracy, preserve movement smoothness, and improve user experience without compromising comfort. Together, the findings support the use of hybrid assistance as a promising strategy for neurorehabilitation. However, one important factor that remains to be addressed is the potential muscle fatigue, particularly when electrical stimulation is applied over longer durations.

Fatigue is a known limitation of FES as it recruits slow-twitch and fatigue-resistant motor units as well as fast-fatiguable ones, even for low-level contractions (Lynch et al., 2008). This often leads to a faster onset of fatigue, as seen in assistive tasks like the Cybathlon cycling race, where participants (with spinal cord injuries) experience a progressive decline in pedal power output during prolonged FES-driven activity. In stroke rehabilitation, FES is often used in conjunction with voluntary motion and involves frequent rest periods, which may mitigate fatigue development. Nevertheless, it is unclear whether and how this mechanism could arise in these contexts. Studying the effect of FES-induced contractions in such scenarios could help confirm whether these are sufficient to prevent fatigue, and that FES does not restrict the intensity or duration of rehabilitation post-stroke, or increase discomfort.

Although our previous experiments in unimpaired individuals (Chapter 4) did not reveal signs of fatigue during hybrid training, those sessions were relatively brief, required low physical demand, and were not specifically designed to detect the more subtle neuromuscular changes associated with fatigue. Moreover, most studies investigating FES-induced fatigue have relied on isometric or tetanic stimulation protocols to provoke fatigue, which do not reflect the dynamic, continuous movement

patterns typically encouraged in stroke rehabilitation, where the goal is to promote voluntary control across a functional range of motion.

To address this gap, the present chapter investigates the development of muscular fatigue during a continuous wrist tracking task involving FES-induced contractions and/or robotic assistance, and voluntary movement. It aims to answer research question QC: *Should muscle fatigue be considered when using a hybrid robot-FES system for stroke rehabilitation?* We adopt a two-part approach:

- First, we present a dedicated study in unimpaired individuals that examines muscle fatigue across three conditions: voluntary movement, FES-induced movement, and combined volitional and FES-driven movements. Fatigue is evaluated both during the task, via EMG-based effort and fatigue metrics, and before and after each condition, to investigate potential changes in the mechanical (MVC) and electrical (M-wave) responses of the muscles.
- Second, we further analyse the data from the stroke feasibility study (Chapter 5) to explore whether similar fatigue-related markers emerge during robot- and/or FES-assisted target tracking training in subacute stroke patients.

The findings provide insight into the physiological demands of FES-based and hybrid assistance in both unimpaired and stroke individuals. They aim to inform whether fatigue should be explicitly accounted for when designing hybrid rehabilitation strategies and help optimise training protocols for clinical deployment.

The study in unimpaired individuals was described in the following publication: Cazenave, L., Pena-Perez, N., Yurkewich, A., & Burdet, E., (2025). FES-Induced and Voluntary-Induced Fatigue in a Rehabilitation-Like Task. *IEEE International Conference On Rehabilitation Robotics*. A verbatim copy of this paper is also included in Appendix A. The study in stroke patients presented in this chapter was carried out in collaboration with the Technical University of Munich (TUM), the Schön Klinik Bad Aibling, and Tecnalia. C. Höhler, C. Krewer, K. Jahn and their colleagues from Schön Klinik Bad Aibling recruited the participants in this study and collected subsequent data, after I set up the device in the clinic and trained them to conduct the experiment. S. Endo and H. Kavianirad assisted in the pre-processing and analysis of the data. I conceived and designed the research in discussion with colleagues at Schön Klinik, developed the experimental protocol and programmed the experimental task, performed the data analysis. I also created the figures in this chapter, and interpreted the results.

6.1 Methods

6.1.1 Study in unimpaired participants

Experimental design

Twenty-two unimpaired individuals (3 left-handed, 11 female), aged 21-30 years old, participated in this experiment, approved by the Research Ethics Committee of Imperial College London (approval number: 21IC6935). Participants completed three block conditions of 25 trials (Fig. 6.1). In each 30 s-trial they tracked a target moving pseudo-randomly along the horizontal axis with their right wrist flexion/extension motions, as previously introduced in Chapter 3, Section 3.2.

The conditions, presented in a random order, required participants to: (i) track the target as accurately as possible, (ii) remain relaxed while FES was applied to their wrist flexor/extensor muscles to track the target, and (iii) track the target as accurately as possible while they received the same FES assistance as in (ii). The randomisation was designed to ensure that all six possible sequences of experimental conditions were presented, with each sequence carried out by at least three participants to maintain balanced exposure across conditions. The general difficulty of the task was increased by adding damping to the robot ($D = 0.39$ Nm s/rad).

The robot-FES system used in this experiment is composed of the HRX-1 one degree-of-freedom wrist robotic interface (HumanRobotiX, UK) and the CLASS V1.0 FES device 16-electrode array (Tecnalia Research & Innovation, Spain). These systems have already been introduced in Chapter 3, Section 3.1, where further details and pictures can be found. Muscle activity was recorded using two 32-channel EMG electrode arrays (GR10MM0804, OT Bioelettronica, Italy) with a Sessantaquattro amplifier (OT Bioelettronica, Italy).

An FES calibration is performed at the start of the experiment and FES assistance is implemented such that the stimulation intensity is proportional to the difference between the target position and the participant's wrist position $e(t)$, as previously introduced in Chapter 4, Section 4.1.5 and 4.1.6. Here, the FES control stiffness (in mA/°) for the flexor and extensor stimulation is equivalent (after calibration) to a robot control stiffness $K = 0.56$ Nm/rad

After completion of each condition, participants perform a maximum voluntary contraction (MVC) exercise, where they are asked to flex and extend their wrist for 3.5 s as forcefully as possible three times on each side. Following this, they are instructed to relax while the maximum calibrated FES was applied for 3.5 s to their wrist flexor (s_f^{max}), followed by their wrist extensor (s_e^{max}), three times as well. For this step, the same calibrated FES intensity is used throughout the experiment.

They also fill out the NASA-TLX questionnaire (Hart et al., 1988), which assesses participants' perceived effort after each condition:

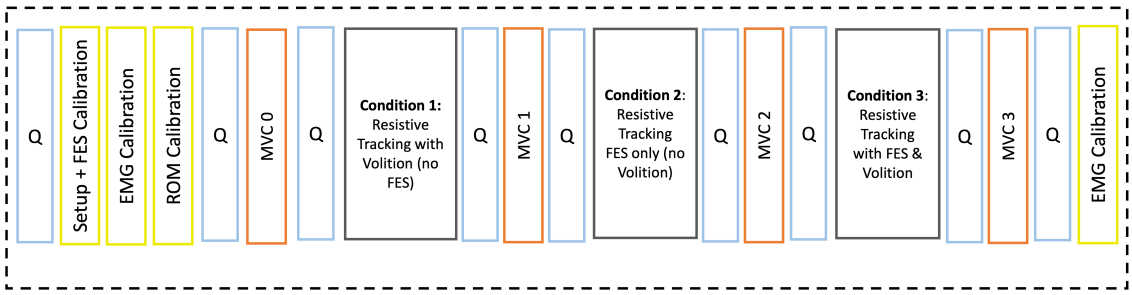


Figure 6.1: Experimental protocol for the study on fatigue with unimpaired participants. The three conditions were presented in random order for each participant and consisted of 25 trials of a 30-second wrist target-tracking task. MVC refers to three repetitions of maximum voluntary wrist flexion and extension, followed by three repetitions of maximum flexor and extensor stimulation while participants were instructed to relax.

- How mentally demanding was the task?
  (1 = very low; 10 = very high)
- How physically demanding was the task?
  (1 = very low; 10 = very high)
- How hurried or rushed was the pace of the task?
  (1 = very low; 10 = very high)
- How successful were you in accomplishing what you were asked to do?
  (1 = very bad; 10 = very good)
- How hard did you have to work to accomplish your level of performance?
  (1 = very low; 10 = very high)
- How insecure, discouraged, irritated, stressed, and annoyed were you?
  (1 = very low; 10 = very high)
- The electrical stimulation was comfortable.
  (from 'strongly disagree' to 'strongly agree')
- The electrical stimulation improved my performance. (from 'strongly disagree' to 'strongly agree')

Data analysis

To analyse whether the target-tracking task induced fatigue, either with or without FES, we focused on five key aspects: i) the perceived mental and physical demand, ii) changes in EMG envelope amplitude during MVC, iii) changes in FES-induced torque and M-wave characteristics during continuous maximum stimulation, iv) tracking error, and v) cocontraction and reciprocal activation of the flexor

and extensor muscles during the condition trials. For evaluating metrics within each condition block, the first three trials used for familiarisation were excluded from the analysis, hence the remaining 22 trials were considered.

EMG pre-processing

EMG was recorded from the participants' wrist flexor and extensor muscles at a frequency of 2000 Hz. The EMG signal was pre-processed as per the pipeline described in Chapter 3, Section 3.3.2. The amplitude of the EMG envelope was normalised by the mean EMG envelope during the first MVC in flexion/extension (MVC0 condition in Fig. 6.1), so muscle activity is reported as a ratio of this maximum MVC amplitude. For subsequent analyses, the channel on the extensor and flexor arrays with the highest envelope amplitude during the EMG calibration was selected. EMG metrics are reported for $N = 21$, as the EMG data for one participant were corrupted.

Metrics computation

To evaluate a potential decrease in MVC, we calculated the difference in muscle activity during the MVC performed before and after each condition. The average EMG value over the peak 1 s window of the 3.5 s MVC was used to characterise the MVC and the normalisation value (Nieminen et al., 1993; Castelein et al., 2015; Ekstrom et al., 2005).

Similarly, to assess changes in FES-induced torque and M-wave characteristics, we computed the difference in mean torque and M-wave metrics during 3 s of continuous stimulation performed before and after each condition. The first 0.5 s of stimulation were excluded from the analysis to account for the delay between stimulation onset and muscle contraction. For M-wave analysis, the 3 s EMG signal was divided into pulse windows, each containing a stimulus artifact that marked the start of the window, followed by the corresponding M-wave. Within each window, we extracted the amplitude, area, and duration of each M-wave phase, averaging these metrics across the 3 s stimulation period for each M-wave phase separately (Rodriguez-Falces et al., 2017). Since this task is dynamic and may induce changes in muscle length and in the relative position of the recording and stimulating electrodes, the two M-wave phases were analysed separately This is because previous work found that the first M-wave phase may be less affected by these structural changes (Rodriguez-Falces et al., 2017). We also analysed these metrics for the full M-wave by summing the parameters extracted from each phase to obtain the overall M-wave amplitude, duration, and area, as these are also commonly used to assess muscular fatigue (Chesler et al., 1997; Tepavac et al., 1997; Badier et al., 1999; Rodriguez-Falces et al., 2018).

We evaluated effort within trials using the cocontraction and the reciprocal activation of the wrist flexor and extensor normalised EMG envelope as described in Chapter 3, Section 3.3.1. The tracking

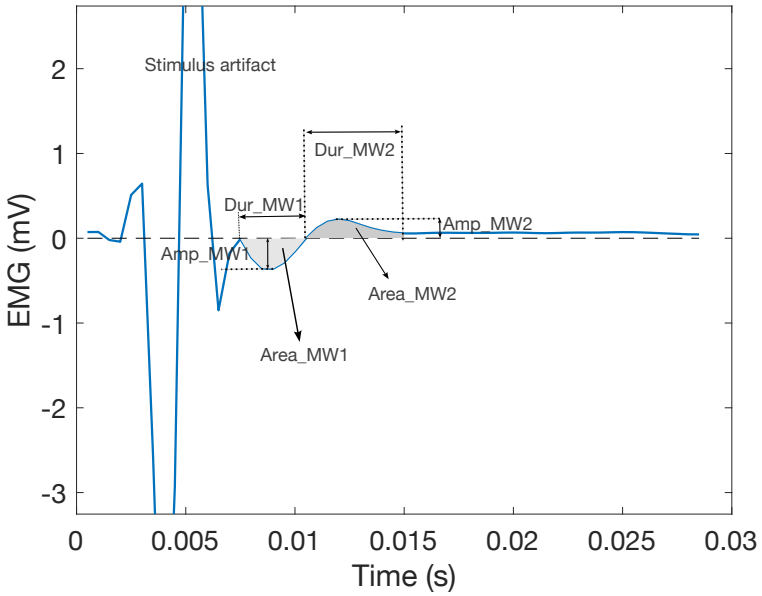


Figure 6.2: An example M-wave response from a participant during the 3 s maximum flexor stimulation while at rest, with the measurements of the M-wave parameters: amplitude, duration, and area of the first (Amp_MW1, Dur_MW1, and Area_MW1) and second (Amp_MW2, Dur_MW2 and Area_MW2) phases. These parameters are also computed for the full M-wave, where the absolute sum of the parameter from each phase is computed (MW amplitude, MW duration and MW area).

performance in each trial was evaluated using the RMSE between the participant and target trajectories, the Spearman's correlation between them, and motion smoothness (SPARC) (Balasubramanian et al., 2015).

Statistics

To analyse the evolution of performance and EMG metrics across trials for each condition (Voluntary, FES, Hybrid), linear mixed-effects models (LMEs) were fitted with restricted maximum likelihood estimation (REML). Each condition was modelled separately to capture within-condition fatigue and performance trends. The dependent variables included the RMSE between the participant and target trajectories, the Spearman's correlation between them, and motion smoothness (SPARC). Trial number was modelled as a continuous fixed effect to assess temporal changes during the session and a subject-specific random intercept was added to account for repeated measures. Analyses were performed in R (version 2024.4.2) using the `lmerTest` package. Additionally, we investigated differences in these metrics between the first and last three trials (excluding familiarisation trials) to explore a potential effect of the condition on the metric change using a one-way ANOVA or Friedman test and corresponding post-hoc tests.

To compare perceived mental and physical demands, MVC levels, FES-induced torque, M-wave parameters, performance metrics, and EMG-based metrics during conditions, we used a one-way repeated measures ANOVA, or a non-parametric Friedman test when data were not normally distributed.

Normality was assessed using the Shapiro-Wilk test. For pairwise comparisons of these metrics between conditions, we used paired sample t-tests or paired Wilcoxon signed-rank tests, controlling for the family-wise error rate using the Bonferroni-Holm correction. To determine whether differences in MVC torque, FES-induced torque, and M-wave parameters before and after each condition differed from a distribution with a mean of zero, we applied one-sample t-tests or Wilcoxon signed-rank tests for each condition individually. Moreover, for these differences, we performed this statistical analysis on the metrics distributions based on the chronological order in which the conditions were presented, regardless of their types, to identify any temporal changes in the metrics. We also conducted the same analysis after categorising the data by condition labels (FES, Volition, Volition-FES) to investigate differences associated with the specific condition types.

The significance level used for these analyses was $\alpha = 0.05$.

6.1.2 Study in stroke patients

Experimental design

The experimental design of this study is described in Chapter 5, Section 5.1.

Data analysis

To analyse whether the target-tracking task, assisted by FES and/or a robot, induced fatigue in subacute stroke patients, we focused on similar aspects as presented for the above study in unimpaired participants.

We explored: i) the perceived mental and physical demand as collected by the NASA-TLX questionnaire, ii) the changes in performance, i.e. normalised RMSE and the correlation between the spectra of the patient and target trajectories, and iii) the changes in muscle activity, i.e. cocontraction and reciprocal activation of the flexor and extensor muscles, from the EMG data collected during the assisted trials, when these were available. Further details about the data collection procedures are described in Chapter 5, Section 5.1, and the EMG pre-processing pipeline and the metrics extraction are described in Chapter 3, Section 3.3.1 and 3.3.2).

We also investigated differences in frequency-based metrics in the unassisted trials of the baseline and evaluation blocks preceding and following the assisted training to explore potential differences in frequency-based metrics arising with the training. To do so, the mean difference between the first three trials of the unassisted evaluation block after the training and the last three trials of the first unassisted block was computed for each participant and session. The metrics in the frequency domain of the EMG used to characterise fatigue (presented in Chapter 3, Section 3.3.2) are as follows: median frequency of the filtered EMG signal from its Fourier transform (Stulen et al., 1981; Arendt-Nielsen

et al., 1989), mean of the instantaneous median frequency of the time-dependent power spectrum (from the Choi-Williams time-frequency distribution) (Choi et al., 1989), and Dimitrov Spectral Index (Dimitrov et al., 2006).

Statistics

The NASA-TLX single-item ratings (mental and physical demand) were compared across groups using one-way ANOVA or non-parametric Kruskal–Wallis test when data were not normally distributed (Shapiro-Wilk test).

To investigate the evolution of task performance and EMG-based effort metrics during the assisted training phase, LMEs with REML were fitted. Fixed effects included Trial number (1–30 within the assisted phase), Session (1–3), and Group (Robot, FES, Hybrid). The dependent variables were normalised RMSE, spectral correlation, normalised CC, and normalised RA. Interactions allowed testing whether fatigue or adaptation trajectories differed by Group or Session. A participant-specific random intercept accounted for baseline heterogeneity. These are referred to as the primary LMEs. Additionally, simplified models were used for visualisation and exploratory comparisons within each group-session pair, where only Trial number was considered as a fixed effect and the participant ID as a random intercept. The dotted regression lines are plotted on top of the figures showing the evolution of each metric over trials in the assisted training and the p-values for the Trial slope are reported for these representative sessions.

To investigate the potential effect of the intervention group on the difference in frequency-domain EMG metrics, used to characterise fatigue, we conducted a one-way ANOVA or a Kruskal–Wallis test, if the normality assumption was not satisfied.

The significance level used for these analyses was $\alpha = 0.05$.

6.2 Results from unimpaired study

6.2.1 Questionnaire Answers

We observed a significant effect of the condition on the NASA-TLX responses for the questions: “How physically demanding was this task?” ($\chi^2(2) = 26.66$, $p < 0.001$) and “How mentally demanding was this task?” ($\chi^2(2) = 30.34$, $p < 0.001$). When participants were asked to relax while FES was applied, the task was perceived as the least demanding. In contrast, the Volition and Volition-FES conditions did not differ significantly in physical ($p = 0.73$) or mental demand ratings ($p = 0.45$) (see Fig. 6.3)

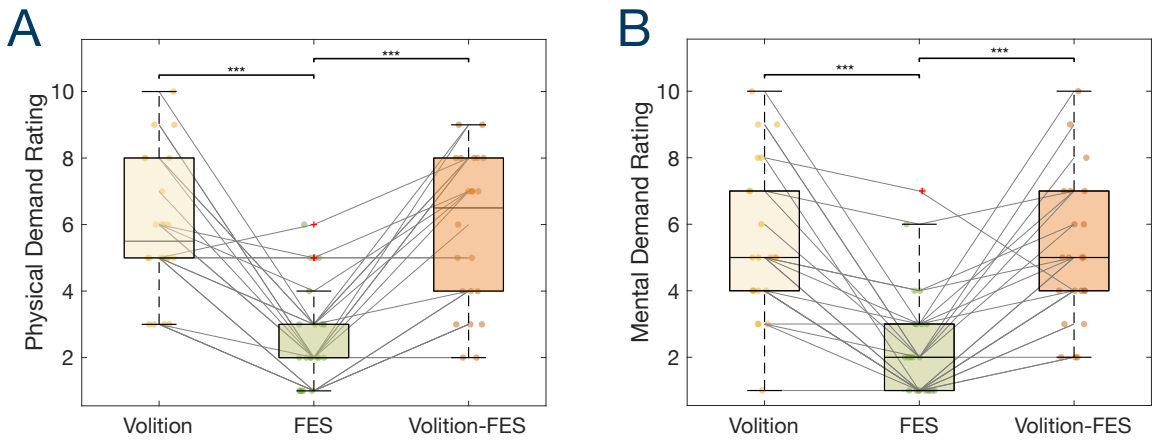


Figure 6.3: Answers to the 10-point NASA-TLX questions on physical demand **(A)** and mental demand **(B)**, with answers from very low (1) to very high (10). Each participant performed all three conditions and the dotted line represents their ratings. $***: p < 0.001$. Comparisons not highlighted are not significant.

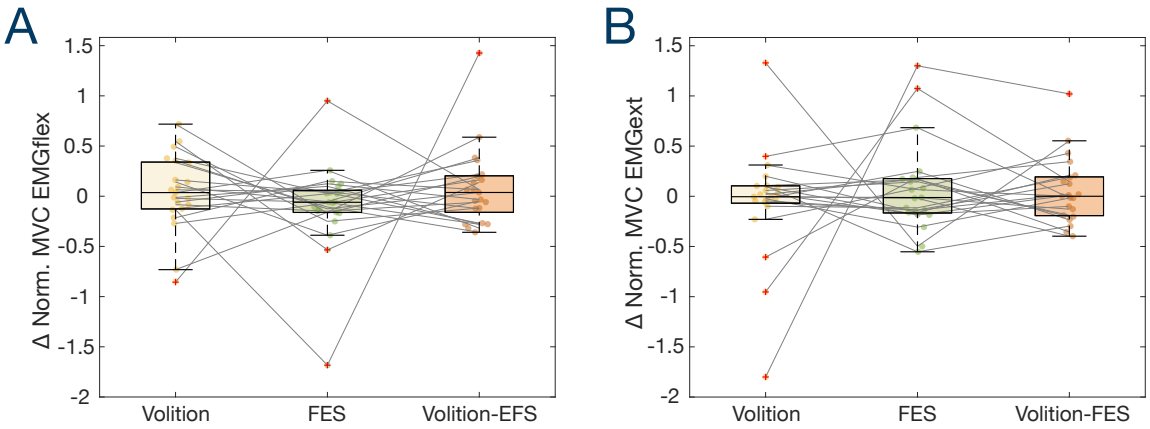


Figure 6.4: Difference in mean normalised EMG during MVC trials for each condition for the flexor MVC **(A)** and extensor MVC **(B)**. A negative difference indicates a decrease in MVC after the condition compared to before the condition.

6.2.2 MVC differences before and after each condition

We investigated the chronological evolution of the normalised EMG amplitude during MVC throughout the experiment by computing the difference between the current MVC and the previous one to explore potential decreases in MVC after each condition (where a negative difference indicates a decrease in MVC) (Additional Figure 6.12). A significant effect of the condition was found for flexor MVC ($\chi^2(2) = 7.71$, $p < 0.05$), but not for extensor MVC ($\chi^2(2) = 0.09$, $p = 0.956$). Post-hoc analyses for flexor MVC did not reveal significant differences between any pair of conditions (all $p > 0.276$).

Furthermore, we calculated the difference between the mean normalised MVC EMG before and after each condition to assess potential decreases in MVC (where a negative difference indicates a decrease) (Fig. 6.6). No significant differences in MVC change across conditions were observed (MVC EMG flexor: $\chi^2(2) = 1.52$, $p = 0.467$; MVC EMG extensor: $\chi^2(2) = 0.10$, $p = 0.954$). Additionally, none of the conditions induced a significant change in MVC compared to zero (all $p > 0.1924$).

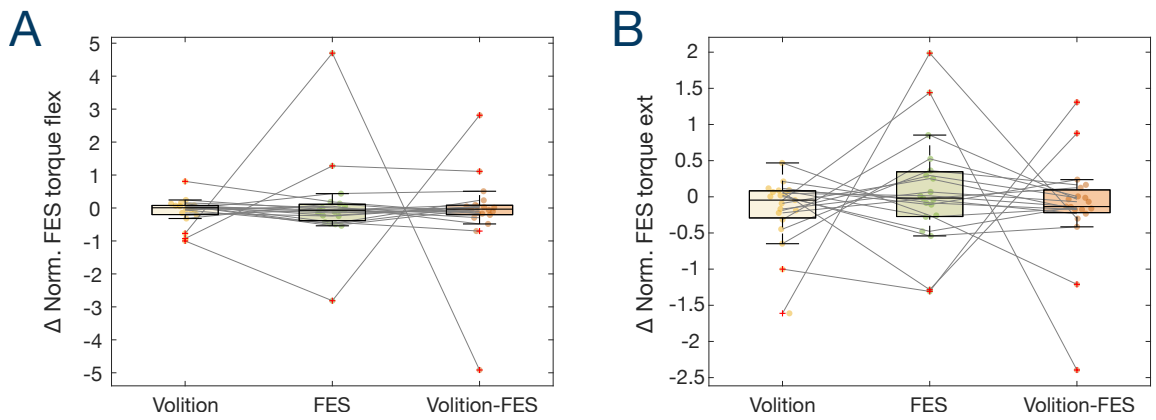


Figure 6.5: Difference in mean normalised FES-induced torque for each condition for the flexor stimulation **(A)** and extensor stimulation **(B)**. A negative difference indicates a decrease in FES-induced torque after the condition compared to before the condition.

6.2.3 FES-induced torque differences before and after each condition

Similarly, we explored the chronological evolution of the torque generated under maximum comfortable stimulation intensity while participants were at rest. We computed the difference between the current FES-induced torque and the previous one (Additional Figure 6.13). No significant differences were found across conditions (FES torque flexor: $\chi^2(2) = 3.26$, $p = 0.1956$; FES torque extensor: $\chi^2(2) = 0.74$, $p = 0.6918$).

Fig. 6.5 shows the difference between FES-induced torque before and after each condition to assess potential decreases in torque (where a negative difference indicates a decrease). No significant differences in FES-induced torque changes across conditions were observed (FES torque flexor: $\chi^2(2) = 4.11$, $p = 0.1284$; FES torque extensor: $\chi^2(2) = 0.42$, $p = 0.8102$). Additionally, there were no significant changes in FES-induced torque within any of the conditions (all $p > 0.1842$).

6.2.4 M-wave parameters differences before and after each condition

Additionally, we evaluated the chronological evolution of various parameters characterising the M-wave, recorded during maximum comfortable stimulation intensity while participants were at rest. We explored differences between the current M-wave peak-to-peak amplitude (Additional Figure 6.14 A,B), duration (Additional Figure 6.14 C,D) and area (Additional Figure 6.14 E,F), and the previous measurements. No significant differences across conditions were observed for these parameters (MW amplitude flexor: $\chi^2(2) = 0.3$, $p = 0.8607$; MW amplitude extensor: $\chi^2(2) = 2.63$, $p = 0.2683$; MW duration flexor: $F(2) = 1.94$, $p = 0.1536$; MW duration extensor: $\chi^2(2) = 0.95$, $p = 0.6227$; MW area flexor: $\chi^2(2) = 1.3$, $p = 0.5220$; MW area extensor: $F(2) = 0.15$, $p = 0.8648$).

Fig. 6.6 illustrates the differences in M-wave parameters before and after each condition to as-

sess potential changes in peak-to-peak amplitude (Fig. 6.6 A,B), duration (Fig. 6.6 C,D) and area (Fig. 6.6 E,F). No significant differences in changes across conditions were observed (MW amplitude flexor: $\chi^2(2) = 0.4$, $p = 0.8187$; MW amplitude extensor: $\chi^2(2) = 0.11$, $p = 0.9487$; MW duration flexor: $\chi^2(2) = 0.7$, $p = 0.7047$; MW duration extensor: $\chi^2(2) = 5.05$, $p = 0.08$; MW area flexor: $\chi^2(2) = 0.7$, $p = 0.7047$; MW area extensor: $\chi^2(2) = 2.63$, $p = 0.2683$).

We also examined changes in parameters for each phase of the M-wave separately but found no significant differences (all $p > 0.0648$). When assessing whether changes within each condition differed from zero, no significant results were found for any full M-wave parameters across conditions (all $p > 0.062$). However, in the Volition-FES condition, significant changes were observed in the MW2 amplitude ($p = 0.0442$) and MW2 area ($p = 0.0329$) during extensor stimulation.

6.2.5 Changes in performance metrics across conditions

Fig. 6.7 shows the changes in each performance metric across trials for each condition. In the Volition and FES conditions, we observed a significant effect of Trial number on RMSE, with a positive slope indicating a slight decrease in tracking performance (Volition: slope = 0.0275, $t(461) = 2.282$, $p = 0.023$; FES: slope = 0.0278, $t(461) = 5.171$, $p < 0.001$). In contrast, the Volition-FES condition showed no significant slope (slope = 0.0027, $t(461) = 0.245$, $p = 0.806$). For the correlation metric, a significant negative slope was observed only in the FES condition (FES: slope = -0.0008, $t(461) = -2.182$, $p = 0.0296$), while the Volition condition showed a marginally significant negative slope (slope = -0.0006, $t(461) = -1.963$, $p = 0.0502$). The Volition-FES condition did not show a significant slope (slope = 0.0002, $t(461) = 0.695$, $p = 0.488$). For the SPARC metric, all conditions had a significantly negative slope, indicating decreased motion smoothness (Volition: slope = -0.0716, $t(461) = -6.027$, $p < 0.001$; FES: slope = -0.2417, $t(461) = -6.849$, $p < 0.001$; Volition-FES: slope = -0.0736, $t(461) = -5.727$, $p < 0.001$). The magnitude of this slope was larger in the FES condition compared to the other two conditions.

We also investigated the difference in performance metrics between the last three trials and the first three trials (excluding the familiarisation trials) for each condition (Additional Figure 6.15). No significant effect of condition on the difference in any performance metric between the start and end of the trials was observed (Δ RMSE: $\chi^2(2) = 0.27$, $p = 0.87$; Δ Spearman's ρ: $\chi^2(2) = 0.64$, $p = 0.73$; Δ SPARC: $\chi^2(2) = 4.36$, $p = 0.12$).

6.2.6 Changes in effort across conditions

We examined how the mean EMG envelope amplitude in the wrist flexor and extensor muscles, as well as the mean cocontraction (CC) and reciprocal activation (RA), varied over trials in each condition to measure voluntary effort during the task (Fig. 6.8). For the flexor EMG, we observed a significant

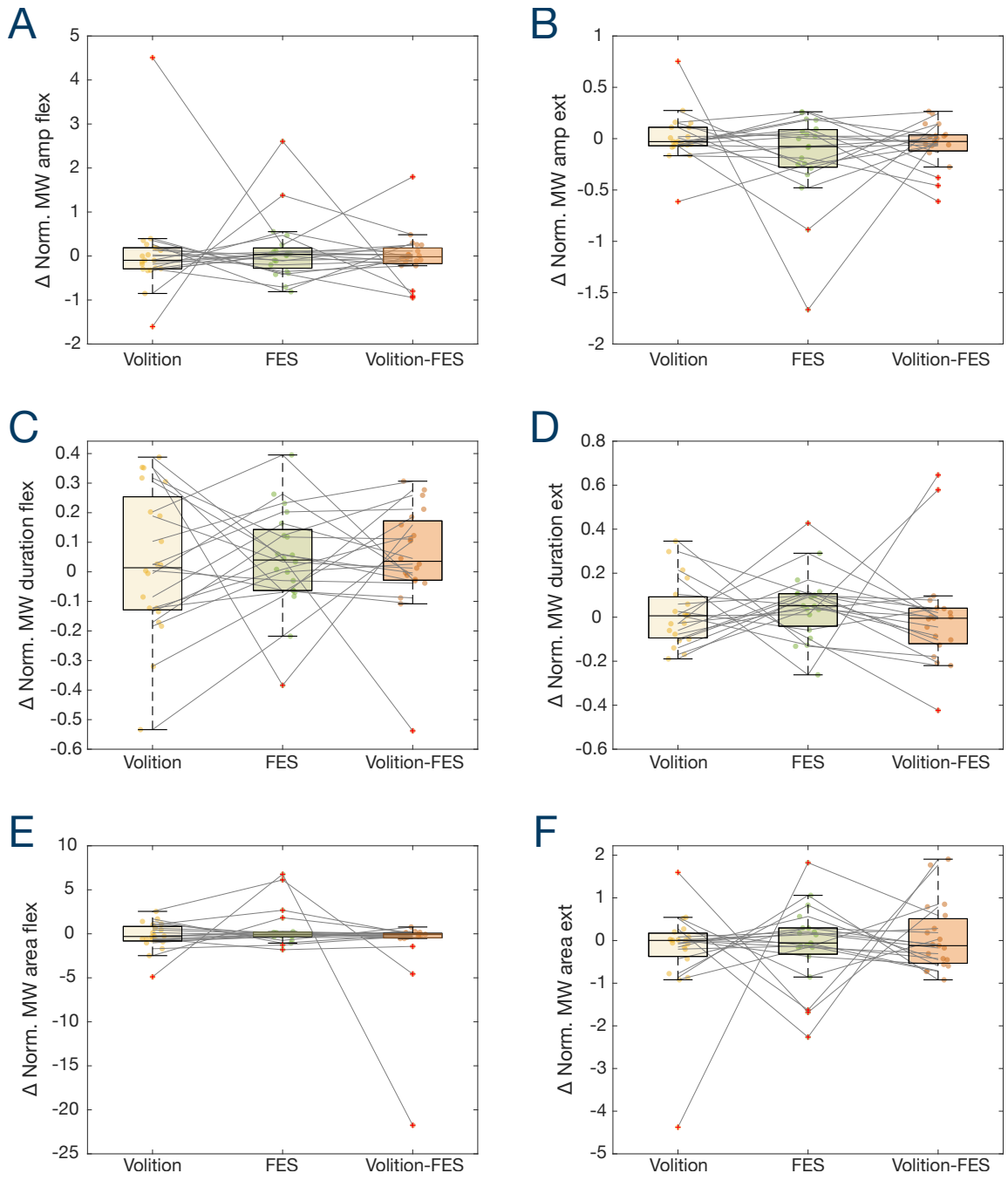


Figure 6.6: Difference in mean normalised M-wave parameters when the maximum comfortable stimulation is applied while at rest, for each condition, for the flexor stimulation **(A,C,E)** and the extensor stimulation **(B,D,F)**. The M-wave parameters presented are the M-wave peak-to-peak amplitude **(A,B)**, the M-wave duration **(C,D)** and the M-wave area **(E,F)**.

negative effect of trial number in the Volition-FES condition (slope = -0.0009, $t(433) = -4.314$, $p < 0.001$) and non-significant negative slopes for the other two conditions (Volition: slope = -0.0007, $t(440) = -1.499$, $p = 0.135$; FES: slope = -0.0002, $t(436) = -1.070$, $p = 0.285$), indicating decreased effort over time. Similar results were found for the extensor EMG (Volition-FES: slope = -0.0011, $t(436) = -3.260$, $p = 0.0012$; Volition: slope = -0.0004, $t(440) = -0.875$, $p = 0.382$; FES: slope = -0.0005, $t(435) = -1.122$, $p = 0.263$).

Negative slopes were also observed in the cocontraction metric, with significant effects in the FES

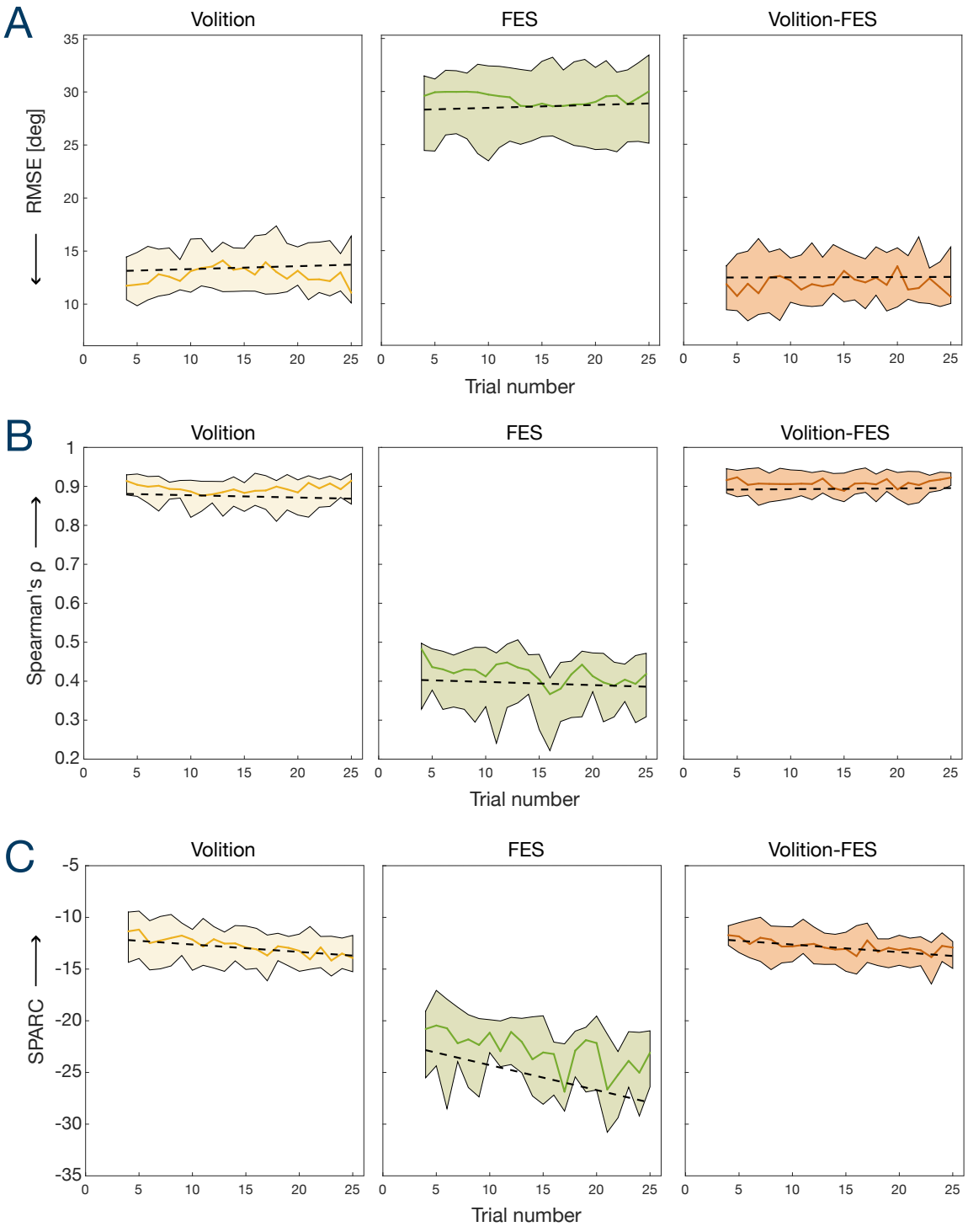


Figure 6.7: Evolution of performance metrics across trials for each condition: root mean square error between the subject's and target's positions **(A)**, correlation between the subject's and target's positions **(B)**, SPARC metric capturing motion smoothness **(C)**. The lines represent the median of each metric computed over all participants and the shaded areas represents the data from the first to third quartile of the metric. The first three trials are excluded as they were used as familiarisation trials and were not considered in the analysis.

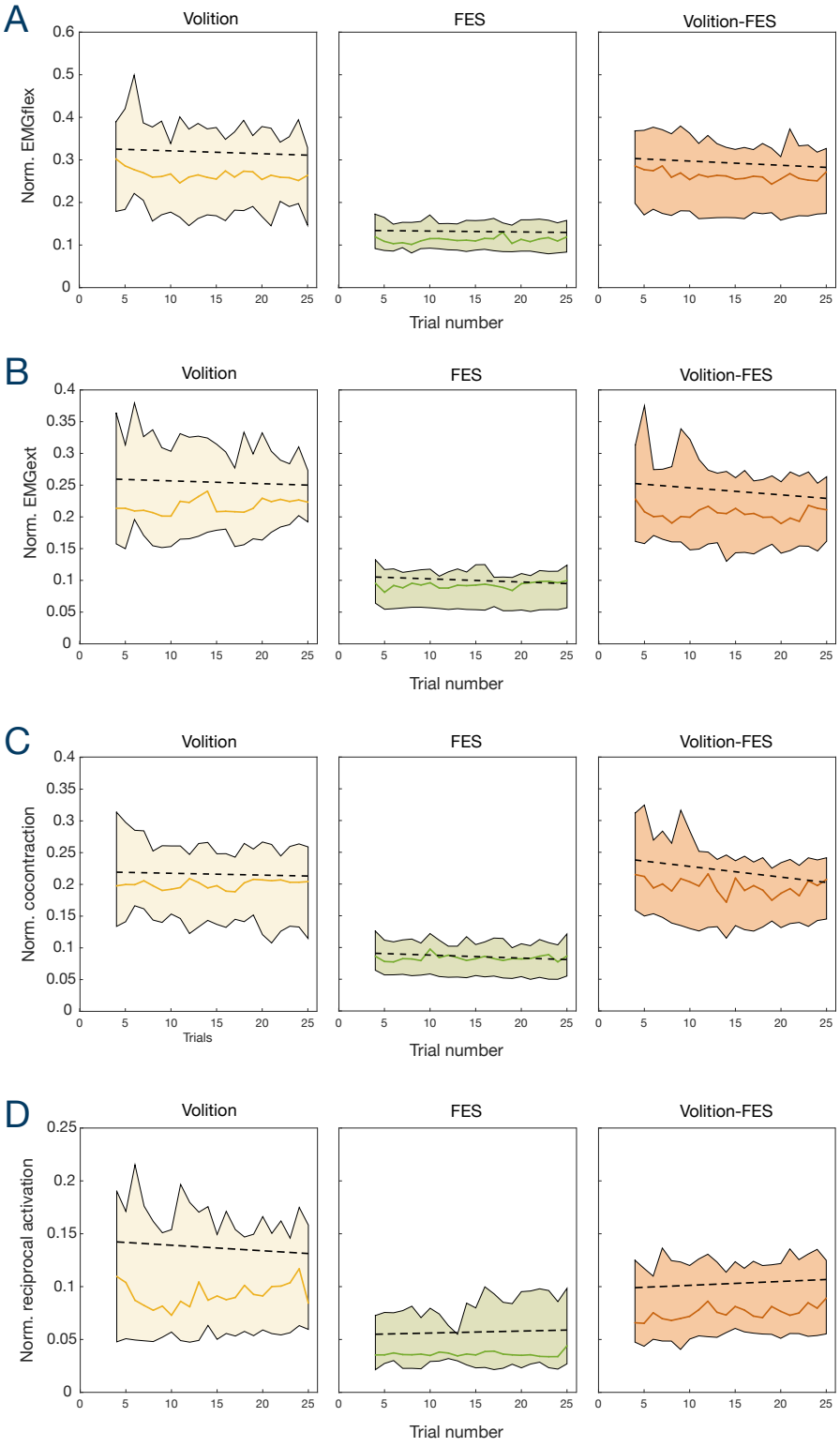


Figure 6.8: Evolution of the normalised EMG envelope across trials for each condition for the wrist flexor **(A)** and the extensor **(B)** muscles . The lines represent the median of each metric computed over all participants and the shaded areas represents the data from the first to third quartile of the metric. The first three trials are excluded as they were used as familiarisation trials and were not considered in the analysis.

(slope = -0.0004, $t(437) = -2.125$, $p = 0.0341$) and Volition-FES (slope = -0.0016, $t(437) = -4.344$, $p < 0.001$) conditions, suggesting adaptation and learning. However, the slope was not significant in the Volition condition (slope = -0.0003, $t(440) = -0.991$, $p = 0.322$). For the reciprocal activation metric, a significant positive slope was observed in the Volition-FES condition (slope = 0.0004, $t(437) = 2.811$, $p < 0.0052$), while non-significant effects were found in the other two conditions (Volition: slope = -0.0005, $t(440) = -1.491$, $p = 0.137$; FES: slope = 0.0002, $t(437) = 1.931$, $p = 0.0541$). Additionally, in the (relaxed) FES condition, the median of the normalised EMG for both muscles was lower compared to the other two conditions where participants actively followed the target (Fig. 6.8).

We also investigated whether the changes in these metrics over trials differed across conditions by computing the difference between the last three and first three trials (Additional Figure 6.16). We did not find a significant effect of condition type on the change in any of the metrics explored (EMG flexor: $\chi^2(2) = 1.81$, $p = 0.405$; EMG extensor: $\chi^2(2) = 1.18$, $p = 0.554$; CC: $\chi^2(2) = 2.67$, $p = 0.264$; RA: $\chi^2(2) = 0.38$, $p = 0.827$).

6.3 Results from stroke study

6.3.1 Questionnaire answers

The intervention group (Robot, FES, Robot+FES) did not significantly affect the NASA-TLX answers to the mental and physical demands items, as rated by patients after the assisted training block (Fig. 6.9) (mental demand: $\chi^2(2) = 1.9409, p = 0.3789$, physical demand: $F(2, 29) = 0.269, p = 0.766$). The ratings for both items were generally low, with the medians in all groups lower than 5/10, indicating a generally low perceived effort for the training task.

6.3.2 Changes in performance metrics across assisted trials

The primary LME of the normalised RMSE, considering the effect of Group, Session, Trial, and their interactions, indicated: a non-significant marginal trend for the effect of Trial (slope = 0.0008, $p = 0.0722$); Session effects (Session 2: $\hat{\beta} = -0.0295$, $p = 0.0082$; Session 3: $\hat{\beta} = -0.0301$, $p = 0.0089$); a Group effect for Hybrid vs. FES ($\hat{\beta} = -0.0842$, $p = 0.0190$); and several interactions (e.g., trial × Session 3, $\hat{\beta} = -0.0015$, $p = 0.0245$; Session 3 × Robot, $\hat{\beta} = 0.0376$, $p = 0.0191$; Session 2 × Hybrid, $\hat{\beta} = 0.0394$, $p = 0.0126$; Session 3 × Hybrid, $\hat{\beta} = 0.0427$, $p = 0.0077$).

In the Session 1 fit (one model per group × session), representing the effect of Trial on the normalised RMSE (black dotted line), slopes were not significant in the FES (slope= -0.0008, $p = 0.0827$), Robot (slope = -0.0003, $p = 0.3990$), or Hybrid (slope = -0.0002, $p = 0.3840$) groups, consistent with the non-significant global Trial effect (Fig. 6.10A).

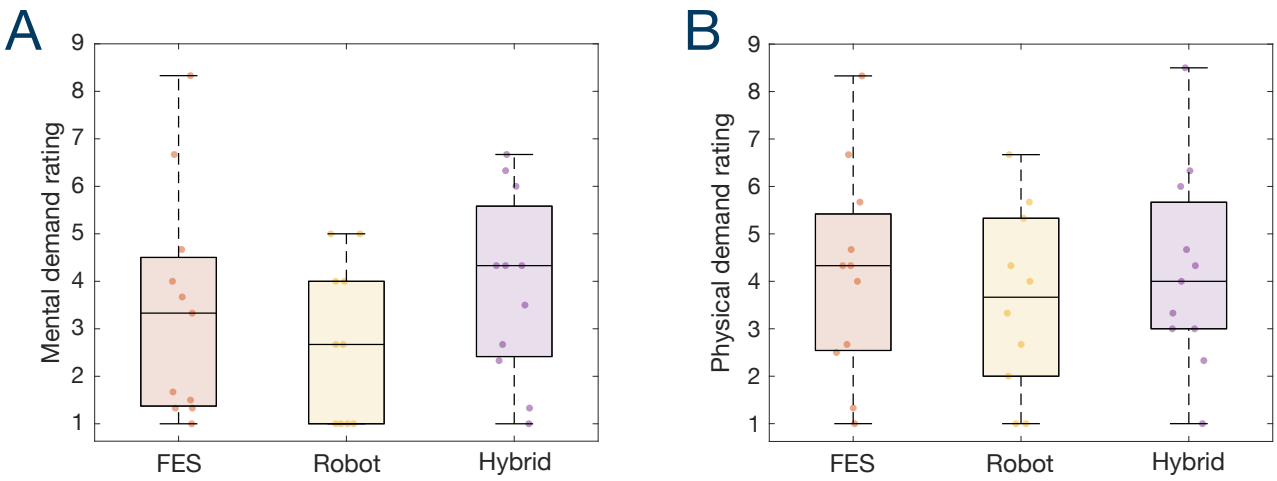


Figure 6.9: Answers to the 10-point NASA-TLX questions on physical demand **(A)** and mental demand **(B)**, with answers from very low (1) to very high (10), averaged over the three sessions.

Similar results were observed for the correlation between the frequency spectra, where the primary model indicated that the main trial effect was not significant (slope= -0.0009, $p = 0.2353$), and other fixed effects and their interactions were not significant either. Within Session 1, all per-group trial slopes were non-significant (FES: slope= -0.0009, $p = 0.2480$; Robot: slope= -0.0004, $p = 0.5530$; Hybrid: slope= -0.0001, $p = 0.8640$) (Fig. 6.10B).

Across both metrics, the primary models indicated that performance during the assisted training did not evolve significantly over trials, while there appeared to be some effect of the Session number on the normalised RMSE scores, with a small but significant decrease from Session 1 to later sessions (negative Session 2 and Session 3 coefficients). This indicates consistent performance and a limited rise in potential fatigue from electrical stimulation during the assisted training, likely to reduce tracking performance.

6.3.3 Changes in EMG metrics across assisted trials

For the cocontraction between the wrist flexor and extensor muscles during the assisted trials, the primary LME quantifying the effect of Group, Session, Trial, and their interactions showed: a negative Trial effect (slope= -0.0035, $p = 0.0037$), a Session 3 increase ($\hat{\beta} = 0.0782$, $p = 0.0119$), and several interactions (e.g., Session 2 $\times$ Hybrid, $\hat{\beta} = 0.1290$, $p = 0.0030$; trial $\times$ Robot, $\hat{\beta} = 0.0047$, $p = 0.0033$).

In the individual Session 1 per-group fits, there is a subtle but significant decrease of cocontraction over trials in the Robot group (slope= 0.0012, $p = 0.0265$), while patients in the FES and Hybrid groups showed no significant effects (FES: slope= -0.0007, $p = 0.2480$; Hybrid: slope= -0.0012, $p = 0.0813$) (Fig. 6.10 C). Significant effects were observed in the Hybrid and FES groups for Sessions 2 and 3, although the magnitude of the negative slopes over trials remained close to zero (slope$>$ -0.0045, $p < 0.0160$).

For reciprocal activation ($\mathrm{RA}_{\mathrm{norm}}$), the global Trial effect was not significant (slope= -0.0010,

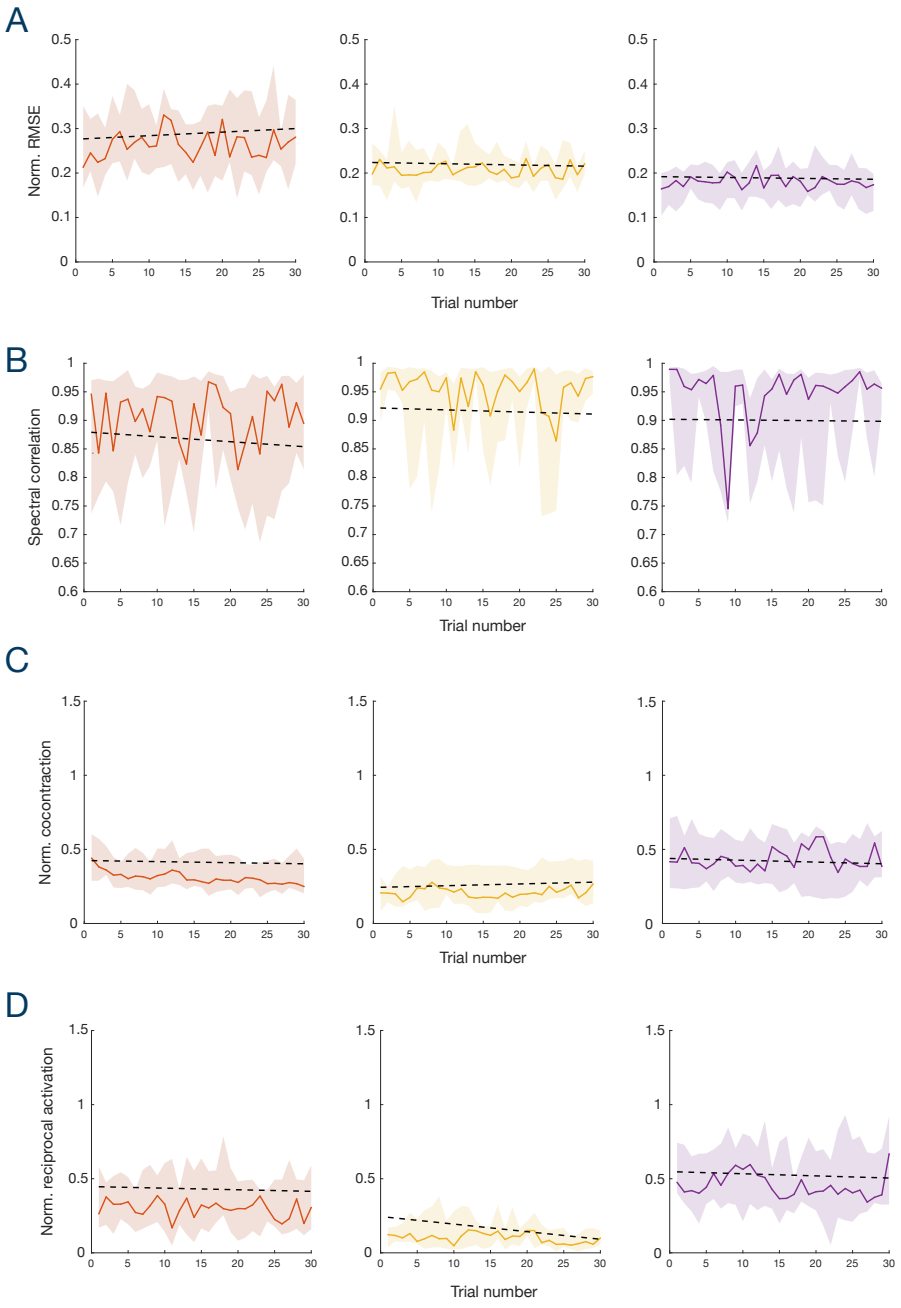


Figure 6.10: Evolution of performance, i.e. normalised RMSE between the target and patient trajectories **(A)** , and the correlation between the frequency spectra of the target and patient trajectories **(B)**; and EMG metrics, i.e. the cocontraction **(C)** and the reciprocal activation **(D)** of the wrist flexor and extensor muscles. The metric values across the assisted trials in Session 1 for each intervention group are plotted. The lines represent the median of each metric computed over all participants and the shaded areas represents the data from the first to third quartile of the metric. The dotted line represents the LME fit characterising the effect of `trial` on each metric for each session $\times$ group.

$p = 0.5946$); reciprocal activation in Session 2 and Session 3 was lower than in Session 1 (Session 2: $\hat{\beta} = -0.1161$, $p = 0.0219$; Session 3: $\hat{\beta} = -0.1078$, $p = 0.0272$); and interaction terms captured group- and session-specific trial dependencies (e.g., Session 2 × Hybrid, $\hat{\beta} = 0.2164$, $p = 0.0015$; Session 3 × Hybrid, $\hat{\beta} = -0.3023$, $p < 0.0001$; trial × Session 2 × Robot, $\hat{\beta} = 0.0091$, $p = 0.0145$).

Within the Session 1 examples, trial slopes were non-significant for the FES (slope= -0.0011, $p = 0.2570$) and Hybrid (slope= -0.0014, $p = 0.1960$) groups, while a small but significant decrease was observed in the Robot group (slope= -0.0051, $p < 0.0001$) (Fig. 6.10 D). Similarly to the cocontraction results, significant effects with subtle negative slopes over trials were also observed in the Hybrid and FES groups for Session 2 (slope> -0.0048, $p < 0.0478$).

Although we found a significant effect of the trial on the cocontraction with a negative slope, likely indicating some learning of the task, this practice-related decrease remained very small and was not consistently observed across groups and sessions. This trend was not confirmed with the reciprocal activation metric, where the trial had no effect on the metric values even when investigating each group separately. These consistent physiological characteristics may suggest task learning but do not indicate any signs of fatigue arising during the task.

6.3.4 Frequency-based EMG metrics differences before and after each condition

Across all frequency-based EMG metrics (median frequency, Dimitrov spectral index, and mean of the instantaneous median frequency), no statistically significant differences were found between intervention groups (all $p > 0.1$). This was consistent for both flexor and extensor muscles. The boxplots in Fig. 6.11 illustrate the distribution of each metric across intervention groups, where a negative difference would indicate a decrease in the metric value after the assisted training block, suggesting a rise in muscle fatigue for the median frequency (A,B) and the instantaneous median frequency (C,D), while a positive difference, i.e. an increase in the Dimitrov spectral index, would indicate fatigue (E,F). The medians of most median frequency metrics in the three intervention groups are above zero, except in the Robot group where we can observe a negative median in the median frequency and mean of the instantaneous median frequency of the extensor EMG, although this is not significantly different from zero. Similarly, for the Dimitrov spectral index, the median for the Robot group is slightly above zero in the flexor and extensor EMG signals, although this is not significant (both $p > 0.4$).

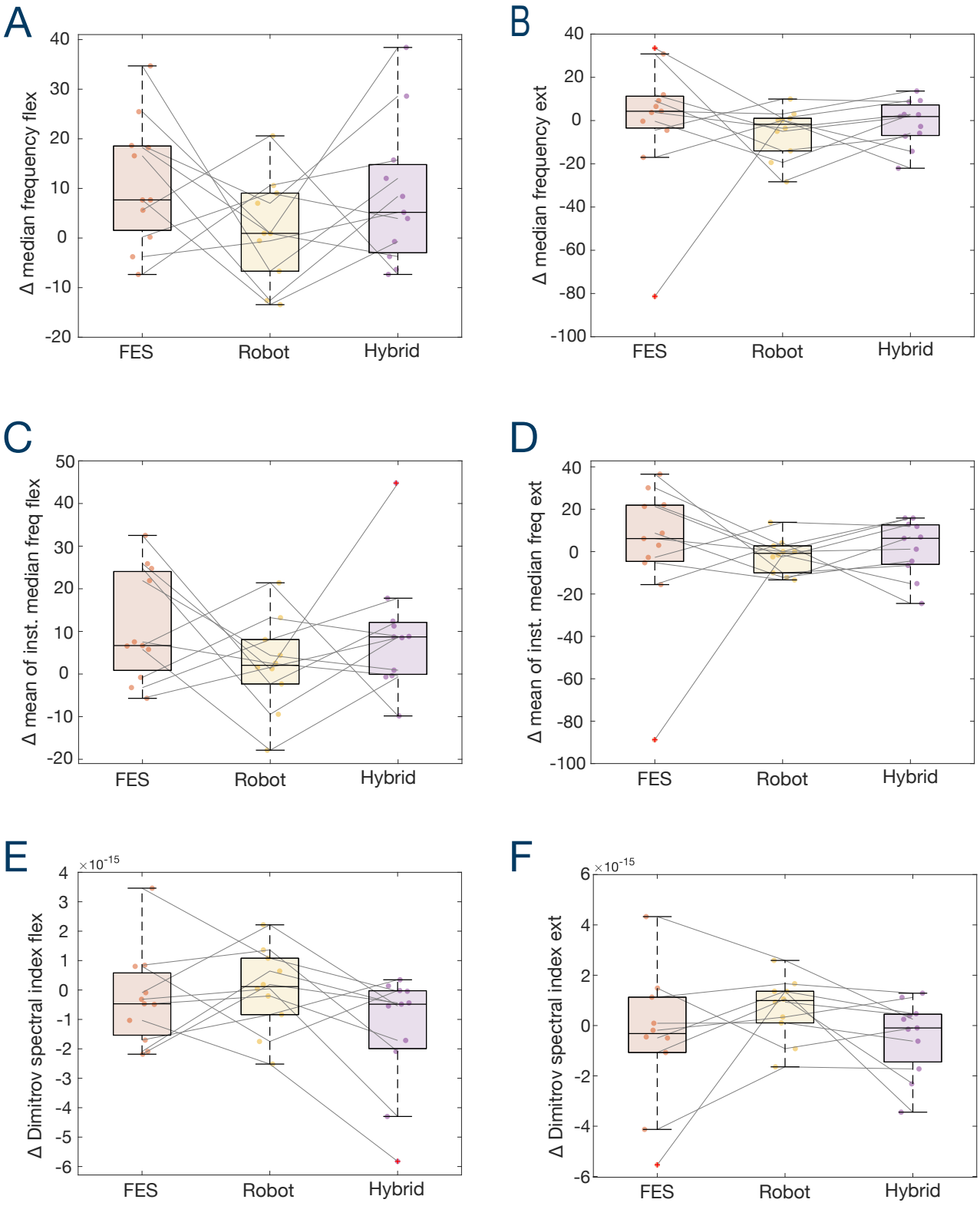


Figure 6.11: Difference in frequency-based EMG metrics between the last three and first three trials for each condition for the wrist flexor (A, C, E) and the extensor (B, D, F) muscles: the difference in median frequency (A,B) and in the mean of the instantaneous median frequency (C,D), as well as the Dimitrov index (E,F) are presented. A negative difference in the median frequency (A,B) and in the mean of the instantaneous median frequency (C,D) would indicate fatigue. A positive difference in Dimitrov index (E,F) would indicate fatigue.

6.4 Discussion

In FES-based training, both for post-stroke rehabilitation and assistance tasks like FES-cycling, there is a growing interest in managing FES-induced fatigue, which is often seen as a limiting factor in the intensity and duration of training (Ibitoye et al., 2016). For example, in the FES-cycling race at the Cybathlon, pilots with spinal cord injuries (SCI) typically experience a noticeable decline in pedal power output over time. Since cycling is a dynamic task with no resting periods, and SCI participants cannot voluntarily activate their muscles, all leg force is generated by electrical stimulation. This differs from typical stroke rehabilitation tasks. Our goal here was thus to investigate the presence and progression of fatigue during a wrist target-tracking task under different assistance conditions, combining evidence from unimpaired individuals and post-stroke participants. Together, these studies provide complementary insights into how assistance modalities influence motor performance, neuromuscular activation, and subjective workload, as well as the extent to which fatigue accumulates during training. This work was conducted to inform the design of motor rehabilitation systems that include FES.

The mechanical and electrical responses of the muscles do not change after FES and/or voluntary motion training. In the unimpaired cohort, no significant changes in MVC torque (Fig. 6.4) or M-wave parameters (Fig. 6.2) were observed before and after any of the training conditions (Fig. 6.4). This indicates that there were no changes in the mechanical or electrical responses of the muscle after this training, involving FES-induced and/or voluntary wrist motion. Since fatigue is typically characterised by a reduction in maximal power or force output (Vøllestad, 1997), the absence of changes in MVC before and after each condition suggests that fatigue did not develop over time in this study. Additionally, the M-wave parameters measured under maximum comfortable stimulation after each condition also remained stable, hence providing further evidence contradicting our initial hypothesis that the Volition-FES condition would result in greater fatigue compared to the Volition condition.

Indeed, previous research comparing FES-induced force and voluntarily maintained force has found that fatigue is greater in the electrical stimulation condition, potentially due to the unnatural recruitment pattern under FES and the typical recruitment of fast and fatigable muscle fibres early on (Bickel et al., 2011). However, despite the fact that this experiment in unimpaired participants was the same as the one used in stroke patients, and involved continuous stimulation for 25 trials of 30 seconds each, it did not induce noticeable muscular fatigue. This may be attributed to the task not being sufficiently challenging or tiring for participants. The median questionnaire ratings indeed suggest that the task was not physically demanding, with ratings consistently lower than or equal to 5/10 across conditions.

The stroke cohort was divided into three groups: FES assistance, Robot assistance, or combined FES+Robot assistance. Patients in all three groups reported comparable medians to the unimpaired cohort in the physical and mental demand items of the NASA-TLX questionnaire (Fig. 6.9), although the conditions presented to both cohorts are not comparable (the FES condition in the unimpaired cohort involved participants relaxing while FES was applied, while in the stroke cohort this corresponds to an FES-assisted training condition encouraging patients to actively move their hand). Furthermore, no significant differences between groups were found, although one could expect robot-based assistance to be less demanding or tiring. This aligns with the unimpaired participants data, suggesting that the assisted tracking task, while continuous, was not experienced as highly effortful in any modality.

In the stroke study, we further investigated the rise of fatigue by comparing several frequency-based EMG metrics, including those suited for a dynamic task such as the one here (Karlsson et al., 2000; Bonato et al., 2001; González-Izal et al., 2010), used to characterise fatigue, in the unassisted trials before and after the assisted training (Fig. 6.11). No significant between-group differences in the change from pre- to post-training were found in any of these metrics, suggesting that there was no stronger increase in muscular fatigue in the FES group compared to the Robot group as we had expected. Furthermore, the medians of the difference in these fatigue indices were mostly close to zero and further statistical investigations did not indicate any significant changes. Hence even when investigating changes within each condition, we did not find any sign of fatigue that would have risen after the assisted training. Across both cohorts, this suggests that under the present task parameters, neither subjective workload nor spectral EMG features indicated a marked accumulation of muscular fatigue.

Although there is a consensus on the rapid increase in muscle fatigue after electrical stimulation in the literature, this is usually tested with fatiguing protocols in unimpaired cohorts typically involving more intense conditions, such as 1-5 minutes of MVC or 1-3 minutes of tetanic stimulations (Rodriguez-Falces et al., 2018) or evaluating the effect of different stimulation parameters during sustained stimulation on generated torque to understand the impact on fatigue (Kroon et al., 2005; Dreibati et al., 2010). Fatigue was typically studied in a similar manner in clinical populations, mostly in individuals with SCIs, to investigate the physiological mechanisms of fatigue (Qiu et al., 2020; Estigoni et al., 2014; Heasman et al., 2000) rather than whether it may be relevant in a typical motor rehabilitation task scenario. A repetitive FES-assisted grasping protocol, which can also be assimilated to a rehabilitation session, found that muscle fatigue did not increase over time (Höhler et al., 2025).

Tracking performance, motion smoothness and effort do not consistently change over time and the type of condition does not affect this change. In both studies in unimpaired and stroke individuals, we also investigated the evolution of metrics potentially associated with muscle fatigue over time, including tracking performance, the EMG envelope of the flexor and extensor muscles, cocontraction, and reciprocal activation (unimpaired study: Fig. 6.7, stroke study: Fig. 6.10).

In the study in unimpaired participants, tracking performance, quantified by the tracking error and the correlation between the participant and target trajectories, decreased significantly although modestly, in both the Volition and FES conditions. SPARC, characterising motion smoothness, also worsened in all conditions, although with a stronger trend in the FES condition. This may suggest that, over time, the stimulation became less effective at contracting the muscles to follow the target trajectory, consistent with previous studies on FES during continuous tasks (Allen et al., 2020). It is also possible that the decrease in tracking performance is related to variations in the electromechanical delay between stimulation and motion onset (Downey et al., 2017), resulting in a delayed motion response relative to the target. This decrease in performance could thus potentially be in part due to fatigue and could be used as a marker of fatigue in a closed-loop control system. This effect may have been enhanced in the FES condition as participants were asked to relax and thus did not compensate for this decrease in performance.

In the stroke study, where similar analyses were performed on the assisted trials, using tracking error and the correlation between the frequency spectra of the target and participant trajectories, we did not find consistent and significant temporal effect (Trial number) on these metrics in any of the intervention group. When significant trial-related trends were obtained, these were also very modest and scarce. Furthermore, there was no effect of the intervention group, except between the Hybrid and FES group, which was not the expected difference from our initial hypotheses.

Regarding physiological measures, unimpaired participants in the Volition-FES condition showed reduced cocontraction and increased reciprocal activation over time, possibly indicating learning and adaptation, where participants reduced their muscle activation over time and learnt to interact with FES assistance (Thoroughman et al., 1999; Franklin et al., 2003). On the other hand, there were no significant changes in the other conditions (Fig. 6.8).

In the stroke population, a negative effect of the Trial number was found on the cocontraction, which was also observed in each intervention group and specific sessions. It could indicate some level of learning and adaptation of the task, although the magnitude of the effect remained very limited (Fig. 6.10). Reciprocal activation showed no global Trial effect but was generally lower in later sessions, with several Group- and Session-dependent interactions, suggesting that these muscle activation patterns also adjusted over the course of training while they did not within-session. Additionally, and similarly as with the unimpaired study, we did not find a Group effect on the physiological metrics.

This lack of consistent significant effect of the trial or the training condition, in both the unimpaired and stroke studies, suggests that no single condition led to greater performance reduction or effort alteration compared to others. This outcome was unexpected given the differing physiological processes underlying voluntary and FES-induced muscle contractions (Bickel et al., 2011). When considered together, both studies thus indicate that continuous, moderately demanding FES-assisted tracking does not seem to induce pronounced fatigue as assessed by MVC, M-wave, subjective ratings, or frequency-domain EMG metrics. Additionally, the decrease in cocontraction, observed in the stroke population, may also reflect beneficial motor learning rather than detrimental fatigue. This supports the feasibility of incorporating such tasks into rehabilitation without risking substantial short-term muscle fatigue.

The sample size and the current filtering procedures limit the interpretation of these results. These results should be interpreted with care as the limited number of participants in both studies does not allow for strong generalisation of these results. Furthermore, these results can be interpreted in the context of this specific target-tracking task, but they cannot be generalised to other tasks such as repetitive FES-assisted grasping and hand opening, which are common in stroke rehabilitation exercises. However, such practice is typically performed in a continuous manner with agonist-antagonist contractions (e.g., open hand with FES, bring object inside the hand, close hand with FES) and with a break after each repetition, similarly as performed here with our dynamic target tracking task involving alternated contraction of the wrist flexor and extensor muscles.

Furthermore, the adaptive filter used in this study to remove the FES component from the corrupted EMG signal has only been validated for computing the signal envelope for torque estimation, not for investigating metrics derived from the signal's frequency spectrum. This presents a significant limitation, as frequency-domain EMG metrics, typically used to assess fatigue, could only be computed in the unassisted trials preceding and following the assisted training in the stroke study and could not be computed within each assisted training.

Finally, the electrode configuration used for stimulation in the study in unimpaired participants may not have been optimal for extracting parameters from the M-wave, as a monopolar configuration is typically recommended. In this study, we used the electrode placement recommended by our clinical collaborators and employed in the study in stroke patients. This choice may have made the recordings more susceptible to crosstalk and positional shifts, particularly since the wrist flexor and extensor muscles of interest are relatively small (Rodriguez-Falces et al., 2018).

6.5 Conclusion

This chapter investigated the presence and evolution of fatigue during a continuous, dynamic target-tracking task performed under different assistance modalities. In unimpaired participants, we evaluated the impact of FES-induced and/or voluntary movement on perceived fatigue, performance, effort, and the electrical and mechanical responses of muscles. Stroke patients also performed a similar task with the assistance of a robot or FES or the combination of both. There, we used similar metrics to quantify fatigue in this clinical population, which is the target of such rehabilitation protocol, focusing on whether FES-assisted practice would induce greater fatigue than robot-assisted modalities. In both populations, neither maximal mechanical or electrical responses, spectral EMG metrics, nor subjective ratings indicated a rise in muscular fatigue after training. Similarly, tracking performance and EMG-derived physiological measures showed only modest trial-related changes, with decreases in cocontraction, suggesting beneficial motor adaptation and learning of the task.

These findings suggest that, under the present task parameters, short-term FES-assisted tracking, whether in isolation or combined with robotic assistance, can be performed without inducing substantial muscular fatigue and that FES-induced fatigue may not be a major factor to be considered. This supports its feasibility as a component of rehabilitation programs, particularly where the goal is to promote active engagement without compromising subsequent sessions. The next chapter builds on these insights in a longitudinal hospital-based study, assessing the effects of three weeks of FES–robot assisted training in stroke survivors, and understand the potential clinical efficacy of such system.

6.6 Additional figures

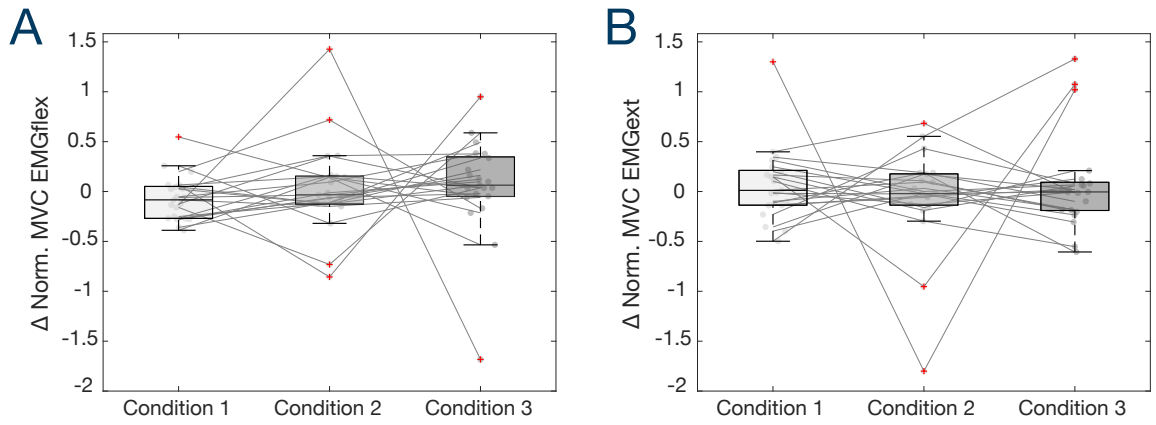


Figure 6.12: Difference in mean normalised EMG during MVC trials after each condition, presented in chronological order for the flexor MVC **(A)** and the extensor MVC **(B)**.

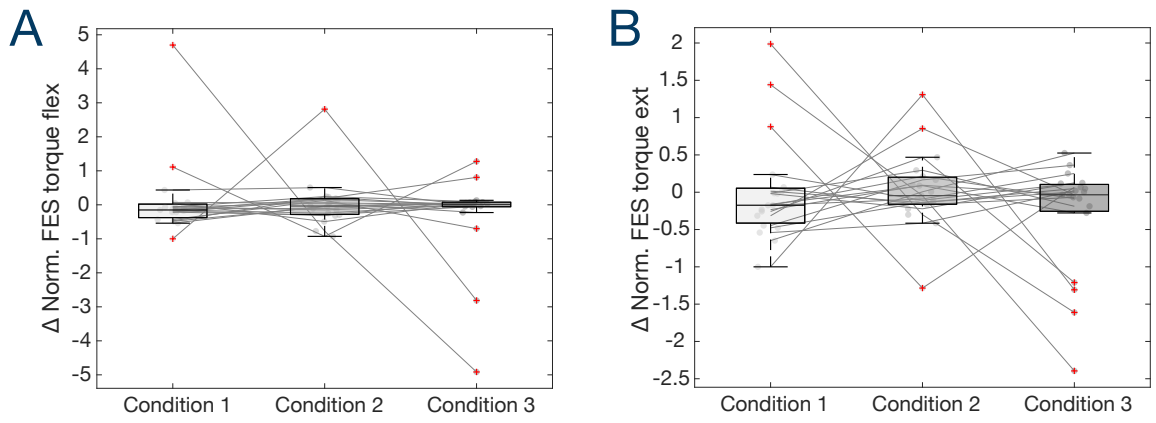


Figure 6.13: Difference in mean normalised FES-induced torque after each condition, presented in chronological order for the flexor stimulation **(A)** and the extensor stimulation **(B)**.

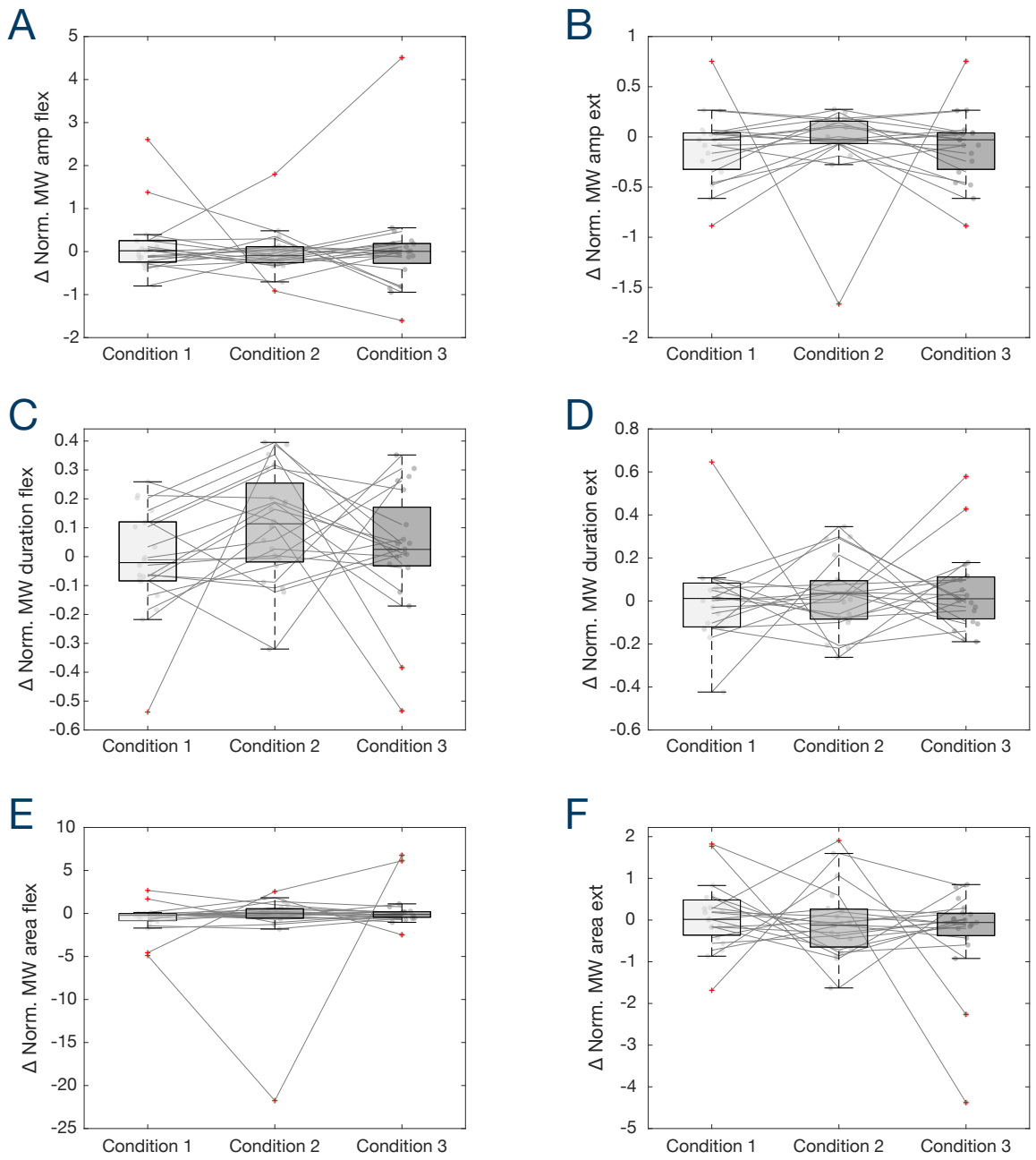


Figure 6.14: Difference in mean normalised M-wave parameters when the maximum comfortable stimulation is applied while at rest, after each condition, presented in chronological order for the flexor stimulation **(A,C,E)** and the extensor stimulation **(B,D,F)**. The M-wave parameters presented are the M-wave peak-to-peak amplitude **(A,B)**, the M-wave duration **(C,D)** and the M-wave area **(E,F)**.

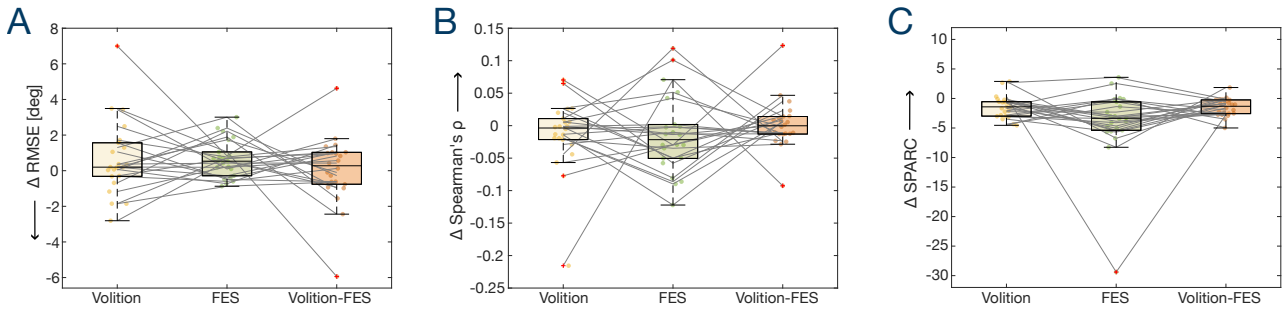


Figure 6.15: Difference in mean performance metrics between the last three and first three trials for each condition: root mean square error between the subject's and target's positions **(A)**, correlation between the subject's and target's positions **(B)**, SPARC metric capturing motion smoothness **(C)**. $* : p < 0.05, ** : p < 0.01, *** : p < 0.001$. Comparisons not shown are not significant.

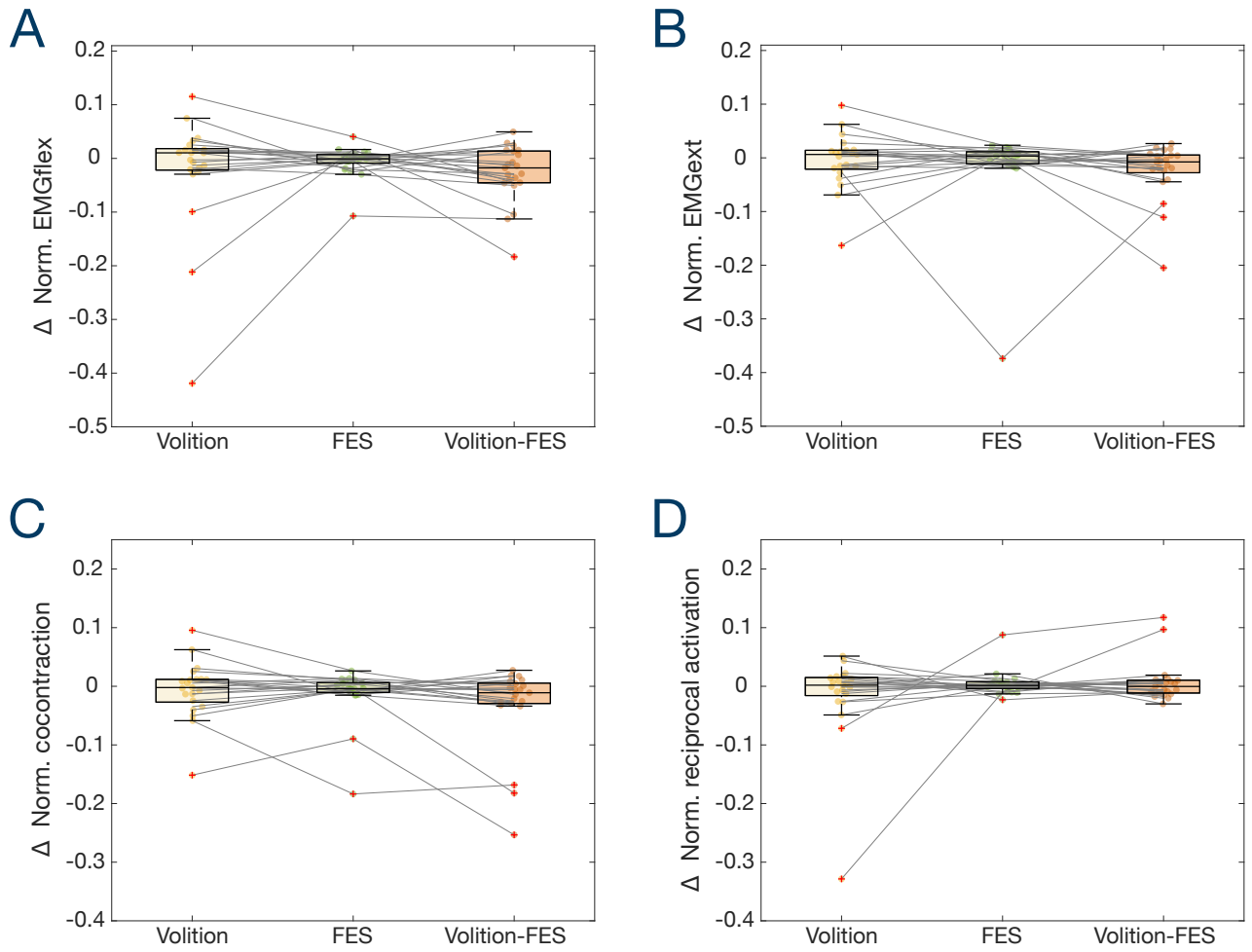


Figure 6.16: Difference in the mean of normalised EMG envelope between the last three and first three trials for each condition: for the wrist flexor **(A)** and the extensor **(B)** muscles.

Chapter 7

Clinical study to evaluate the effects of additional hybrid robot-FES rehabilitation

The previous chapters established the technical feasibility, usability, and short-term physiological effects of a hybrid robot-FES system for upper-limb rehabilitation after stroke. We have seen in Chapter 4 that hybrid assistance improved performance and engagement in unimpaired individuals, without inducing fatigue. In Chapter 5, a short three-session feasibility study with subacute stroke patients conducted at Schön Klinik, Bad Aibling in Bayern, Germany demonstrated that the system was safe and well-tolerated, and facilitated motor performance and voluntary effort across different assistance modes. Furthermore, Chapter 6 demonstrated that hybrid and FES-based assistance did not lead to significant muscular fatigue even under repeated use in dynamic tasks.

Collectively, these findings support the safety and the potential of using the hybrid system in clinical environments. However, these earlier studies employed a simple controller with equal robotic and FES support that did not consider the intrinsic limited bandwidth and delay in FES, and used a fixed assistance level, limiting its adaptability to individual patient needs. Moreover, the short training duration did not allow for the evaluation of potential clinical benefits.

This chapter investigates the research question QD: *How does hybrid robot-FES rehabilitation affect functional and physiological recovery after stroke?* To address this question, we conducted a three-week intervention study with subacute stroke patients at Charing Cross Hospital, an Imperial NHS trust hospital in London. Participants in the intervention group completed daily training sessions using the hybrid system in addition to their usual conventional therapy sessions. This intervention consisted of performing a wrist tracking task, where the level of FES and robotic assistance and the difficulty were adapted to individual capabilities. We used a controller distributing the relative effort between the robot and FES assistance, by considering the limitations of the FES response, and based

on task performance, to ensure that the system is optimally supporting each patient throughout their training. Clinical assessments of upper-limb motor function and recovery were conducted at baseline, mid- and post-intervention, and at one-month follow-up to evaluate changes over time and retention. Patients continued receiving their usual conventional care throughout the intervention. To evaluate the effect of supplementary training with the hybrid robot-FES system, these outcomes are compared to a control group of stroke patients who received only the conventional care, without additional sessions, and were assessed at the same time points.

Furthermore, the hybrid system enabled the continuous collection of kinematics and EMG data throughout the intervention. These data were used to compute objective metrics such as tracking accuracy, motion smoothness, and effort. By analysing the evolution of these features over the course of training, we aim to characterise the underlying physiological changes that may accompany functional recovery. Qualitative feedback from the patients was also collected to investigate their perception of this rehabilitation training paradigm.

Through this final experimental chapter, we assess the clinical relevance of hybrid robot-FES therapy, and its potential to improve upper-limb function beyond standard care.

The controller presented in this chapter was developed in collaboration with Satoshi Endo and Hossein Kavianirad of the Technical University of Munich, who designed the dynamic allocation between FES and robotic assistance and identified the FES-torque mapping, while the adaptation was developed at Imperial. The experimental protocol was also developed in collaboration with Satoshi and Hossein. Victoria Reboredo and I screened, recruited and collected patient data at Charing Cross Hospital with the assistance of the medical and therapy team on-site. I contributed to conceiving and designing the research, developing the experimental protocol and programming the experimental task, performing the data analysis and created the figures in this chapter, and interpreted the results. Victoria analysed the questionnaire answers and conducted the thematic analysis.

7.1 Methods

7.1.1 Participants

The study was run at Charing Cross Hospital in London, UK. It was approved by the Research Ethics Committee of the Health Research Authority of England and was sponsored by Imperial College London (REC reference: 21/SC/0370, ClinicalTrials.gov ID: NCT05253989). We started screening patients from the stroke wards' patient records on 17 February 2025. The study participants are subacute stroke patients, recruited during their stay in the Stroke wards in Charing Cross Hospital after an ischaemic or haemorrhagic infarction.

All participants or their legal representatives signed an informed consent form before participating



Figure 7.1: A patient tracks a randomly moving target on-screen with wrist flexion/extension.

in the experiment. Patients recruited in the intervention arm of the study received a three-week wrist training using our hybrid robot-FES device on top of their usual care and therapy sessions. Patients recruited in the control arm of the study participated in the assessments but did not receive any additional therapy on top of their usual care and therapy sessions. Patients from the intervention and control groups were recruited following the same inclusion criteria: age > 18 years old, cognitively able to follow instructions, with functional impairments in the wrist or fingers as assessed by the Medical Research Council score (MRC ≤ 4) and a low level of pain or no pain in the wrist or fingers at rest (Numeric Rating Scale < 4). Patients were excluded if they had an unstable medical condition, a severe psychiatric disorder, or other concomitant neurological disorders affecting upper extremity motor function, or if they were enrolled in another interventional neurorehabilitation trial. Patients in the intervention arm of the trial were excluded in case of any of the following FES-related criteria: pregnancy, presence of implantable devices or other metal implants in the stimulated area, no motion or muscle contraction resulting from FES, the presence of pain during stimulation in the forearm muscles, patients with severe epilepsy and cancer or wounds in the stimulated area, peripheral nerve damage.

We screened patients using the electronic health records platform of Charing Cross Hospital, where we identified potential patients who met the main inclusion / exclusion criteria (e.g. medically stable, functional impairments in the upper-extremity, cognitive abilities, etc.). We approached patients in the stroke wards to present the study and gave them the patient information sheet when they mentioned they were interested in participating in the study. We also asked the medical and therapy team for further inputs regarding the use of FES with a patient and their responsiveness and compliance to therapy sessions, e.g. if a patient is very tired and already finding it difficult to attend their usual care sessions, if the patient presents any aggressive behaviours towards the team, etc. We typically visited

the patient again one or two days later to ask them if they remembered about the study and if they were still interested. If this was the case, they then signed the informed consent form to confirm their participation in the study and we arranged a time with them to complete the first baseline assessments. In some cases, it was not clear whether patients were able to give consent, hence we also discussed with their family members and they also signed the consultee consent form in addition to the patient. We also offered family members to be present for the assessments and the first intervention sessions.

7.1.2 Experimental design and procedure

Patients in the intervention group received a 3-week wrist training using the hybrid robot-FES system presented in Chapter 3 and used in Chapter 5 in a feasibility study (Fig. 7.1). We aimed for each patient to complete five sessions every week, with each session lasting 30-45 minutes. Barriers to the completion of these five sessions included additional medical procedures/diagnoses (repeat CT scan, use of Holter for 24 h, investigation of infection, etc.), increased pain on a particular day, fatigue or low mood resulting in the patient refusing to participate on a particular day.

Each session was identical, and similar to the protocol presented in Chapter 5. It started with a ROM calibration, followed by an FES calibration; the patient then trained in the wrist target-tracking task.

The *ROM calibration* used in this study is identical to the one in Chapter 5 (Section 5.1.2), with a passive ROM assessment, where the experimenter moves the handle of the robot in the flexion and extension directions and an active ROM assessment, where the patient is asked to actively move their wrist as far as possible in both directions. Each assessment is repeated three times.

The *FES calibration* procedure is similar to the one described in Chapter 3, Section 4.1.5, where the electrode location, comfortable maximum stimulation (s_f^{max} for the wrist flexion, and s_e^{max} for the wrist extension), and the motor threshold (s_f^{min} and s_e^{min}), for the wrist flexion and extension movements, were identified. The motor threshold was defined as the smallest stimulation amplitude that led to a torque output of at least 0.2 Nm while the patient was asked to rest. This threshold value was empirically defined as one that could generate the onset of a movement. Subsequently, the robot moved the wrist at three different joint angle positions, i.e. resting position, and 15° before the flexion and extension angles recorded in the passive ROM. At each angle, the wrist flexor or extensor was stimulated at the calibrated maximum or motor threshold for that muscle (s^{max} or s^{min}). Twelve combinations of angle, motion direction, and stimulation amplitude were presented in a randomised sequence, while the patient was asked to remain relaxed. Based on the FES amplitude, the wrist angle, and the resulting torque, a user-specific non-linear recruitment curve for the flexion and extension movement is modelled using cubic splines, used to provide FES-based assistance during the wrist target-tracking task.

Patients then performed a *wrist target-tracking task*, where they were instructed to track the target as accurately as possible using wrist flexion/extension movements of their impaired hand, represented on-screen by another character. The target trajectory is defined as:

$$q^*(t) = q^*_{mid} + q^*_{max} \sin\left(\omega_1 t^+\right) \sin\left(\omega_2 t^+\right) \tag{7.1}$$

where t is the elapsed time, $t^+ = t + t_0$ with t_0 the starting time selected to ensure the target starts at the position of the user and to prevent consistent prediction of the target trajectory. q^*_{mid} is the middle point of the target range, and q^*_{max} half the target range. ω_1 and ω_2 determine the target speed and are determined by the difficulty level during that trial.

The first five trials were unassisted and designed to determine a patient's baseline performance at the start of the session, while the subsequent 30 trials were assisted by the hybrid robot-FES system, depending on the patient's needs. The final five trials were also unassisted to evaluate potential changes with respect to the baseline. If their timetable allowed, patients were then asked whether they wanted to continue with the assisted training, and they could do so until they asked to stop. Each trial lasted 12 seconds with a 3-second break. The rest time could be prolonged as desired by the patient. After the first training block and the first evaluation block, the patients answered a set of questions.

This intervention was in addition to patients' usual care and therapy and did not affect the nature of the treatment they received in the hospital. Patients in the control group did not receive any additional intervention on top of their usual care and therapy. Similarly, being recruited in this trial did not restrict the nature or intensity of therapy they would normally receive as part of their hospital stay.

7.1.3 Hybrid robot-FES system

Setup

The *electrical stimulation and robotic devices* used have been described in Chapter 3, Section 3.1. The pulse frequency of the stimulation is set to 25 Hz and the pulse width to 300 μs as these values have been used clinically (Kapadia et al., 2013). The amplitude of the stimulation varies (with 0.1 mA resolution) during the experiment. To maintain hygiene standards, device-specific cleaning protocols were followed. Muscle activity of the wrist flexor (flexor carpi radialis) and wrist extensor (extensor carpi radialis longus) was recorded using a forearm EMG bracelet (Neubond, UK), with 12 channels recording muscle activity at a frequency of 1000 Hz.

Control principle

The total torque τ^{hyb} provided by the hybrid system, formed by the robot and FES, to assist the patient in the tracking task increases with the error e_q between the patient's wrist angle q and the target angle q^* and its velocity $\dot{e}_q$ as follows:

$$\tau^{hyb}(t) = k_p e_q(t) + k_d \dot{e}_q(t)\,, \quad e_q(t) = q^*(t) - q(t)\,, \tag{7.2}$$

where the control gains k_p and k_d determine the level of assistance. This torque τ^{hyb} is then distributed between FES assistance τ^{fes} and robotic assistance τ^{rob} as the convex sum of their torque:

$$\tau^{fes}(t) = \alpha \tau^{hyb}(t)\,, \quad \tau^{rob}(t) = (1-\alpha)\tau^{hyb}(t)\,, \tag{7.3}$$

where the parameter α defines their relative contribution. This allocation is designed to prioritise FES over robotic assistance by using as much FES assistance as its dynamics allow. We favour FES over robotic assistance because FES training is recommended by most national clinical guidelines (Salbach et al., 2022; Intercollegiate Stroke Working Party, 2023; Veterans Affairs/Department of Defense, 2024; Stroke Foundation, 2024) and has been shown to yield clinical benefits for post-stroke recovery. In this implementation, the robotic component primarily serves to enhance the comfort and smoothness of the assistance, rather than to provide therapeutic benefit by itself. The robot complements the FES by delivering smooth, precisely timed corrective torques that prevent overshooting or instability, which can arise when stimulation-induced contractions vary over time or between muscles. This is particularly relevant during continuous tracking tasks, where maintaining fine control of movement is essential for task success and patient comfort. The relative contributions of FES and robotic assistance are adapted based on the complementary characteristics of each actuator, on the patient's real-time performance and the intrinsic response properties of the stimulated muscles. This adaptation is designed to ensure that (i) stimulation is prioritised when it can induce the required torque level and a slow response is sufficient, and (ii) robotic torque takes over when fast, precise corrections are required. Such synergy results in stable and smooth motion trajectories, while maximising neuromuscular engagement from FES. This control strategy may also enhance the comfort and overall user experience, supporting patients' willingness to participate in longer and more frequent sessions, which may positively affect functional recovery outcomes.

Assistive torque allocation (defined by α and l in Eq 7.4 below) depends on each patient's torque-response to stimulation, including the FES torque saturation and the dynamic constraints of FES such as bandwidth, time constant, and electromechanical delay between stimulation and motor output. These are obtained during the patient-specific FES calibration in which the torque-response to varied stimulation intensities at multiple wrist angles is modelled. This means that whenever the constraints

of this actuator are not relevant, e.g. when low levels of torque are required and when slow torque responses are needed, the FES assistance is used primarily, while the robotic assistance is favoured when quick corrective torques are required. This approach was preferred over explicit compensation, as the electromechanical delay may not be reproducible over individuals and over time, while here the controller inherently prioritises robotic assistance over FES when rapid corrective torques are required, i.e., where the electromechanical delay of FES could result in delayed or counterproductive assistance.

The allocation dynamics is computed from:

$$\begin{aligned} \alpha_i &= \bar{\alpha}_i + \frac{\zeta_i}{\tau^{hyb}}, \\ \dot{\zeta}_i &= -l_i\zeta_i + l_i(\alpha_i^s - \bar{\alpha}_i)\tau^{hyb},\ i = 1, 2 \end{aligned} \tag{7.4}$$

where the subscript i denotes flexor ($i = 1$) or extensor ($i = 2$) muscles. The direction of the desired assistive torque sign(τ^{hyb}) specifies which muscle group, flexor or extensor, is activated. For brevity, the subscript i is omitted (i.e., $_i$) when no confusion arises. The variable $\bar{\alpha}$ denotes the nominal cooperative gain, and ζ is the allocation variable associated with flexor and extensor activation. A detailed description and analysis of the dynamic allocation principle as well as procedures for selecting the coefficients in the above equations, is presented in [CiteToDynamicAllocationPaper].

Controller implementation

The torque-current map of the Maxon motor used in the HRX-1 device determines the current needed to generate the desired robot torque τ^{rob}.

For the FES, the required torque is converted to the desired stimulation intensity u^{fes} using the patient-specific FES-torque map at the current wrist angle q of the patient. This non-linear recruitment curve $r(u^{fes}, q)$ is obtained from the FES calibration of each patient and used to define the desired stimulation intensity:

$$\begin{aligned} J(u^{fes}, q, \tau^{fes}) &= r(u^{fes}, q) - \tau^{fes} \\ u^{fes\star} &= \arg\min_{u^{fes}} J(u^{fes}, q, \tau^{fes}) \\ &\text{s.t.} \quad 0 \leq u^{fes} \leq u_{max}^{fes}\ , \end{aligned} \tag{7.5}$$

where u^{fes} denotes the FES intensity command and $u_{\max}^{fes}$ its maximum threshold. For flexion and extension, the corresponding recruitment curve and maximum intensity threshold are considered separately.

Table 7.1: Difficulty levels

Level	Target range (% PROM)	Assistance level (% K_p^{max})	Target speed (% ω^{max})
1	30	100	100
2	60	100	100
3	100	100	100
4	100	60	100
5	100	30	100
6	100	0	100
7	100	0	75
8	100	0	50

Difficulty adaptation

We developed a rule-based adaptation that adjusts the difficulty level of the task to match the patient's abilities and provides challenging but rewarding training (Csikszentmihalyi, 1990; Guadagnoli et al., 2004). The target range, the amount of total assistance τ^{hyb} provided to the user and the target speed, are adjusted based on the tracking performance, resulting in seven difficulty levels described in Table 7.1. The lowest level is defined by a slow target speed, full assistance and a target range set as 1/3 of the passive ROM of the patient. The maximum level of assistance corresponds to control gains $k_p^{max} = 3.3$ Nm/rad and $k_d = 0.9$ Nm.s/rad. The target speed also changes with the difficulty level using the ω_1 and ω_2 in Eq. 7.1. In levels 1 to 6, the target speed is slow and they are defined as: $\omega_1^{max} = 3.868$ and $\omega_2^{max} = 7.188$. Similarly the target range increases with higher levels, up to the full PROM of the patient. These parameters are similar to those used in our previous feasibility study (Cazenave et al., 2023), and difficulty levels were determined based on discussions with clinicians involved in stroke rehabilitation at Schön Klinik and Charing Cross Hospital.

The performance metric used to adjust the level of difficulty is a compound score of the normalised RMSE between the patient and target trajectories, and the phase lag between the main frequencies of the spectra of the position profile of the target and that of the patient. The algorithm is designed such that the difficulty level can be updated every five trials based on the average performance metric. The performance threshold to increase difficulty is 80% and 50% to decrease it, so that patients remain motivated by the score reward while still being challenged (Cameirão et al., 2010; Lambercy et al., 2009). In the first session, the initial level is calibrated based on the performance in the first five baseline unassisted trials, where an average score above 75% leads to starting level 6, a score above 50% at starting level 5, and above 25%, a starting level 4. For any other score, training difficulty begins at level 3, as we assume it is favourable to let the patient move across their full passive range of motion. The difficulty level would then decrease progressively if the patient cannot perform well with this large target range.

7.1.4 Clinical study outcomes

The primary outcome measure was the change in upper-limb impairment measured by FM-UE from baseline to one-month follow-up after the end of the three-week training, which captured recovery. It is a widely used, reliable, validated measure of motor impairment in stroke patients (Gladstone et al., 2002). Here, we considered the minimal clinically important difference (MCID) to be approximately 10% of the maximum score, or 6.6 points (Gladstone et al., 2002). This is however used as a reference only, as other MCIDs have been used in the literature and can typically vary from 4.25 to 13 points, depending on the stage of the stroke and the level of impairment at baseline (Page et al., 2012; See et al., 2013; Huynh et al., 2023; Hiragami et al., 2019).

Secondary clinical outcome measures included changes from baseline to one-month follow-up in the ARAT, an assessment of upper-limb activity and function, with the MCID for the paretic arm being 12 points (Lang et al., 2008). The changes in ARAT and FM-UE from baseline to the middle and end of the intervention (after 3 weeks) were also investigated. Measures of therapy compliance included the number of sessions completed and the number of trials completed.

The choice of FM-UE and ARAT as clinical outcomes follows recent recommendations, which advocate combining impairment- and activity-level measures in line with the International Classification of Functioning, Disability and Health (ICF) framework (World Health Organization, 2001), to capture both motor recovery and its functional translation (Prange-Lasonder et al., 2021).

7.1.5 Kinematics and physiological outcomes

The change in the passive and active ROM of the patient from baseline to the end of the three-week training was also considered as a metric to characterise improvements in joint mobility and voluntary motor control. It is commonly used in upper-limb rehabilitation research and evidence has shown that active ROM can capture upper-extremity recovery after stroke (Beebe et al., 2009). On the other hand, decreased passive ROM could indicate the presence of increased joint stiffness or contractures (Indrawati et al., 2018).

Additionally, a maximum voluntary contraction (MVC) task was performed at the start, middle and end of the training after the FES calibration, to assess potential changes in wrist flexor and extensor strength. This was recorded at their resting position and patients were asked to flex/extend as hard as they could while focusing on their forearm muscles and avoiding the use of their bicep muscle or shoulder to help. They had three seconds to prepare, where the countdown was displayed on-screen, and had to contract maximally for 5 s followed by a 30 s rest. This was repeated twice in each direction. The second trial was used for further analysis as patients typically used compensatory strategies or misunderstood the task in the first trial. The torque generated during the MVC was used as a measure of strength, and can characterise the level of hemiplegia (Kristensen et al., 2017).

In-trial kinematics and physiological metrics were also considered. As previously presented in Chapter 3, Section 3.3.1 and 3.3.2 and used in Chapter 4, kinematic performance was characterised using the normalised RMSE between the patient and target trajectories, the correlation between the frequency spectrum of the target and the patient trajectories and motion smoothness (with SPARC). All metrics were calculated for each trial during the five baseline unassisted trials to investigate changes in the task performance over sessions. Reciprocal activation and cocontraction during unassisted trials were also analysed to investigate changes in effort and motor learning. EMG was recorded at the start, the end and in the middle of the intervention, and muscle activity metrics are therefore presented for these three sessions only.

The controller was also evaluated by exploring patients' performance and adaptation parameters, such as α, characterising the relative contribution of the FES and robot, and the difficulty level of the task over time.

7.1.6 Statistical analysis

To assess changes in clinical scores over the intervention, linear mixed-effects models (LMEs) with restricted maximum likelihood estimation (REML) were fitted using the time points as a fixed effect and a random intercept for each participant to account for repeated measures within individuals. Time points included Baseline, Mid, End and one-month Follow-up. Planned contrasts compared changes from Baseline to End, Baseline to Follow-up, and End to Follow-up. P-values were corrected for multiple comparisons using the Bonferroni-Holm method. A similar model was fitted for the MVC torque metric, assessing strength, although there was no follow-up data collected, so only post-hoc differences between Baseline and End were considered.

Similarly for kinematic metrics, and active and passive ROM, LMEs were fitted with Session number as a fixed effect. For each model, a planned contrast between the first and last available session was used to assess training-related improvements, and a participant-specific intercept was used. This approach allowed us to model within-subject correlations while estimating group-level effects of session number on performance and clinical scores.

All statistical analyses were performed in R (version 2024.4.2) using the `lmerTest` and `emmeans` packages. The significance level was set at $\alpha = 0.05$ for all tests.

In addition, to evaluate the group effect at the primary endpoint, an analysis of covariance (ANCOVA) was conducted on the FM-UE score at the end of the intervention, with the baseline FM-UE score included as a covariate to account for individual differences in initial motor impairment. The model thus assessed whether FM-UE improvements differed significantly between the intervention and control groups after adjusting for baseline values. Based on the observed effect size from this analysis, a power calculation was carried out to estimate the required sample size for future randomised

controlled trials (RCT) using the `pwr.f2.test()` function in R. A significance level of $\alpha = 0.05$ and a statistical power of 0.9 were used.

7.1.7 Subjective outcomes

Open-ended feedback was also collected at the end of the training from participants in the intervention group. Questions to direct the interview included:

- How was your overall experience using the device?
- Did you find the device comfortable to use?
- Did you enjoy using the device?
- Do you think you could or would want to use this system at home if it were available?
- Would you recommend this type of therapy to other stroke patients? Why?
- Is there anything you would change or add about the device and/or intervention?
- Is there anything else you would like to share about your experience?

This feedback was collected during the one-month follow-up session, except for one patient who could not complete the three-week intervention due to a transfer to another care facility but who completed eleven sessions over two weeks and was therefore able to provide feedback on the system. For participants with language barriers, a family member and/or a translation app supported communication with their consent.

The qualitative feedback from patients was analysed using thematic analysis following the guidelines established by Braun and Clarke (2006). Given the exploratory nature of the research questions, an inductive thematic analysis was conducted, allowing themes to emerge from the data rather than being imposed by pre-existing theoretical frameworks.

The answers were written down and were analysed using inductive thematic analysis and allowing themes to emerge from the data rather than being imposed by pre-existing theoretical frameworks (Braun et al., 2006). Notes on potential bias from translation or family interpretation were maintained throughout the analysis.

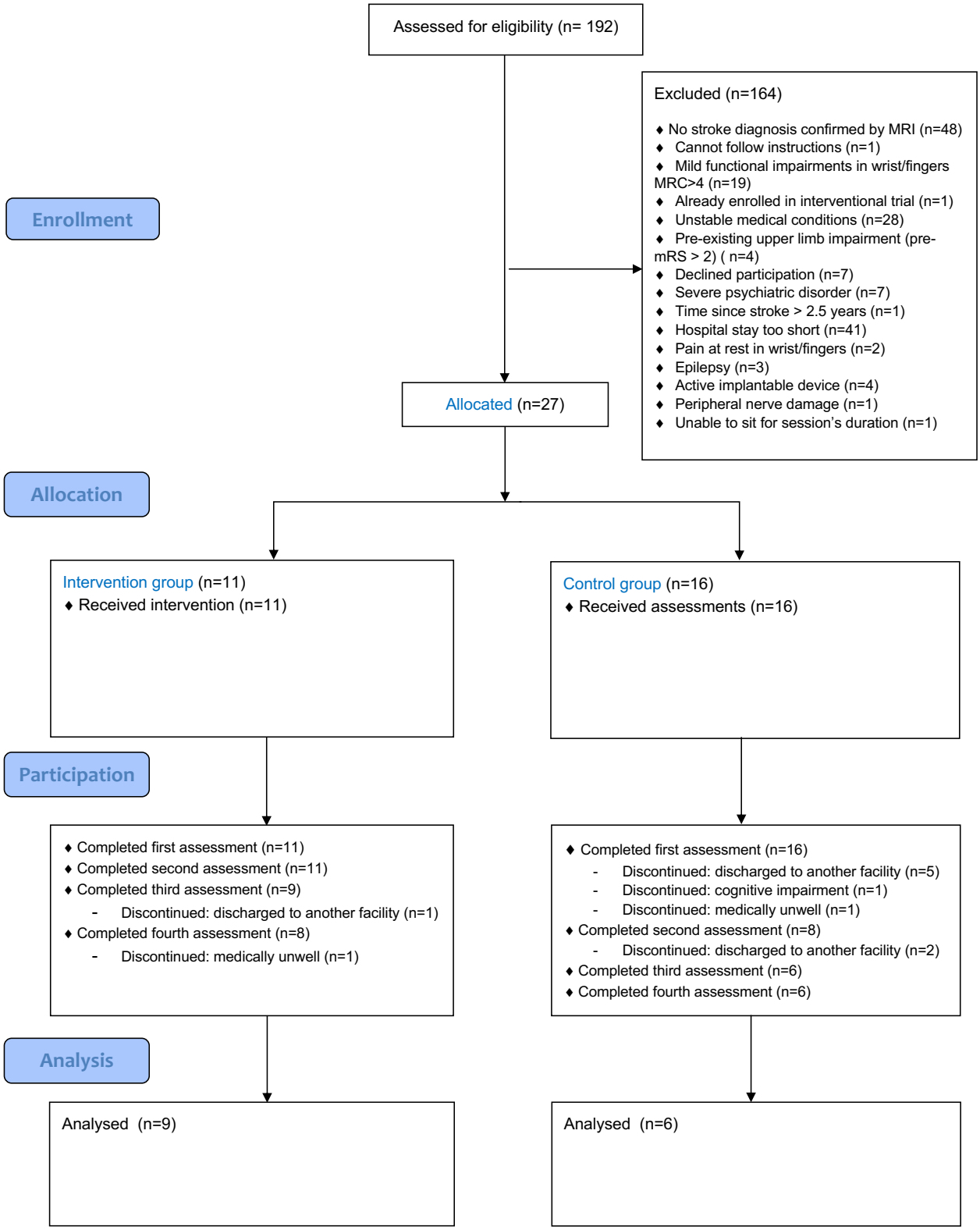


Figure 7.2: Consolidated Standards of Reporting Trials (CONSORT) diagram, showing participant screening, group allocation, participation and data analysis.

Table 7.2: Patient demographics

Group	Sex (M | F)	Age, years, mean (sd)	Side of paresis (R | L)	Time since stroke, weeks, mean (sd)	FM-UE mean (sd)	ARAT mean (sd)
Total	10 | 8	64 (17)	6 | 12	3 (2)	31 (22)	20 (22)
Intervention	6 | 3	57 (18)	3 | 6	3 (1)	33 (21)	21 (21)
Control	4 | 5	71 (9)	3 | 6	3 (1)	28 (26)	20 (25)

FM-UE: Fugl-Meyer Upper Extremity score, maximum possible score: 66.

7.2 Results

7.2.1 Participants

192 patients were screened from February 17 2025 to August 18 2025 (Fig. 7.2). 28 patients were recruited, with 13 patients in the intervention arm and 15 patients in the control arm. In the intervention group, nine patients completed the full intervention, including one who did not complete the last follow-up at 1-month due to the occurrence of a second stroke. In the control group, seven patients completed the third and fourth assessments. Two more patients have been recruited but have not completed their fourth assessments. The demographics for these 18 patients are presented in Table 7.2. In the intervention group, four patients were severely impaired (Fugl-Meyer Upper-Extremity score (FM-UE)$\leq$25), one moderately impaired (25$\leq$FM-UE$\leq$40) and four mildly impaired (FM-UE$>$40) (Woytowicz et al., 2017). In the control arm, four were severely impaired, two moderately impaired and three mildly impaired.

The protocol was such that five sessions per week were planned for the three-week intervention. However, there were several barriers to this schedule, including patient fatigue from their conventional treatment sessions, low mood or increase of pain. Additional medical procedures were also sometimes required, due to investigation of heart function, infection, etc. This led to the reduction of the number of sessions in some patients, where on average 13 sessions were completed per intervention (SD: 2, range across patients: 9-15). The number of trials planned per session was forty, with five unassisted baseline trials, thirty assisted training trials and five unassisted evaluation trials. However, due to fatigue over time, some patients could not complete the total number of trials, especially at the start when getting used to the exercise. On the other hand, after a few sessions, some patients wanted to continue training further after these forty trials and continued assisted training. On average, 39 trials were completed per session (SD: 4, mean range across patients: 32-45).

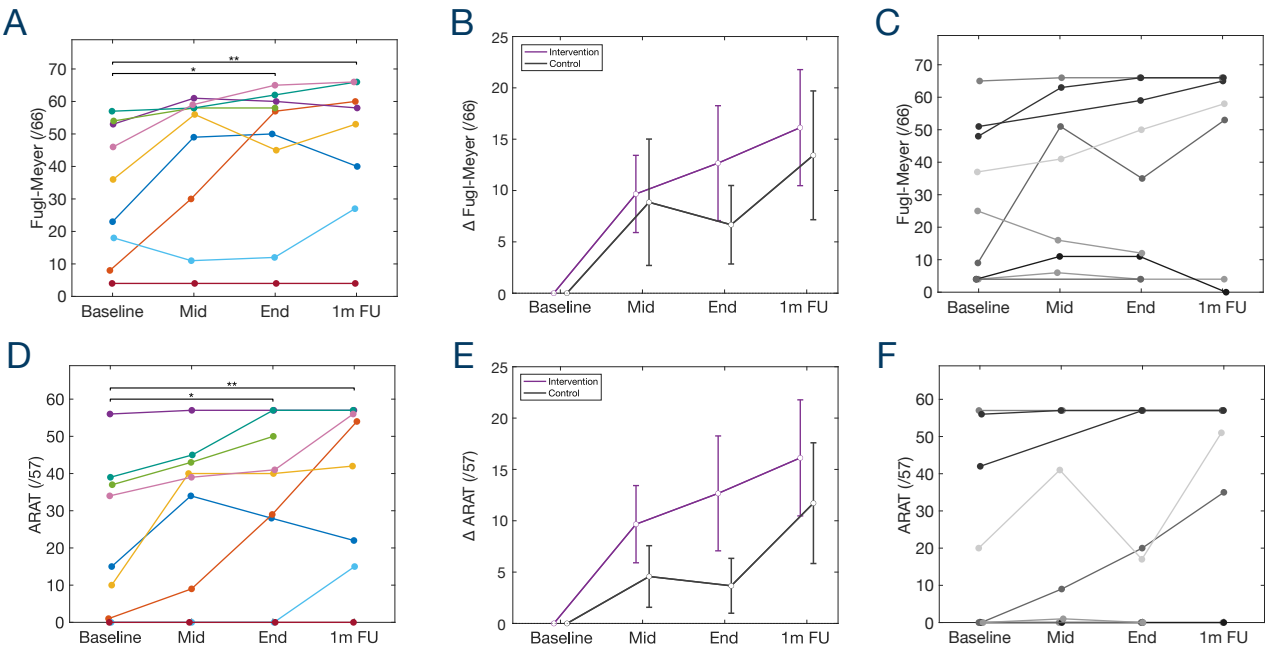


Figure 7.3: Evolution of the FM-UE **(A-C)** and ARAT **(D-F)** over sessions for the intervention group **(A,D)** and the control group **(C,F)**, and the relative score changes **(B,E)**. In figures A,C,D,F, each dot and line represents one patient's score over time. For figures B and E, the dot represents the mean change with respect to baseline and the bar represents the standard error of the mean.

7.2.2 Clinical scores improvements

The FM-UE was used to quantify motor recovery after stroke at four timepoints within the study, i.e. the start, middle and end of the intervention as well as at one-month follow-up. A significant positive effect of the assessment timing on the FM-UE score was observed in the intervention group ($F(3,23.04) = 4.84$, $p = 0.0093$) (Fig. 7.3 A,B). Post-hoc planned contrasts showed that FM-UE scores increased significantly from baseline to the end of the intervention, with a mean improvement of 12.7 points ($p = 0.0129$), higher than the MCID of the FM-UE of 6.6 points and beyond most suggested MCIDs in the literature, previously mentioned. Scores further improved from baseline to one-month follow-up, with a mean increase of 15.4 points ($p = 0.0058$) and the difference between the end of the intervention and the follow-up is not significant (2.73 points, $p = 0.5406$). FM-UE sub-score analyses (shoulder/elbow and wrist/hand) were conducted as well (Additional Figure 7.12). The effect of time on the shoulder/elbow sub-score was not significant ($F(3,23.06) = 2.66$, $p = 0.0072$). For the wrist/hand sub-score, a significant effect of time was observed ($F(3,23.03) = 6.39$, $p = 0.0026$) and planned contrasts showed a significant increase between baseline and the end of the intervention ($p = 0.0027$), and between baseline and one-month follow-up ($p = 0.0023$)(Fig. 7.12 C,D).

Similarly for the ARAT, which evaluates functional impairments in stroke patients, where an increase in the total score was observed ($F(3,23.04) = 6.21$, $p = 0.0030$) (Fig. 7.3 D,E). Planned contrasts indicated that ARAT scores improved significantly between baseline and the end of the intervention, with an average increase of 12.2 points ($p = 0.016$). Improvements were even larger

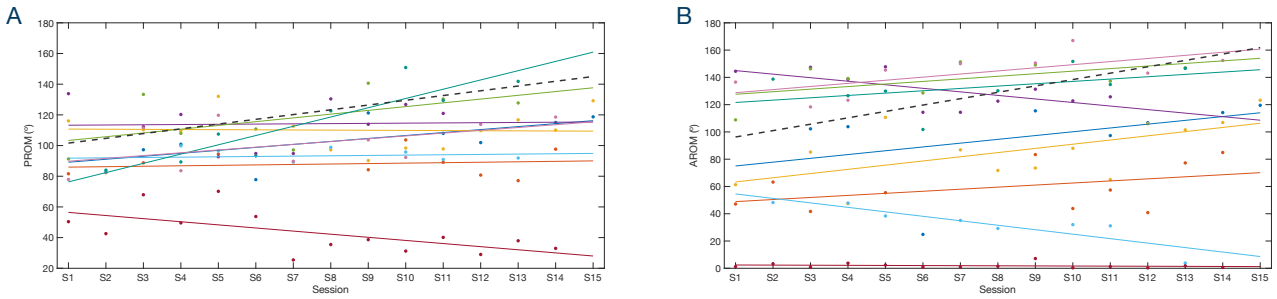


Figure 7.4: Passive range of motion **(A)** and active range of motion **(B)** over sessions. Each patient is represented by a different colour, where the dots indicate the ROM value at each session and the lines show the linear regression for each patient. The black dashed line represents the population-level trend estimated by the linear mixed-effects model.

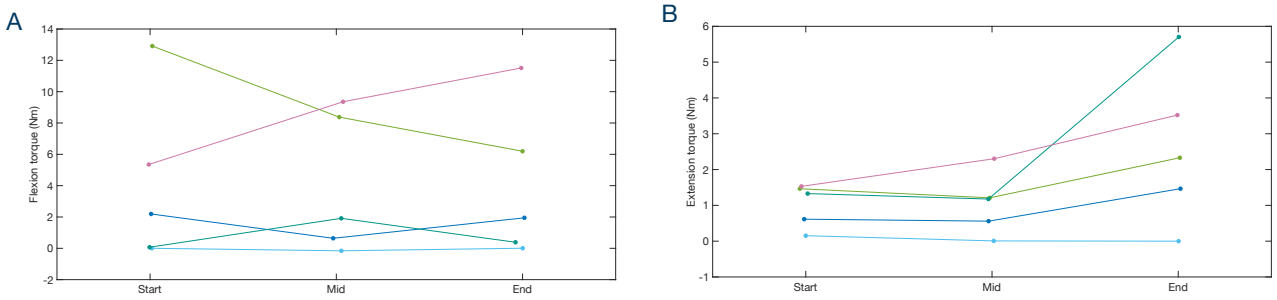


Figure 7.5: Torque generated during the maximal voluntary contraction task in the flexion **(A)** and the extension **(B)** directions, at the start, middle and end of the intervention. Each patient is represented by a different colour, where the dots indicate the torque value for that session.

when comparing baseline to the one-month follow-up, with a mean increase of 18.3 points ($p = 0.0011$), which are both beyond the MCID of 12 points of the ARAT score.

The effect of time on the clinical scores was not tested in the control group as only seven participants had completed the four assessments at this date, although we are completing the follow-up for two patients (Fig. 7.3 C,F). However, similar trends are observed in this patient cohort although the variance across participants seems larger compared to the intervention group, including when observing the change in clinical scores (Fig. 7.3 B,E).

In addition, an ANCOVA was conducted to assess whether post-intervention FM-UE scores differed between groups when controlling for baseline FM-UE values. Baseline FM-UE significantly predicted FM-UE at the end of training ($\beta = 0.910$, $p < 0.0001$), whereas the effect of Group was not statistically significant ($\beta = -3.259$, $p = 0.366$). The partial eta-squared for the Group effect was 0.16, corresponding to a medium effect size ($f = 0.44$). Based on this effect size, a power analysis indicated that a total of 54 participants (27 per group) would be required to achieve 90% power to detect a significant difference in FM-UE at the end of the intervention while controlling for baseline impairment.

7.2.3 Increase in range of motion and strength

The passive and active ROM of the patient's wrist in the flexion/extension directions was recorded at the start of every session, once the setup of the system was complete (Fig. 7.4). PROM increased over time for patients in the intervention group although the statistical change was slightly above the 5% threshold ($F(1,78.417) = 3.8194$, $p = 0.052$) (Fig. 7.4 A). The session number had a significant positive effect on the AROM of the patients ($F(1,78.085) = 6.8132$, $p = 0.01084$) and a significant difference between the first and last sessions was also observed with an average increase of 17.4 degrees ($p = 0.0108$) (Fig. 7.4 B). The patient whose PROM decreased over time likewise showed no improvement in active movement and remained with a dense weakness (dark red line in Fig. 7.4).

Motor strength in the wrist flexor and extensor muscles was also recorded at the start, middle and end of the intervention, although this was only measured in five patients due to technical issues with the EMG recording device and hence the MVC not being performed when these issues occurred. Most patients displayed an increase in their wrist extensor maximal torque over sessions, which suggests a gain of strength (Fig. 7.5 B). Results for the contraction of the flexor muscles are more mixed, although torque levels are generally higher in the flexion direction (Fig. 7.5 A).

7.2.4 Task performance improvements

The change in performance in the unassisted baseline trials of the target-tracking task was also evaluated, where a significant decrease in the normalised RMSE between the patient and target trajectories was observed ($F(1,106.1) = 4.7868$, $p = 0.03087$) (Fig. 7.6 A). Post-hoc tests also revealed a significant difference between the first and last sessions ($p=0.0309$). Conversely, the spectral correlation decreased over time, indicating that patients could not follow the target's pattern as well at the end of the training, although the effect of the session number was not significant ($F(1,106.23) = 0.0707$, $p = 0.7909$) (Fig. 7.6 B). Regarding the motion smoothness, quantified by SPARC, a positive significant effect of time was observed ($F(1,106.11) = 9.6451$, $p = 0.002435$) (Fig. 7.6 C). The difference between the SPARC level at the start and end of the three-week training was also significant ($p=0.0024$), indicating an increase in motion smoothness.

Muscle activity was also investigated when the recording was available and the data suggests a decrease in cocontraction over time, which would indicate motor learning occurring over sessions (Fig. 7.7 A). The reciprocal activation does not seem to change for most patients, except for one patient who has quite limited active range of motion (Fig. 7.7 B).

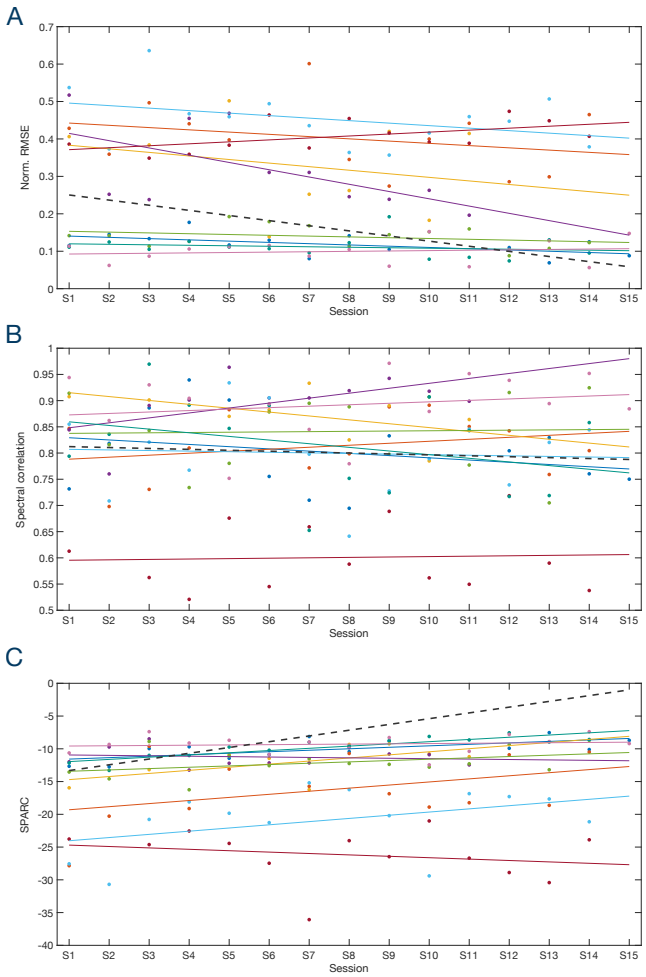


Figure 7.6: Tracking performance across sessions quantified by the normalised RMSE between the patient and target trajectories **(A)**, the spectral correlation between the two trajectories **(B)** and the motion smoothness of the patient **(C)**. Each patient is represented by a different colour, where the dots indicate the performance value at each session and the lines are the linear regression for each patient. The black dashed line represents population-level trend estimated by the linear mixed-effects model.

7.2.5 Patients' subjective feedback

The analysis of patients' answers (see Section 7.6) to the semi-structured interview indicated that satisfaction and acceptance were uniformly high, with all nine interviewed patients reporting a positive overall experience, comfort, and enjoyment. When asking about the potential to use this device at home, eight mentioned they would like to continue using it and one had reservation due to the setup complexity which may not be appropriate for independent home use. Furthermore, all patients answered positively when asked whether they would recommend the therapy to other stroke survivors.

Various themes emerged from the patients' answers through this analysis: (i) therapeutic effect, (ii) user-centred experience, which are both associated with the interaction with the technology; (iii) future use for rehabilitation and (iv) supportive interaction and motivation, which extend beyond the immediate intervention context to encompass broader rehabilitation trajectories and social processes.

(i) Therapeutic effect. Participants consistently reported perceived improvements in their physical abilities and sensation (e.g. "beneficial for sensation and movement, opening and closing of the

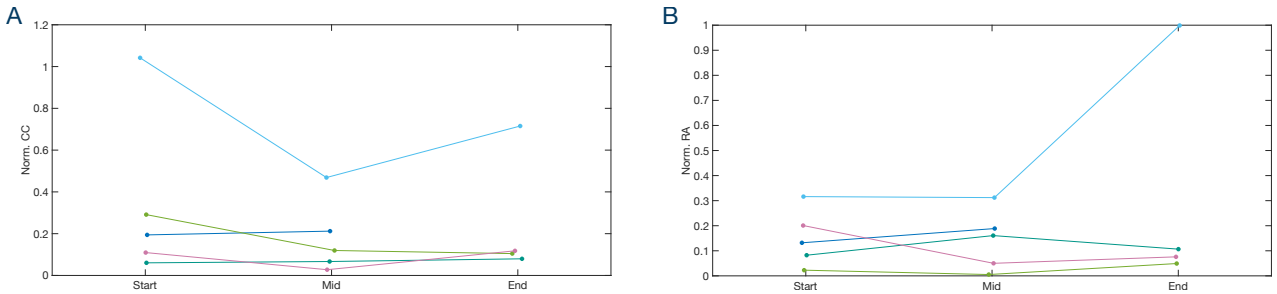


Figure 7.7: Cocontraction **(A)** and reciprocal activation **(B)** during the baseline unassisted trials at the start, middle and end of the intervention. Each patient is represented by a different colour, where the dots indicate the metric value for that session.

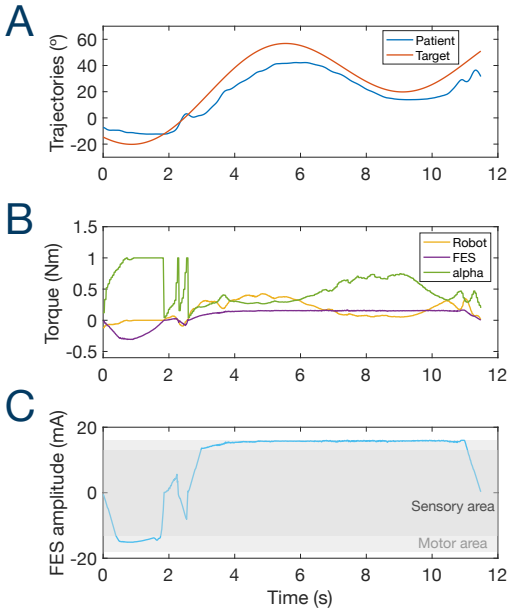


Figure 7.8: Example trial for a representative patient. **(A)** Patient and target trajectories. **(B)** Assistive torque from the robot and FES, with the coefficient α indicating the shared load between actuators. **(C)** FES amplitude applied to the wrist flexor (negative amplitude for visualisation) and the wrist extensor. The comfortable amplitude range is marked by the grey areas, where the maxima and the motor thresholds for each muscle contraction were calibrated during the FES calibration phase of the experiment.

arm"). They also described some motivational effects from the intervention ("game and scoring was motivating", "staff was very motivating"). Several patients spoke about renewed hope and momentum in recovery.

(ii) User-centred experience. Comfort and adaptability were central ("comfortable, no pain"; "once you know the positioning, it is comfortable"). The device added variety and engagement to therapy (the visuals and the interactive tasks broke routine).

(iii) Future use for rehabilitation. Most patients wanted continued access to the system and to this training, ideally at home, with high intended frequency (e.g., "2–3 times/day"). The sole reservation concerned independence of setup (needing two people), highlighting usability requirements for home deployment. All patients mentioned they would definitely recommend the use of the device, and they seemed to want others facing similar challenges to benefit from these resources as well. This suggests that participants were evaluating the intervention's suitability for a broader patient population.

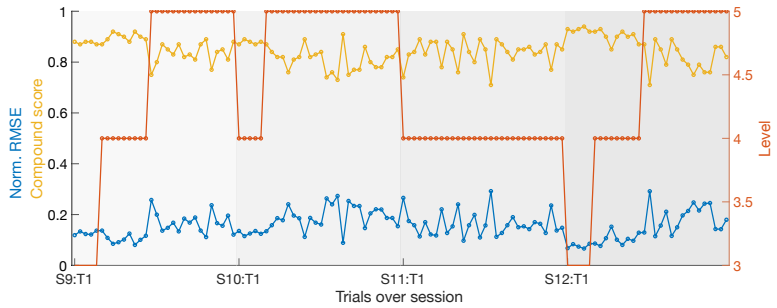


Figure 7.9: Evolution of the tracking performance (normalised RMSE in blue) and the difficulty level (in red) during the assisted training trials (30 trials) across several sessions for a representative patient.

(iv) Supportive interaction and motivation. This theme relates to the crucial role of interpersonal relationships and team dynamics in shaping the therapeutic experience. This theme, while not explicitly queried in the interview, emerged organically from participants' responses, highlighting its fundamental importance to their overall experience. Many patients credited the team's empathy, encouragement, and "company" as integral to the experience ("felt cheered like at a football game"). Participants highlighted personalised calibration and sensitivity to pain/fatigue as key to engagement. Patients also mentioned that the team was "understanding and helpful" and "went out of [their] way to make it easy and possible for me". These accounts suggest that participants experienced the intervention as individually tailored rather than standardised, contributing significantly to their satisfaction and engagement.

7.2.6 Controller evaluation

The trajectories and assistive torque and FES amplitudes for an example trial are displayed in Fig. 7.8. In panel B, the α coefficient, that indicates the relative contribution between the two actuators, varies over time depending on the torque needed and the FES dynamic constraints and its torque saturation level. For instance, around 2 seconds, there is a change of direction in the error signal between the patient and target trajectories, requiring a small but fast corrective torque (Fig. 7.8 A). Here, a drop in the α coefficient value can be observed, in order to increase the load of the robotic assistance in place of FES to correct for this error (Fig. 7.8 B).

After that, α slowly increases again which favours in turn the FES assistance. This controller is indeed designed to prioritise FES wherever possible, following clinical recommendations for stroke rehabilitation. This can be seen by the FES amplitudes, that are in the motor region of stimulation, whenever the dynamics allow it (Fig. 7.8 C). The parameters characterising the FES dynamics, i.e. the delay between stimulation onset and torque output, the bandwidth and the time constant, of the FES-torque response, as well as the torque saturation levels are obtained during the FES calibration phase where the time-response of the torque signal to a stimulation, at a specific amplitude and wrist angle was recorded (Fig. 7.10). A user-specific 3-dimensional map for the flexor and extensor muscles

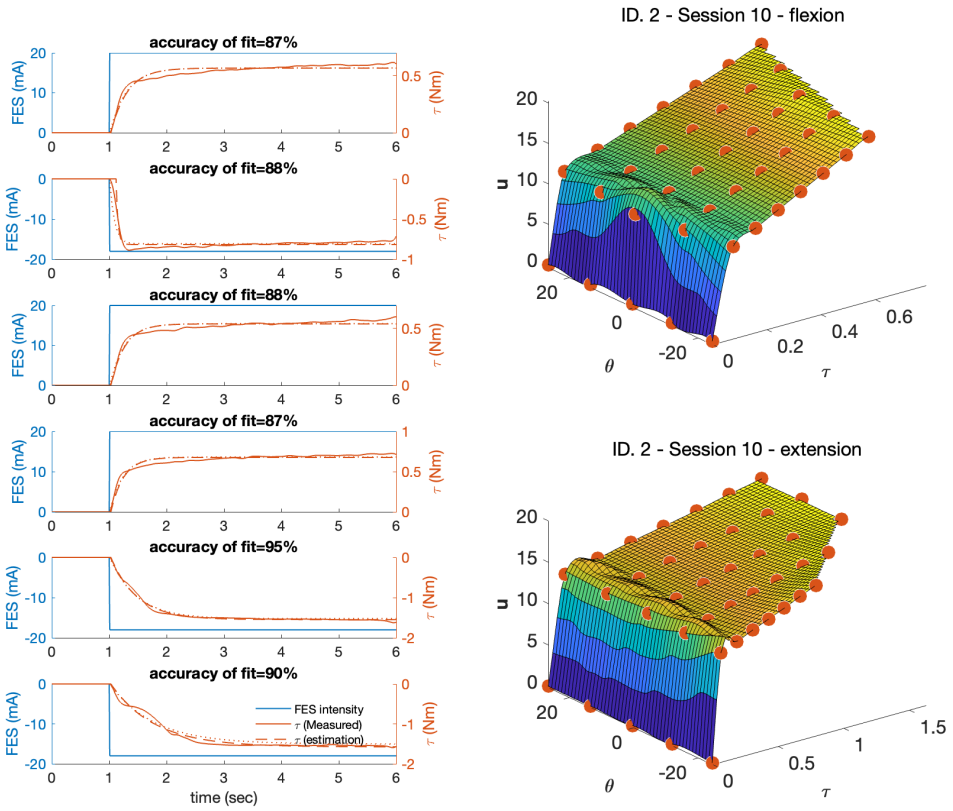


Figure 7.10: FES calibration procedure showing the torque response to FES at specific amplitudes and wrist angles, which is used to model a three-dimensional map applied throughout the tracking task to determine the FES amplitude required.

is then modelled, as can be seen on the right-hand panels and used throughout the tracking task to determine the required FES amplitude based on the desired torque and α coefficient value.

Fig. 7.11 A displays the evolution of the coefficient α over sessions. Interestingly, there is a significant increase in the relative contribution of FES compared to the robotic assistance over time ($F(1,106.18) = 11.827$, $p = 0.00083$), with most patients reaching an α level beyond 0.5 in the last session. This suggests that as patients learn and improve their performance in the task, they require less robotic assistance.

Regarding the difficulty adaptation, Fig. 7.9 shows the evolution of the tracking performance and the difficulty level over assisted trials of three sessions. The difficulty level was dynamically adjusted based on a compound score, displayed on-screen as a reward to the patient, and calculated from the normalised RMSE and the phase lag between the frequency spectra of the patient and target trajectories. Within each session, the level could vary across trials, with the starting level determined by the level reached in the last trial of the previous session, reduced by one. Subsequently, the level was updated every five trials according to the mean compound score over these trials. The change in the difficulty level over sessions for all patients can be seen in Fig. 7.11 B. Although the difficulty level increased for most patients, there is no significant effect of the session number on the difficulty level

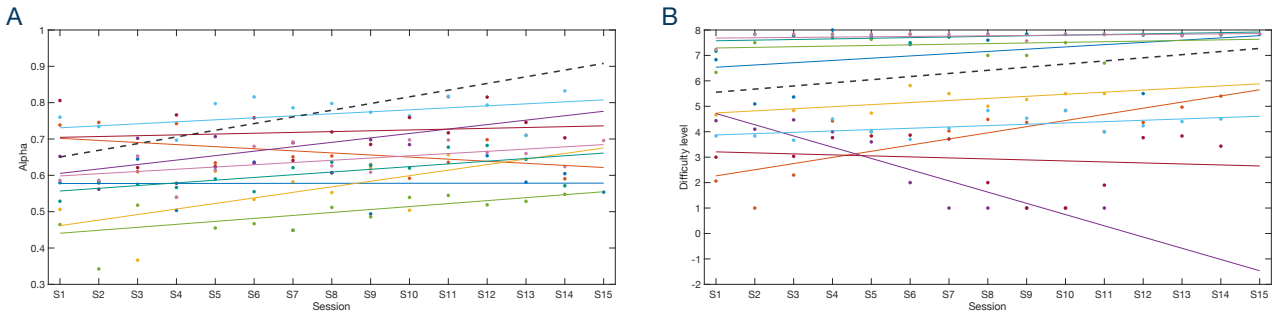


Figure 7.11: Controller parameter changes over sessions. **A.** Changes in α which defines the share between the FES and robotic assistance where higher values indicate greater FES contribution. **B.** Evolution of the difficulty level over time.

($F(1,106.07) = 2.3116$, $p = 0.1314$).

7.3 Discussion

The aim of this study was to evaluate the feasibility and clinical efficacy of a hybrid robot-FES rehabilitation protocol for patients with subacute stroke. Over a three-week intervention, subacute stroke patients trained in an assisted wrist target-tracking task 3-5 times a week, where FES was prioritised whenever its dynamics and torque saturation constraints allowed, and robotic assistance was used otherwise. The level of difficulty of the task was adapted based on each patient's performance over time to maximise their engagement and promote learning. We assessed the impact of the intervention on clinical, kinematic, and physiological outcomes, as well as patient satisfaction and the technical performance of the hybrid controller. The clinical assessments were recorded at the same time points for a control group to evaluate the clinical efficacy of the training.

Patients receiving the hybrid rehabilitation protocol improved their upper-limb function above the minimal clinically important difference. Our results demonstrate significant improvements in upper-limb motor function as measured by the FM-UE, with a mean improvement of 12.4 points (MCID: 6.6) from the start to end of intervention, and ARAT, with a mean improvement of 10.9 points from start to end and 19 points from start to follow-up (MCID: 12). Improvements in functional outcomes such as the ARAT can be expected from this wrist-focused training, as greater wrist extension can contribute to hand opening and object grasping, which are required to complete several tasks in this assessment. Several participants also reported perceivable gains in functional use of the hand after training, consistent with prior evidence that distal training can generalise to proximal performance (Hu et al., 2015; Huang et al., 2020).

These findings align with previous hybrid intervention studies, though hybrid interventions in subacute stroke populations are limited in the literature. Ambrosini and colleagues conducted a 9-week intervention in stroke patients both in the subacute and the chronic phase and found an 18-point

increase in the ARAT score from baseline to the end of intervention and the one-month follow-up, results that are quite similar to our intervention. Among other studies investigating hybrid robot-FES interventions, most have focused on chronic stroke populations and typically reported clinical scores beyond the MCID, with intervention varying from 4 to 7 weeks, with similar changes in score from baseline to the end of the intervention from 12 to 18 points in the ARAT (Hu et al., 2015; Huang et al., 2020; Qian et al., 2017). On the other hand, two subacute intervention of 2 weeks showed improvements in the FM-UE score although this did not exceed the MCID (Grigoras et al., 2016; Miyasaka et al., 2016). This suggests that although our training was short, patients reached similar improvement levels than in longer protocols. This may be due to the higher intensity of our training compared to other protocols which typically schedule three sessions per week.

Moreover, improvements were maintained at one-month follow-up, suggesting retention of motor gains beyond the training period. It can also be observed that the change in FM-UE occurred faster than in the change in ARAT, due to the nature of these assessments. Indeed, the FM-UE mostly assesses individual joint motions, while the tasks in the ARAT are quite functional and typically require the synergistic and coordinated use of the whole upper-extremity.

These positive results also highlight the need to run clinical trials in subacute settings, when there is a heightened plasticity window of spontaneous recovery. Interventions initiated early after stroke could thus enhance the effects of training on sensorimotor recovery compared to those started in the chronic stage (Krakauer, 2020; Zeiler et al., 2013). Even though more challenges are typically encountered when interventions are performed in a ward for subacute stroke patients, due to their cognitive impairments, post-stroke fatigue and overall reduced motivation and engagement (Stinear et al., 2013), there is evidence that starting motor rehabilitation early on can lead to better outcomes, hence such trials may be more beneficial for patients (Horn et al., 2005).

Regarding therapy compliance, the intervention could be integrated within patients' usual schedule, although this was usually difficult due to the lack of patient timetable in the subacute stroke ward. However patients completed on average 13 ± 2 sessions, which is reasonably close to the initial scheduling plan of 15 sessions in three weeks. This is not often reported in other hybrid studies but Ambrosini and colleagues also found similar adherence levels with 26 sessions completed on average with respect to the 27 sessions planned over 9 weeks (Ambrosini et al., 2021). In our study, two patients were discharged earlier and before the end of the intervention which led to them missing a couple of sessions at the end of the intervention. In another case we organised transport for the patient to return to the hospital for the last few sessions, although this could not be arranged every day as the patient needed their carer to come with them and thus reduced the total number of sessions for these patients. However, as it can be seen in the CONSORT diagram (Fig. 7.2), 27 patients were initially recruited, while only 14 patients completed the four assessments (with one patient from the intervention arm who had a second stroke hence could not complete the fourth assessment). This

highlights the challenge of running clinical trials in a subacute stroke ward, as the medical condition of many patients is quite unstable, hence even if a patient can consent and participate in the first few days of an intervention, it does not mean that they will be able to do so throughout the protocol duration. Furthermore, as we are recruiting patients in the early stage post-stroke, some patients may be discharged back home or to another facility within the duration of the trial, even though we checked patients' home addresses before recruiting them to ensure their postcode was within the range of this hospital. We decided to keep the trial duration to 3 weeks following discussions with the therapy team at Charing Cross Hospital as they mentioned patients usually stayed a couple of weeks in the ward and that the team could have some visibility of the discharge planning typically up to 3 weeks.

The clinical scores improvements with this intervention should however be interpreted with care due to the relatively small sample size and the incomplete dataset for the control group, which restricts definitive comparisons. Indeed, since we tested this intervention on subacute stroke patients, it is difficult to separate the effect of our training and the effect of their usual treatment sessions, on top of the spontaneous recovery occurring in the first months after stroke (Byrnes et al., 2001). Moreover, baseline impairment severity remains the best predictor of recovery after stroke (as was also observed in this study), hence the motor and functional gains can be mostly attributed to patients' spontaneous recovery (Van Der Vliet et al., 2020). A control group can thus help to better identify the benefits from the intervention only, however at this point the number of patients in this group being smaller, it is difficult to make a comparison. The control group also received in total less therapy hours (if we consider that patients received on average the same amount of usual therapy), hence it can be expected that the patients in the intervention group would have better clinical outcomes due to the dose-response relationship in subacute stroke patients (Lang et al., 2015), although it is likely that such technology-aided rehabilitation in hospitals would be used in a similar manner as tested here, as a complement to conventional physiotherapy and occupational therapy sessions. The power analysis performed here indicated that to achieve a 90% power to detect a significant difference in FM-UE scores at the end of the intervention (controlling for baseline impairment), 27 patients per group would have to participate in the study.

Furthermore, these results also indicate that the recovery trajectories are quite patient-specific (Fig. 7.3 A), where some patients with low baseline (e.g., dark red) did not improve at all or needed a longer time to start improving (light blue). Furthermore, one patient (dark blue) had a new issue in their shoulder at the one-month follow-up assessment and was waiting for a steroid injection to help with the pain. This meant that they could not lift their shoulder beyond 45° which lowered their FM-UE and ARAT score. Furthermore, long-term retention beyond one month, although initially planned, could not be performed due to the limited time to complete this study. Future studies should involve larger cohorts with balanced control arms and extended follow-up periods to confirm retention of the observed improvements.

Patients' range of motion, wrist extensor strength and task performance increased over sessions. Analysis of secondary outcomes further supports the therapeutic benefit of the intervention. Active wrist range of motion increased significantly over sessions, with most patients also demonstrating gains in maximal wrist extension torque. This is an encouraging finding given the common impairment of extensor activation after stroke. On the other hand maximal flexion torque did not increase, although baseline levels were generally higher compared to the extension torque values. These results are in line with typical strength patterns after stroke with a weaker extensor (Hu et al., 2006). Moreover, it seems that this improvement in wrist extension motion and strength was translated functionally as can be seen by the improvement in the FM-UE and the ARAT scores requiring wrist extension and hand opening tasks in conjunction with other coordinated joint movements. This is consistent with previous findings identifying correlations between the ARAT score and stroke patients' active range of motion and strength in flexion and extension (Burridge et al., 2009).

Improvements were also observed in task performance, where reductions in tracking error and increases in movement smoothness suggested motor learning across session. Additionally, increases in motion smoothness have been found to be linked with motor recovery (Rohrer et al., 2002; Saes et al., 2021), where this seems to occur similarly in these results. These converging findings highlight that the intervention not only improved clinical scores but also targeted specific impairments at the joint, muscle, and movement execution levels. Additionally, there was a decrease in cocontraction throughout the sessions in a few patients, suggesting learning of the task and a more functional use of the agonist-antagonist pair and the ability to selectively activate the flexor or extensor muscle, which has been observed in previous studies targeting wrist rehabilitation (Hu et al., 2010; Song et al., 2013).

Patients were satisfied and motivated by using the system for their upper-limb rehabilitation. The thematic analysis of patient feedback revealed uniformly high satisfaction with the intervention. Patients valued the comfort, engagement, and variety that the device brought to therapy. The consistent reports of improved sensation, movement, and hope suggest meaningful therapeutic benefits beyond traditional rehabilitation approaches. The multi-modal nature of the intervention, combining visual, stimulation, and motor elements, appears to address multiple aspects of stroke recovery simultaneously. The pattern of responses also suggests the device supported fundamental psychological needs that drive adherence in rehabilitation: competence (visible progress and feedback/scoring), autonomy (desire for self-paced home use), and relatedness (supportive therapeutic alliance). Together, these likely contributed to high enjoyment and strong advocacy.

Importantly, nearly all patients expressed interest in continuing training at home, underscoring the acceptability of the intervention and its potential for translation to community-based rehabilitation. The main barrier identified was the need for simplified setup to allow independent setup and use.

However, translation and family-mediated responses may have biased these results, although we

mitigated this via simple, consistent prompts and reflexive note-keeping. Sample size was small and context-specific, so findings are exploratory rather than generalisable. Nonetheless, thematic convergence across diverse participants strengthens confidence in the core conclusions.

A patient-specific hybrid controller, that considers the constraints of the FES, can be successfully implemented with stroke patients. From a technical perspective, this study demonstrates the feasibility of implementing a patient-specific hybrid controller in a clinical context, where the personalisation occurs at various levels: the FES-torque map, the allocation parameters that share the load between the FES and the robotic assistance, and the changes in the difficulty level based on the patient's performance. The controller successfully prioritised FES contribution while dynamically compensating for its inherent physiological constraints (e.g., electromechanical delay, torque saturation). By distributing assistance between robotic and electrical stimulation inputs, the controller maintained task performance while ensuring patient comfort and safety. Typical example trials (Fig. 7.8) confirmed that the system adapted to rapid trajectory changes by transiently shifting assistance towards the robot and reallocating to FES when conditions allowed.

Furthermore, the α coefficient defining the relative contribution of the two actuators increased over time, i.e. there was a larger share of FES within the total assistance in later sessions (Fig. 7.11 A). This indicates that as patients performed better in the task, they may have needed less rapid corrective torques that the FES can typically not provide due to its dynamic constraints. This may also be related to the fact that patients needed less assistance over sessions, as can be seen with the increase in difficulty level (Fig. 7.11 B). These findings provide proof-of-concept that such patient-specific hybrid control strategies can be reliably deployed with stroke survivors, and without needing lengthy calibrations for the parameter identification of the FES-torque response, as is typically required with other personalised hybrid controllers, preventing their use in clinical populations. Indeed, only twelve recordings of the output torque at various combinations of (angle, stimulation amplitude) were required to build the FES-torque map and obtain the controller parameters. This procedure lasted less than 4 minutes, and therefore did not significantly reduce the training phase.

The difficulty adaptation algorithm was also successfully implemented and allowed patients to be engaged throughout the training. Although the difficulty level did not significantly increase over sessions, this is due to the patient displayed in purple as when removing this patient, the effect of the session number on the difficulty level is significant ($F(1,96.024) = 12.291$, $p = 0.0006934$). They were discharged back home in the middle of the intervention and completed the last few sessions from home. We arranged transport for this patient to return to the hospital accompanied by their carer, so they could complete the three weeks. However, we observed a decline in their cognitive level and the journey may have induced some stress which could have affected their performance. It seems that the patient's understanding of the task decreased over time, which could have led to the observed

performance reduction.

7.4 Conclusion

This final experimental chapter evaluated the clinical relevance of the hybrid robot–FES rehabilitation protocol in subacute stroke patients through a three-week intervention study, building on the earlier chapters that demonstrated the safety, feasibility, and short-term physiological effects of hybrid assistance in both unimpaired individuals and stroke patients. Patients in the intervention group achieved clinically meaningful improvements in upper-limb function, as reflected by the gains in FM-UE and ARAT scores that exceeded established MCIDs. Significant improvements were also observed in active range of motion, wrist extensor strength, and task performance metrics such as tracking accuracy and movement smoothness. These findings indicate that hybrid rehabilitation can drive functional recovery and enhance motor control when integrated alongside conventional therapy.

Patients also reported high satisfaction, comfort, and motivation, highlighting the acceptability of the intervention and its potential for sustained engagement. Importantly, the patient-specific shared-control strategy successfully accounted for the physiological constraints of FES and could be implemented reliably in a clinical environment. Together, these results support the feasibility, safety, and therapeutic value of hybrid robot–FES rehabilitation in subacute stroke.

7.5 Additional figures

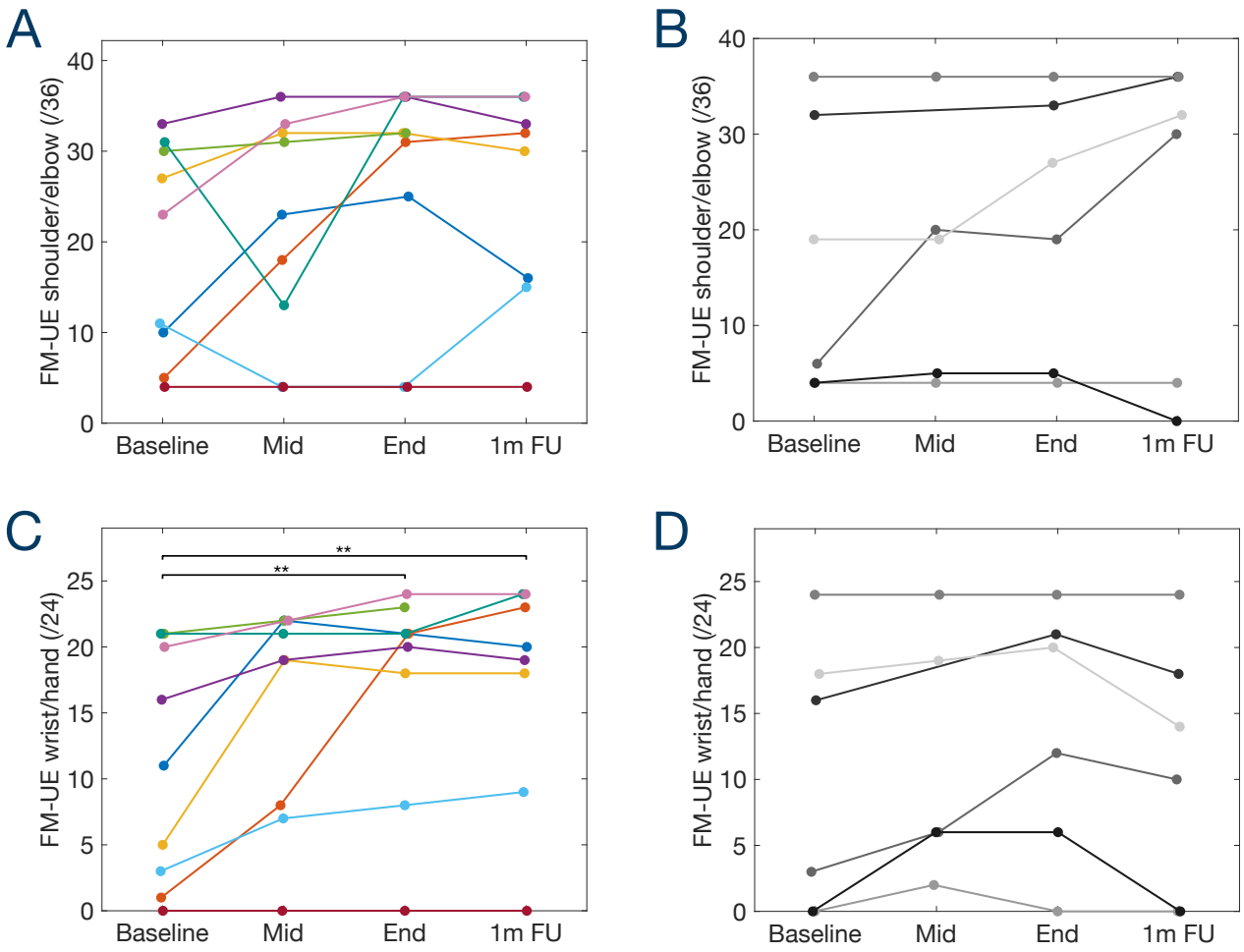


Figure 7.12: Evolution of the FM-UE shoulder/elbow (subsection A) **(A,B)** and FM-UE wrist/hand (subsections B,C) **(C,D)**, for patients in the intervention group **(A,C)** and the control group **(B,D)**. Each dot and line represents one patient's score over time.

7.6 Questionnaire answers

ID	How was your overall experience using the device?	Did you find the device comfortable to use?	Did you enjoy using the device?	Do you think you could or would want to use this system at home if it were available?	Would you recommend this type of therapy to other stroke patients? Why?	Is there anything you would change or add about the device and/or intervention?	Is there anything else you would like to share about your experience?	Notes
ID 1	"My mom had a very positive experience using the device. It was helpful in improving her mobility and gave her hope for further recovery".	"Yes, she found the device comfortable and easy to adapt to. The setup was supportive, and she felt secure during the sessions".	"She enjoyed using the device very much. It added variety to her therapy and made the sessions more engaging".	"Absolutely. Having access to this system at home would be incredibly valuable for continuing her rehabilitation more frequently and at her own pace".	"Yes, definitely. This therapy offers targeted and effective rehabilitation that can significantly support stroke recovery, especially for those who need structured, repeatable exercises".	"At this stage, we don't have any major suggestions. The intervention was well organised. If anything, longer access to the device would be beneficial".	"We are grateful for the opportunity to participate in this program. It gave my mom motivation and noticeable progress. Thank you for all your efforts and support".	Feedback provided by daughter due to language barrier, patient consented, daughter acted as translator
ID 2	"It was a nice experience. I enjoyed the images, hand movement, the fish, the electrical stimulation and robot were nice".	"It makes the hand very sensitive/increase sensation of the hand. It would feel more sensitive for a couple of days, in an ok way, not uncomfortable".	"I am fairly happy with it".	"Yes".	"Could be useful for patients, to get sensation back".	"No".	"Would be good to have/would like to try a version for the leg".	
ID 3	"I think it helped, I enjoyed the company of doing it. The team was understanding and helpful".	"Glad to do it, whole experience was good, would tell someone else to do it".	"Would use it again".	"Would like to use it at home, if made to use at home and if it would be helpful for me, then I would use it alone at home".	"I would tell other patients to do it".	Nothing reported.	"You (refers to the research team) went out of your way to make it easy and possible for me".	

ID	How was your overall experience using the device?	Did you find the device comfortable to use?	Did you enjoy using the device?	Do you think you could or would want to use this system at home if it were available?	Would you recommend this type of therapy to other stroke patients? Why?	Is there anything you would change or add about the device and/or intervention?	Is there anything else you would like to share about your experience?	Notes
ID 8	"Very good experience, I found it useful to train".	"Comfortable, no pain".	"Very good experience, I found useful to train. It is something different to do".	"Yes, would use at home".	"Very good, useful and easy, would recommend it".	"Would not change anything".	Daughter was present during session and reported that they "think the patient has been very well looked after, and that the experience was rewarding, keep the good work!"	Daughter present during session
ID 11	"Liked it, improved movement".	"Yes".	"Yes, stimulation was very good, comfortable".	"Would like to continue, to keep going, also at home".	"Yes".	"No".	"No".	

ID	How was your overall experience using the device?	Did you find the device comfortable to use?	Did you enjoy using the device?	Do you think you could or would want to use this system at home if it were available?	Would you recommend this type of therapy to other stroke patients? Why?	Is there anything you would change or add about the device and/or intervention?	Is there anything else you would like to share about your experience?	Notes
ID 13	"Was excellent and helpful, anyone with stroke and weakness should do it. Movement is necessary to heal either with robot or on own, incredibly helpful. I strongly recommend it as a requirement, not an option. The team made it good, enjoyed the chats about the good looking Hollywood actors".	"The first time was uncomfortable as unfamiliar how to position body. Once you know, it is comfortable".	"Yes".	"Definitely would do it 2 to 3 times per day, must be helpful in wrist and finger and thinking about the movement part and recommended healing process".	"I strongly recommend it as a requirement, not an option".	"As much feedback as possible, analysis of data at session 1 and session 12, it would provide motivation to see the progress/change, being able to see how you've been doing".	"The team is incredible on how to make it work, they're open and sensitive to people's feelings and pain. They made it easy".	

ID	How was your overall experience using the device?	Did you find the device comfortable to use?	Did you enjoy using the device?	Do you think you could or would want to use this system at home if it were available?	Would you recommend this type of therapy to other stroke patients? Why?	Is there anything you would change or add about the device and/or intervention?	Is there anything else you would like to share about your experience?	Notes
ID 16	"Very positive, being able to use it".	"Yes, because we did not increase the mA too high".	"Yes, because it changed my routine instead of staying in the same room. Rather glad to be in a different floor to have a longer journey".	"Yes, certainly I would like to try to use it".	"Yes, I would recommend it because it all seems to work, all techniques together (refers to treatment received at hospital)".	"No, potentially looking at show in the screen better how to move in certain direction and how strong to move, represent that a bit more in the software, maybe would be good to have a picture or extra camera to show the actual wrist itself. The dots in the screen representing that don't seem to be enough to correlate the hand and the dots in the screen".	"I would like to know if you would keep in touch in some way, at the end of the project and how you will present the results and all, in the graph you've got a dotted line, and you may want to make that clear in the documentation, so it is clear in the final result. Please keep in touch with me whenever you want to".	Did not finish intervention, lost to follow up due to being transferred to another healthcare facility. Patient provided comments about the general care received in NHS and healthcare facility, that have been removed from the general data collection due to confidentiality and not related to the questions asked.

ID	How was your overall experience using the device?	Did you find the device comfortable to use?	Did you enjoy using the device?	Do you think you could or would want to use this system at home if it were available?	Would you recommend this type of therapy to other stroke patients? Why?	Is there anything you would change or add about the device and/or intervention?	Is there anything else you would like to share about your experience?	Notes
ID 20	"It was fine, good".	"Yes it was comfortable".	"Yes".	"Probably no with current setting, as it would need 2 people to help setting it up, so would need to be easier to use to use at home by myself".	"Yes, to have something to do, some activity to do at the hospital".	"No, it was ok".	"It was all good".	
ID 21	"Interesting, feeling of stimulation was good, I found it beneficial for sensation and movement, opening and closing of the arm".	"Yes".	"Game and scoring was motivating, staff (refers to research team) was very motivating, each session felt like I was cheered up like in a football game".	"Yes, could be useful to use the device at home".	"Yes".	"No".	"Thank you for this opportunity, I enjoyed each session".	

Chapter 8

Discussion

8.1 Summary of results

This thesis investigated hybrid robot-FES assistance and rehabilitation in subacute post-stroke patients. Hybrid systems that combine robotic and FES assistance can in principle, overcome the limitations of each modality by delivering smooth, comfortable support while eliciting muscle contraction and providing sensory feedback. While clinical trials in stroke patients have shown promising results, most hybrid systems do not use both actuators to the same joint and often rely on simple triggering mechanisms, potentially limiting patient engagement (Resquin et al., 2016; Höhler et al., 2024). This also constrains our understanding of how each modality and their combination affects motor behaviour, physiological adaptations, and user experience.

Therefore, in my thesis I examined the design, control, and clinical evaluation of a hybrid robot-FES system for upper-limb rehabilitation, and whether such a system could be used safely and effectively to support motor recovery after stroke. The thesis's primary contribution was the development of experimental work in unimpaired and post-stroke individuals, which expands our knowledge on how the use of robot and FES to assist motion impacts recovery, performance, effort, fatigue, and engagement. To do so, a simple, portable one-DOF system was developed that allows both FES and robotic assistance to act on the same joint with minimal setup, while facilitating its integration in subacute clinical settings and enabling clearer interpretation of hybrid assistance effects.

This involved four main studies that addressed the following research questions: how does robotic and/or FES assistance affect unimpaired individuals' behavioural and physiological features? (QA); can a hybrid robot-FES system be used to aid the rehabilitation and assessment of sensorimotor functions in stroke individuals? (QB); should muscle fatigue be considered when using a hybrid robot-FES system for stroke rehabilitation? (QC); how does hybrid robot-FES rehabilitation affect functional and physiological recovery after stroke? (QD). To address these questions, this thesis comprised a series of experimental studies, starting with unimpaired participants and progressing to

clinical applications in subacute stroke patients. Each chapter built on the findings of the previous one, evaluating safety, usability, short- and long-term effects.

Chapter 3 presented the tools and metrics used throughout the thesis. It described the one-DOF hybrid robot-FES system designed for wrist flexion/extension training, as well as the associated sensors, performance and physiological metrics. These elements formed the methodological foundation for the subsequent experiments. The one-DOF system is compact and light and can be easily moved and mounted on a table. This allowed us to conduct experiments in subacute stroke wards where space is limited. Experiments could be performed in the shared therapy room of the ward or in patients' rooms. Furthermore, the target-tracking task used in this study allowed to assess and train participants' sensorimotor control and observe the effect of robotic and FES assistance on performance and physiological responses over time, with the integration of kinematic, torque and EMG sensors in the device. Such a task is useful as it also trains continuous control, hand-eye coordination, while providing a high number of repetitions and enhanced feedback with the robot and FES, which are beneficial in rehabilitation post-stroke to drive neuroplastic changes (Nudo, 2006; Murphy et al., 2009).

Chapter 4 reported a proof-of-concept study in unimpaired participants evaluating how robotic, FES, and hybrid assistance affected wrist tracking performance, muscular effort, fatigue, and user experience. Results showed that robotic and hybrid assistance significantly improved tracking accuracy and reduced temporal delay. FES and hybrid assistance elicited greater muscle activation than robotic-only support, suggesting increased engagement. Additionally, none of the modalities induced significant fatigue over time, and hybrid assistance was rated as both effective and comfortable by participants. These findings established the technical feasibility of the system and informed its adaptation for clinical use.

Chapter 5 investigated the feasibility of using the hybrid system in subacute stroke patients during a short-term study conducted at Schön Klinik, Bad Aibling in Germany. Patients were divided into three groups, receiving robot, FES or hybrid assistance during the wrist target-tracking task, and trained over three sessions. All assistance modalities improved task performance, and FES and hybrid assistance promoted muscle activation. Patient feedback confirmed the system's usability and comfort. However, due to the short training duration and fixed difficulty, no consistent training-related improvements were observed. These results justified the need for a longer, more personalised intervention to assess therapeutic benefits. Furthermore, using the extracted kinematic and EMG metrics to estimate patients' FM-UE scores resulted in high errors, indicating that the device's potential for assessing impairment severity is limited.

Chapter 6 addressed the potential concern of muscle fatigue that can arise when FES is applied, due to the unnatural recruitment pattern it uses. A dedicated fatigue study was conducted in unimpaired participants, where behavioural, EMG, and subjective fatigue markers were analysed during the dynamic task. Similar analyses were applied to stroke patients using data from Chapter 5. Across

both populations, no substantial fatigue effects were found, supporting the use of hybrid assistance in repeated rehabilitation sessions without compromising safety or comfort. Furthermore, these findings suggest that it may not be necessary to consider fatigue as a major factor when developing adaptive hybrid control algorithms.

Chapter 7 presented the final experimental study, a three-week intervention conducted in an NHS hospital in subacute stroke patients. Stroke patients in the intervention group trained daily using the hybrid system, assisted by a dynamic allocation controller that optimally distributed actuation between the robot and FES, based on their individual constraints. Training intensity and task difficulty were adapted to individual capabilities. Patients in the control arm of the study received their usual treatment care and did not take part in additional sessions. Clinical assessments for patients in both groups were collected at the same time points. Patients training with the hybrid system showed significant and clinically meaningful improvements in motor impairment and function, as measured by FM-UE and ARAT scores. Gains in active range of motion, wrist extensor strength, tracking performance, and motion smoothness were also observed, alongside high satisfaction and engagement. Comparison with the control group was not feasible due to the small number of participants recruited in this group at this date. These findings provide evidence for the clinical relevance of hybrid robot-FES rehabilitation, and the feasibility to implement a patient-specific control strategy, successfully accounting for the limitations of FES.

8.2 Limitations and future directions

While the work presented in this thesis demonstrates promising clinical results in the implementation and use of patient-specific hybrid rehabilitation in subacute stroke patients, several limitations remain and present opportunities for further exploration.

A key limitation of this thesis is the relatively small sample size in both clinical studies. In the feasibility study conducted at Schön Klinik (Chapter 5), approximately ten stroke patients per group completed the assisted training. Similarly, in the study at Charing Cross Hospital (Chapter 7), nine patients completed the intervention, while only six patients have been enrolled in the control group (with three more ongoing). This limited the statistical power to detect between-group differences and prevented a more robust comparison of rehabilitation outcomes. Related to this is the heterogeneity of the participants in the recruited sample, which posed additional challenges for interpreting recovery trends. In the Schön Klinik study, most participants were severely impaired, although a few presented with moderate to mild deficits. The Charing Cross study featured a more balanced distribution, with roughly half of the participants falling into each category. This variability highlights the usability and safety of the system across a wide range of impairment levels, but it also introduces between-patient differences in recovery potential, which complicates the interpretation of group-level effects

and recovery trajectories. Future work should therefore aim for a larger sample size to confirm the therapeutic benefits of personalised hybrid rehabilitation. This would also support the generalisability of the findings and allow for more granular subgroup analyses. This could also help identify which subgroups benefit most from hybrid training.

The duration of the rehabilitation intervention was also shorter than initially planned. While the study at Charing Cross Hospital was originally designed as an eight-week intervention, discussions with the care team on-site highlighted the logistical constraints related to such duration. Indeed, due to the short duration of hospital stays in the subacute ward and the challenges associated with having patients return to the hospital after discharge, we decided to shorten the intervention period to three weeks. While improvements were still observed, a longer training period would provide more insight into the effects of hybrid therapy on recovery and allow observation of plateauing or delayed gains, especially in more severely impaired patients, some of which only started to show improvements within the follow-up period. Future studies could consider conducting the intervention in dedicated neurorehabilitation wards, where longer stays (typically 12 weeks) are common. However, this strategy may also introduce selection bias, as only patients with higher predicted recovery potential are typically admitted to such wards. Furthermore, these wards are not often stroke-specific, hence it would probably take a much longer time to recruit the same amount of participants due to the limited number of beds.

Device-related constraints also influenced the study design and participant selection. The use of our system required patients to be able to sit upright. This required the exclusion of patients with poor trunk control and that could not transfer into a chair, which is common in early post-stroke individuals. This limited the inclusion of patients in the earliest stages of recovery, where interventions may be particularly beneficial for promoting neuroplasticity. In addition, the current setup required participants to be positioned upright with the arm placed inside the device, without the shoulder being elevated or hyperextended. This made bedside use infeasible and reduced the accessibility of the device to many patients in the subacute stroke ward. Future versions of the system could explore alternative mechanical configurations or more portable designs to enable training earlier in the recovery process and directly at the bedside. However, such a setup could limit the focus and engagement of the patient as they would remain in bed.

Another limitation is the restriction of the types of movements trained by the device, i.e. only single DOF wrist flexion and extension motions could be performed. This was beneficial for isolating motor control at a specific joint, limiting confounding effects from proximal compensations, enabling us to evaluate the effect of FES and robot assistance in a more controlled environment. Moreover, wrist extension is a functionally relevant motion, commonly impaired after stroke, and training this motion could also help with hand opening. However, the wrist rarely moves in isolation during ADLs, and focusing solely on this joint may limit the transfer of improvements to functional tasks. Despite this, evidence suggests that single-joint training can be as effective as multi-joint approaches in promoting

upper-limb recovery after stroke (Milot et al., 2013; Fluet et al., 2014), and using a simple, portable system that is easy to setup and operate offers practical advantages for use in clinical settings, where session times and space are limited. The HRX-1 robot used in this work was configured for wrist flexion/extension but can be adapted to other single-joint movements, such as elbow flexion/extension and forearm pronation/supination. Future work could adapt the control algorithms and protocol to other joint configurations, and consider extending it to support multi-joint tasks. For example, it could be adapted to train wrist flexion/extension paired with hand closing/opening, where the handle could be replaced with a compliant and instrumented graspable interface (Nehrujee et al., 2021).

Finally, the training paradigm itself presents some limitations in terms of task variety and individualisation. Only one task, the continuous wrist tracking, was used throughout the training. While the task featured difficulty adaptation to maintain engagement and challenge, it may have been too complex initially for some severely impaired patients, who would have benefited from simpler tasks such as point-to-point movements, without time-constraints, before attempting continuous tracking. Conversely, mildly impaired participants reached the highest difficulty level quite early in the intervention. Further progression in difficulty, including resistance to motion by adding damping to the robot, could have helped increase patients' strength. Future iterations could include a progression of task types, and expanded difficulty levels, such as adding resistance or providing tailored training for wrist flexors and extensors, when patients have asymmetric motor impairments. The adaptation of the difficulty level, currently performed with a rule-based algorithm and with fixed discrete levels, could be improved by using an adaptive algorithm with continuous adjustment of the task. To do so, patients' performance metrics could be continuously monitored to update the task parameters in real time, ensuring that the level of challenge remains appropriate. Such adaptive control could automatically decrease task complexity for lower-functioning patients, by transitioning to simpler, point-to-point movements, particularly in wrist extension, and progressively reduce assistance before introducing resistance for higher-functioning patients to promote strength gains.

The insights gained here can be leveraged to design a randomised controlled trial (RCT), with the same two groups as tested in the feasibility study of Chapter 7. Based on a power calculation assuming 90% power and $\alpha = 0.05$, and estimating the effect observed in the feasibility study, it would require approximately 27 participants per group to detect a meaningful group effect on FM-UE at end of intervention, controlling for patients' baseline FM-UE. Accounting for 10-20% drop-out, this would lead to a total sample size of 60-68 patients for this RCT. In terms of inclusion criteria, the RCT should stratify or restrict eligibility to stroke patients who are most likely to benefit, excluding both severely impaired (not likely to improve over time) and very mildly impaired (whose gains may plateau), and focusing on those in the moderate recovery cluster, who are predicted to have some capacity for improvement Van Der Vliet et al., 2020. With regard to intensity and dose, the RCT should commit to a high-frequency schedule similar to the one used in the feasibility study, such as

5 sessions per week over 4-5 weeks, each session lasting 45 min, to test the additive effect of hybrid robot-FES training. This additional therapy time would exceed the 1000 minutes recommendation, which can yield meaningful improvements in ADLs and upper-limb functions (Kwakkel et al., 2004; Clark et al., 2021). Outcome assessments should be aligned with the International Classification of Functioning, Disability and Health (ICF) framework (World Health Organization, 2001), where impairment level (body function) could be captured by the FM-UE (Duncan et al., 1983), the activity level by the ARAT (Lyle, 1981), and the participation level through patient-reported measures such as the Arm Activity Measure (Ashford et al., 2013) or the Motor Activity Log (Hammer et al., 2010). To capture immediate and sustained effects, these assessments could be recorded at baseline, mid-intervention, end-of-intervention, and 1-month and 3-month follow-up. In addition, continuous kinematic and EMG data during training sessions could be used to explore changes in motor control and strength, and explore which features correlate with long-term functional gains.

8.3 Application and considerations

Conducting clinical trials in the subacute phase of stroke recovery offers valuable opportunities, but is also associated with various logistical and clinical challenges. One of the most striking difficulties I encountered while conducting the experimental work of this thesis (especially of Chapter 7) was the complexity of recruiting and retaining participants in a hospital environment. Although many patients were initially screened, only a fraction met the eligibility criteria, often due to pre-existing comorbidities, prior upper-limb impairments, cognitive deficits, or frailty (see CONSORT diagrams of both clinical studies in Chapter 5 and Chapter 7). In particular, running studies in the subacute ward in Charing Cross Hospital (Chapter 7) highlighted the following recruitment challenges: patients were frequently unstable, highly fatigued, or undergoing numerous conventional therapy sessions that had to take precedence. This was associated with some level of selection of patients, and potentially led to recruitment bias, where the results in this study would not generalise to the wider stroke population, as the recruitment criteria drastically reduced the number of potential patients (in Chapter 5, 2032 patients were screened and 30 completed the intervention; in Chapter 7, 192 were screened and 15 completed the intervention). This highlights the disparity between the clinical realities of inpatient care and the ideal conditions needed for consistent intervention and data collection. This also suggests that generally, rehabilitation trials in the literature may overestimate the clinical outcomes of specific interventions due to this screening phase, which typically excludes patients with complex clinical diagnoses. Moreover, changes in mood levels and hospital-related anxiety were common and impacted participation and engagement, although most patients completed over three sessions per week in the study at Charing Cross Hospital (Chapter 7). The stroke ward at the hospital also had extremely limited space with only one room where the

intervention could be conducted, which was used for staff meetings and family meetings, group therapy sessions, as well as patients during family visits. This made it challenging for us, as it required fitting the intervention session when the patient was available (although they often did not have any timetable) and when the room was available.

The unpredictability of hospital discharge timelines further complicates rehabilitation research early post-stroke. Although the original protocol was designed for an eight-week intervention, practical constraints at Charing Cross Hospital, primarily related to the early discharge of patients from the subacute ward, led to a reduction to three weeks. Planning future interventions in rehabilitation-specific wards might help extending training duration and facilitate study completion. However, this introduces further selection bias, as such wards typically admit patients with better prognoses, fewer comorbidities, and higher levels of independence, as patients need to be able to sustain the intensive treatment offered in these facilities. This obviously does not reflect the broader stroke population. There is a balance to find between feasibility of running interventions in inpatient centres early after stroke, and generalisability of findings across the whole stroke population.

These difficulties explain why the majority of upper-limb rehabilitation trials are conducted in chronic stroke patients. Indeed, fewer than 12% of all RCTs targeting motor rehabilitation are initiated within 30 days post-stroke, and most of these are pharmacological or involve conventional therapy modifications (Stinear et al., 2013). On the other hand, stroke patients in the chronic stage are clinically stable, more likely to have completed diagnostic and surgical procedures, and have adjusted psychologically to their condition over time. As such, recruitment, retention, and protocol adherence are considerably easier; such studies also typically do not require a control group as patients can usually act as their own baseline since their motor impairments do not evolve any more. However, focusing research solely on the chronic phase misses the critical early window for spontaneous biological recovery, where neuroplasticity is most responsive to rehabilitation. Identifying effective interventions during this period can accelerate recovery, reduce long-term disability, and support integration into standard clinical care pathways (Stinear et al., 2013). Early-phase therapies are also more likely to align with existing hospital workflows and to be covered by public health systems, offering a more accessible alternative to treatments after six months post-stroke, which are often financed by patients or their families. In this context, this work proposes pragmatic strategies to overcome barriers in early-phase intervention studies, and provides evidence towards the feasibility of deploying such technology-assisted rehabilitation intervention.

Despite these challenges, this thesis also highlighted several important benefits of conducting neurorehabilitation research in subacute settings. Patients were generally highly receptive to participating when their physical and mental status allowed it, and many reported a strong sense of motivation and satisfaction when involved in these sessions, that broke up the monotony of hospital routines. Additionally, technologies like FES and robotic assistance provided meaningful visual and proprioceptive feedback, especially for patients with limited voluntary movement. Patients were able to see their muscles contracting, even when initiated externally. This seemed to strengthen motor imagery and reinforce the perception of agency. This link between multisensory feedback and motion can help reinforce neural pathways involved in motor control (Carey et al., 2018). During sessions, patients also mentioned the impact of seeing their hand move on their engagement and motivation, which can also be beneficial for their recovery. Moreover, one of the patients recruited in the intervention arm of the study in Charing Cross Hospital (Chapter 7) presented dense upper-limb weakness and had shoulder pain. It seemed that they had developed anxiety around movements of their affected limbs, and as a result, therapists in the care team did not frequently treat their arm. However, having tried FES for their leg, this patient was very keen to participate in the study. With the initial ROM calibration, the patient felt comfortable training with the system as they were aware and in control of the mobility range covered during the session. This highlights the safety provided by technology-assisted rehabilitation, that provides highly repeatable movements. Throughout the intervention, pain levels were reduced (FM-UE pain score from 12/24 at baseline to 20/24 at the end of the intervention and at one-month follow-up, where 24 indicates no pain during passive motion of the upper-limb). Such effects, though anecdotal, warrant further investigation in future studies using structured psychometric tools.

The studies also had a noticeable impact on clinical practice and staff engagement, demonstrating the reciprocal benefit of research conducted in hospitals. Many therapists expressed interest in the device and its outcomes, where demonstration sessions were organised prior to starting the intervention, and throughout it. Therapists also asked to attend training sessions to better understand how the hybrid system could complement their therapy. The therapy team also started using FES in their own sessions a couple of months after we started the clinical trial in the ward. Beyond the clinical team, families and patients also showed strong curiosity and support, particularly when they could observe signs of progress. Regarding the case of the patient with shoulder pain mentioned above, starting the intervention with them also induced changes within their conventional treatment, where therapists introduced upper-limb sessions and passive mobility training.

Lastly, one of the most important insights I gained through this thesis is the importance of context-awareness in rehabilitation technology development. As an engineer, spending extensive time in clinical environments revealed how complex stroke recovery can be, and how many dimensions can affect a patient's rehabilitation journey. Factors such as family involvement, psychological state, staffing resources, therapy schedules, and ward logistics all had an influence on this study and seemingly on patients' rehabilitation outcomes. For engineers and scientists working on new rehabilitation technologies, immersing themselves in this reality early on in their project could help immensely. Understanding the variety of motor impairments, but also their interaction with cognitive abilities, psychological state, pain and sensory deficits, as well as the environment in which patients evolve and recovery occur, is essential for designing systems that can be useful and truly integrated into a patient's journey.

References

Akizuki, K. and Y. Ohashi (2015). "Measurement of functional task difficulty during motor learning: What level of difficulty corresponds to the optimal challenge point?" In: *Human Movement Science* 43.

Alhaag, M. H., M. Z. Ramadan, I. M. Al-harkan, F. M. Alessa, H. Alkhalefah, M. H. Abidi, and A. E. Sayed (2022). "Determining the fatigue associated with different task complexity during maintenance operations in males using electromyography features". In: *International Journal of Industrial Ergonomics* 88.

Allen, B. C., K. J. Stubbs, and W. E. Dixon (2020). "Characterization of the Time-Varying Nature of Electromechanical Delay During FES-Cycling". In: *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 28.10.

Allen, I. E. and C. A. Seaman (2007). "Likert Scales and Data Analyses". In: *Quality progress* 40.7.

Alon, G., A. F. Levitt, and P. A. McCarthy (2008). "Functional Electrical Stimulation (FES) May Modify the Poor Prognosis of Stroke Survivors with Severe Motor Loss of the Upper Extremity: A Preliminary Study". In: *American Journal of Physical Medicine & Rehabilitation* 87.8.

Alon, G., K. S. Sunnerhagen, A. C. Geurts, and A. Ohry (2003). "A home-based, self-administered stimulation program to improve selected hand functions of chronic stroke". In: *NeuroRehabilitation* 18.3.

Ambrosini, E. et al. (2017). "The combined action of a passive exoskeleton and an EMG-controlled neuroprosthesis for upper limb stroke rehabilitation: First results of the RETRAINER project". In: *International Conference on Rehabilitation Robotics*.

Ambrosini, E., S. Ferrante, T. Schauer, C. Klauer, M. Gaffuri, G. Ferrigno, and A. Pedrocchi (2014). "A myocontrolled neuroprosthesis integrated with a passive exoskeleton to support upper limb activities". In: *Journal of Electromyography and Kinesiology* 24.2.

Ambrosini, E. et al. (2021). "A Robotic System with EMG-Triggered Functional Eletrical Stimulation for Restoring Arm Functions in Stroke Survivors". In: *Neurorehabilitation and Neural Repair* 35.4.

Ao, D., R. Song, and K.-y. Tong (2015). "Sensorimotor Control of Tracking Movements at Various Speeds for Stroke Patients as Well as Age-Matched and Young Healthy Subjects". In: *PLOS ONE* 10.6. Ed. by G. Cymbalyuk.

Arendt-Nielsen, L., K. R. Mills, and A. Forster (1989). "Changes in muscle fiber conduction velocity, mean power frequency, and mean EMG voltage during prolonged submaximal contractions". In: *Muscle & Nerve* 12.6.

Ashford, S., M. Slade, and L. Turner-Stokes (2013). "Conceptualisation and development of the arm activity measure (ArmA) for assessment of activity in the hemiparetic arm". In: *Disability and Rehabilitation* 35.18.

Badier, M., C. Guillot, C. Danger, F. Tagliarini, and Y. Jammes (1999). "M-wave changes after high- and low-frequency electrically induced fatigue in different muscles". In: *Muscle & Nerve* 22.4.

Balasubramanian, S., A. Melendez-Calderon, and E. Burdet (2012). "A Robust and Sensitive Metric for Quantifying Movement Smoothness". In: *IEEE Transactions on Biomedical Engineering* 59.8.

Balasubramanian, S. (2015). *Motor impairments following stroke.*

Balasubramanian, S., A. Melendez-Calderon, A. Roby-Brami, and E. Burdet (2015). "On the analysis of movement smoothness". In: *Journal of NeuroEngineering and Rehabilitation* 12.1.

Ballester, B. R., N. S. Ward, F. Brander, M. Maier, K. Kelly, and P. F. M. J. Verschure (2022). "Relationship between intensity and recovery in post-stroke rehabilitation: a retrospective analysis". In: *Journal of Neurology, Neurosurgery & Psychiatry* 93.2.

Bard, G. and G. G. Hirschberg (1965). "Recovery of voluntary motion in upper extremity following hemiplegia". In: *Archives of Physical Medicine and Rehabilitation* 46.

Bardi, E., S. Dalla Gasperina, A. Pedrocchi, and E. Ambrosini (2021). "Adaptive Cooperative Control for Hybrid FES-Robotic Upper Limb Devices: a Simulation Study". In: *Annual International Conference of the IEEE Engineering in Medicine & Biology Society.*

Barker, R. N., S. G. Brauer, and R. G. Carson (2008). "Training of Reaching in Stroke Survivors With Severe and Chronic Upper Limb Paresis Using a Novel Nonrobotic Device: A Randomized Clinical Trial". In: *Stroke* 39.6.

Barker-Collo, S. and V. Feigin (2006). "The impact of neuropsychological deficits on functional stroke outcomes". In: *Neuropsychology Review* 16.

Barss, T. S., B. W. M. Sallis, D. J. Miller, and D. F. Collins (2021). "Does increasing the number of channels during neuromuscular electrical stimulation reduce fatigability and produce larger contractions with less discomfort?" In: *European Journal of Applied Physiology* 121.9.

Basteris, A., S. M. Nijenhuis, A. H. Stienen, J. H. Buurke, G. B. Prange, and F. Amirabdollahian (2014). "Training modalities in robot-mediated upper limb rehabilitation in stroke: a framework for classification based on a systematic review". In: *Journal of NeuroEngineering and Rehabilitation* 11.1.

Beebe, J. A. and C. E. Lang (2008). "Absence of a proximal to distal gradient of motor deficits in the upper extremity early after stroke". In: *Clinical Neurophysiology* 119.9.

Beebe, J. A. and C. E. Lang (2009). "Active Range of Motion Predicts Upper Extremity Function 3 Months After Stroke". In: *Stroke* 40.5.

Bentley, P., G. Kumar, P. Rinne, S. Buddha, J. Kallingal, C. Hookway, P. Sharma, A. Mehta, and C. Beckmann (2014). "Lesion locations influencing baseline severity and early recovery in ischaemic stroke". In: *European Journal of Neurology* 21.9.

Bertani, R., C. Melegari, M. C. De Cola, A. Bramanti, P. Bramanti, and R. S. Calabrò (2017). "Effects of robot-assisted upper limb rehabilitation in stroke patients: a systematic review with meta-analysis". In: *Neurological Sciences* 38.9.

Bickel, C. S., C. M. Gregory, and J. C. Dean (2011). "Motor unit recruitment during neuromuscular electrical stimulation: a critical appraisal". In: *European Journal of Applied Physiology* 111.10.

Blank, A. A., J. A. French, A. U. Pehlivan, and M. K. O'Malley (2014). "Current Trends in Robot-Assisted Upper-Limb Stroke Rehabilitation: Promoting Patient Engagement in Therapy". In: *Current Physical Medicine and Rehabilitation Reports* 2.3.

Bo, W., L. Cavuoto, J. Langan, H. Subryan, S. Bhattacharjya, M.-C. Huang, and W. Xu (2022). "A progressive prediction model towards home-based stroke rehabilitation programs". In: *Smart Health* 23.

Bolton, D. A., J. H. Cauraugh, and H. A. Hausenblas (2004). "Electromyogram-triggered neuromuscular stimulation and stroke motor recovery of arm/hand functions: a meta-analysis". In: *Journal of the Neurological Sciences* 223.2.

Bonato, P., S. Roy, M. Knaflitz, and C. De Luca (2001). "Time-frequency parameters of the surface myoelectric signal for assessing muscle fatigue during cyclic dynamic contractions". In: *IEEE Transactions on Biomedical Engineering* 48.7.

Börner, H., G. Carboni, X. Cheng, A. Takagi, S. Hirche, S. Endo, and E. Burdet (2023). "Physically interacting humans regulate muscle coactivation to improve visuo-haptic perception". In: *Journal of Neurophysiology* 129.2.

Bourbonnais, D. and S. V. Noven (1989). "Weakness in Patients With Hemiparesis". In: *The American Journal of Occupational Therapy* 43.5.

Braun, V. and V. Clarke (2006). "Using thematic analysis in psychology". In: *Qualitative Research in Psychology* 3.2.

Burchielli, D., N. Lotti, F. Missiroli, C. Bokranz, A. Pedrocchi, E. Ambrosini, and L. Masia (2022). "Adaptive Hybrid FES-Force Controller for Arm Exosuit". In: *International Conference on Rehabilitation Robotics*.

Burdet, E., D. Franklin, and T. Milner (2013). *Human robotics: neuromechanics and motor control*.

Burridge, J. H., R. Turk, S. V. Notley, R. M. Pickering, and D. M. Simpson (2009). "The relationship between upper limb activity and impairment in post-stroke hemiplegia". In: *Disability and Rehabilitation* 31.2.

Byrnes, M. L., G. W. Thickbroom, B. A. Phillips, and F. L. Mastaglia (2001). "Long-term changes in motor cortical organisation after recovery from subcortical stroke". In: *Brain Research* 889.1.

Caldiroli, D., F. Molteni, A. Sommariva, S. Frittoli, E. Guanziroli, P. Cortellazzi, and E. Orena (2014). "Upper limb muscular activity and perceived workload during laryngoscopy: comparison of Glidescope® and Macintosh laryngoscopy in manikin: an observational study". In: *British Journal of Anaesthesia* 112.3.

Camardella, C., M. Germanotta, I. Aprile, G. Cappiello, Z. Curto, A. Scoglio, S. Mazzoleni, and A. Frisoli (2023). "A Decision Support System to Provide an Ongoing Prediction of Robot-Assisted Rehabilitation Outcome in Stroke Survivors". In: *2023 International Conference on Rehabilitation Robotics (ICORR)*. Singapore, Singapore.

Cameirão, M. S., S. B. i. Badia, E. D. Oller, and P. F. Verschure (2010). "Neurorehabilitation using the virtual reality based Rehabilitation Gaming System: methodology, design, psychometrics, usability and validation". In: *Journal of NeuroEngineering and Rehabilitation* 7.1.

Canning, C. G., L. Ada, and N. J. O'Dwyer (2000). "Abnormal muscle activation characteristics associated with loss of dexterity after stroke". In: *Journal of the Neurological Sciences* 176.1.

Carey, L. M., T. A. Matyas, and C. Baum (2018). "Effects of Somatosensory Impairment on Participation After Stroke". In: *The American Journal of Occupational Therapy* 72.3.

Carmichael, S. T. (2006). "Cellular and molecular mechanisms of neural repair after stroke: Making waves". In: *Annals of Neurology* 59.5.

Castelein, B., B. Cagnie, T. Parlevliet, L. Danneels, and A. Cools (2015). "Optimal Normalization Tests for Muscle Activation of the Levator Scapulae, Pectoralis Minor, and Rhomboid Major: An Electromyography Study Using Maximum Voluntary Isometric Contractions". In: *Archives of Physical Medicine and Rehabilitation* 96.10.

Cazenave, L., M. Einenkel, A. Yurkewich, S. Endo, S. Hirche, and E. Burdet (2023). "Hybrid Robotic and Electrical Stimulation Assistance Can Enhance Performance and Reduce Mental Demand". In: *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 31.

Chen, C.-L., F.-T. Tang, H.-C. Chen, C.-Y. Chung, and M.-K. Wong (2000). "Brain lesion size and location: Effects on motor recovery and functional outcome in stroke patients". In: *Archives of Physical Medicine and Rehabilitation* 81.4.

Chen, T., B. Zhang, Y. Deng, J.-C. Fan, L. Zhang, and F. Song (2019). "Long-term unmet needs after stroke: systematic review of evidence from survey studies". In: *BMJ Open* 9.5.

Chesler, N. C. and W. K. Durfee (1997). "Surface EMG as a fatigue indicator during FES-induced isometric muscle contractions". In: *Journal of Electromyography and Kinesiology* 7.1.

Choi, H.-I. and W. Williams (1989). "Improved time-frequency representation of multicomponent signals using exponential kernels". In: *IEEE Transactions on Acoustics, Speech, and Signal Processing* 37.6.

Choi-Kwon, S. and J. S. Kim (2011). "Poststroke fatigue: an emerging, critical issue in stroke medicine". In: *International journal of stroke* 6.4.

Cieza, A., K. Causey, K. Kamenov, S. W. Hanson, S. Chatterji, and T. Vos (2020). "Global estimates of the need for rehabilitation based on the Global Burden of Disease study 2019: a systematic analysis for the Global Burden of Disease Study 2019". In: *The Lancet* 396.10267.

Clark, B., J. Whitall, G. Kwakkel, J. Mehrholz, S. Ewings, and J. Burridge (2021). "The effect of time spent in rehabilitation on activity limitation and impairment after stroke". In: *Cochrane Database of Systematic Reviews* 2021.10. Ed. by Cochrane Stroke Group.

Colebatch, J. G. and S. C. Gandevia (1989). "The distribution of muscular weakness in upper motor neuron lesions affecting the arm". In: *Brain* 112.3.

Coleman, E. R., R. Moudgal, K. Lang, H. I. Hyacinth, O. O. Awosika, B. M. Kissela, and W. Feng (2017). "Early Rehabilitation After Stroke: a Narrative Review". In: *Current Atherosclerosis Reports* 19.12.

Connell, L. A. and S. F. Tyson (2012). "Clinical reality of measuring upper-limb ability in neurologic conditions: A systematic review". In: *Clinical Rehabilitation* 26.3.

Connell, L., N. Lincoln, and K. Radford (2008). "Somatosensory impairment after stroke: frequency of different deficits and their recovery". In: *Clinical Rehabilitation* 22.8.

Csikszentmihalyi, M. (1990). *Flow: The Psychology of Optimal Experience*. Vol. 1990.

De Los Reyes-Guzmán, A., I. Dimbwadyo-Terrer, F. Trincado-Alonso, F. Monasterio-Huelin, D. Torricelli, and A. Gil-Agudo (2014). "Quantitative assessment based on kinematic measures of functional impairments during upper extremity movements: A review". In: *Clinical Biomechanics* 29.7.

del-Ama, A. J., Á. Gil-Agudo, J. L. Pons, and J. C. Moreno (2014). "Hybrid FES-robot cooperative control of ambulatory gait rehabilitation exoskeleton". In: *Journal of NeuroEngineering and Rehabilitation* 11.1.

Devereaux, P. J. and S. Yusuf (2003). "The evolution of the randomized controlled trial and its role in evidence-based decision making". In: *Journal of Internal Medicine* 254.2.

Dimitrov, G. V., T. I. Arabadzhiev, K. N. Mileva, J. L. Bowtell, N. Crichton, and N. A. Dimitrova (2006). "Muscle Fatigue during Dynamic Contractions Assessed by New Spectral Indices". In: *Medicine & Science in Sports & Exercise* 38.11.

Dimitrova, N., J.-Y. Hogrel, T. Arabadzhiev, and G. Dimitrov (2005). "Estimate of M-wave changes in human biceps brachii during continuous stimulation". In: *Journal of Electromyography and Kinesiology* 15.4.

Dimyan, M. A. and L. G. Cohen (2011). "Neuroplasticity in the context of motor rehabilitation after stroke". In: *Nature Reviews Neurology* 7.2.

Dodds, T. A., D. P. Martin, W. C. Stolov, and R. A. Deyo (1993). "A validation of the functional independence measurement and its performance among rehabilitation inpatients". In: *Archives of Physical Medicine and Rehabilitation* 74.5.

Downey, R. J., M. Merad, E. J. Gonzalez, and W. E. Dixon (2017). "The Time-Varying Nature of Electromechanical Delay and Muscle Control Effectiveness in Response to Stimulation-Induced Fatigue". In: *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 25.9.

Dreibati, B., C. Lavet, A. Pinti, and G. Poumarat (2010). "Influence of electrical stimulation frequency on skeletal muscle force and fatigue". In: *Annals of Physical and Rehabilitation Medicine* 53.4.

Dromerick, A. W., C. E. Lang, R. L. Birkenmeier, J. M. Wagner, J. C. Miller, T. O. Videen, W. J. Powers, S. L. Wolf, and D. F. Edwards (2009). "Very early constraint-induced movement during stroke rehabilitation (VECTORS): a single-center RCT". In: *Neurology* 73.3.

Dromerick, A. W. et al. (2021). "Critical Period After Stroke Study (CPASS): A phase II clinical trial testing an optimal time for motor recovery after stroke in humans". In: *Proceedings of the National Academy of Sciences* 118.39.

Dudley-Javoroski, S., A. E. Littmann, S.-H. Chang, C. L. McHenry, and R. K. Shields (2011). "Enhancing Muscle Force and Femur Compressive Loads Via Feedback-Controlled Stimulation of Paralyzed Quadriceps in Humans". In: *Archives of Physical Medicine and Rehabilitation* 92.2.

Duncan, P. W., N. B. Propst, and S. G. Nelson (1983). "Reliability of the Fugl-Meyer assessment of sensorimotor recovery following cerebrovascular accident". In: *Physical Therapy* 63.10.

Dunkelberger, N., J. Berning, E. M. Schearer, and M. K. O'Malley (2023). "Hybrid FES-exoskeleton control: Using MPC to distribute actuation for elbow and wrist movements". In: *Frontiers in Neurorobotics* 17.

Dunkelberger, N., S. A. Carlson, J. Berning, K. C. Stovicek, E. M. Schearer, and M. K. O'Malley (2022). "Shared Control of Elbow Movements with Functional Electrical Stimulation and Exoskeleton Assistance". In: *International Conference on Rehabilitation Robotics*.

Dunkelberger, N., E. M. Schearer, and M. K. O'Malley (2020). "A review of methods for achieving upper limb movement following spinal cord injury through hybrid muscle stimulation and robotic assistance". In: *Experimental Neurology* 328.

Ekstrom, R. A., G. L. Soderberg, and R. A. Donatelli (2005). "Normalization procedures using maximum voluntary isometric contractions for the serratus anterior and trapezius muscles during surface EMG analysis". In: *Journal of Electromyography and Kinesiology* 15.4.

Emken, J., J. Bobrow, and D. Reinkensmeyer (2005). "Robotic Movement Training As an Optimization Problem: Designing a Controller That Assists Only As Needed". In: *9th International Conference on Rehabilitation Robotics, 2005. ICORR 2005.*

Eraifej, J., W. Clark, B. France, S. Desando, and D. Moore (2017). "Effectiveness of upper limb functional electrical stimulation after stroke for the improvement of activities of daily living and motor function: a systematic review and meta-analysis". In: *Systematic Reviews* 6.1.

Estigoni, E., C. Fornusek, N. Hamzaid, N. Hasnan, R. Smith, and G. Davis (2014). "Evoked EMG versus Muscle Torque during Fatiguing Functional Electrical Stimulation-Evoked Muscle Contractions and Short-Term Recovery in Individuals with Spinal Cord Injury". In: *Sensors* 14.12.

Fallahi, M., M. Motamedzade, R. Heidarimoghadam, A. R. Soltanian, and S. Miyake (2016). "Effects of mental workload on physiological and subjective responses during traffic density monitoring: A field study". In: *Applied Ergonomics* 52.

Feigin, V. L., E. Nichols, T. Alam, M. S. Bannick, E. Beghi, and et al. (2019). "Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016". In: *The Lancet Neurology* 18.5.

Feigin, V. L. et al. (2021). "Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019". In: *The Lancet Neurology* 20.10.

Ferrarin, M. and A. Pedotti (2000). "The relationship between electrical stimulus and joint torque: a dynamic model". In: *IEEE Transactions on Rehabilitation Engineering* 8.3.

Findlater, S. E. and S. P. Dukelow (2017). "Upper Extremity Proprioception After Stroke: Bridging the Gap Between Neuroscience and Rehabilitation". In: *Journal of Motor Behavior* 49.1.

Fluet, G. G., A. S. Merians, Q. Qiu, A. Davidow, and S. V. Adamovich (2014). "Comparing integrated training of the hand and arm with isolated training of the same effectors in persons with stroke using haptically rendered virtual environments, a randomized clinical trial". In: *Journal of NeuroEngineering and Rehabilitation* 11.1.

Franklin, D. W., R. Osu, E. Burdet, M. Kawato, and T. E. Milner (2003). "Adaptation to Stable and Unstable Dynamics Achieved By Combined Impedance Control and Inverse Dynamics Model". In: *Journal of Neurophysiology* 90.5.

Fujiwara, T., Y. Kasashima, K. Honaga, Y. Muraoka, T. Tsuji, R. Osu, K. Hase, Y. Masakado, and M. Liu (2009). "Motor Improvement and Corticospinal Modulation Induced by Hybrid Assistive Neuromuscular Dynamic Stimulation (HANDS) Therapy in Patients With Chronic Stroke". In: *Neurorehabilitation and Neural Repair* 23.2.

Gammeri, R., C. Iacono, R. Ricci, and A. Salatino (2020). "Unilateral Spatial Neglect After Stroke: Current Insights". In: *Neuropsychiatric Disease and Treatment*.

Gandolfi, M., I. Boscolo Galazzo, R. Gasparin Pavan, F. Cruciani, N. Vale, A. Picelli, S. F. Storti, N. Smania, and G. Menegaz (2023). "eXplainable AI Allows Predicting Upper Limb Rehabilitation Outcomes in Sub-Acute Stroke Patients". In: *IEEE Journal of Biomedical and Health Informatics* 27.1.

Ganesh, G., A. Takagi, R. Osu, T. Yoshioka, M. Kawato, and E. Burdet (2015). "Two is better than one: Physical interactions improve motor performance in humans". In: *Scientific Reports* 4.1.

Gladstone, D. J., C. J. Danells, and S. E. Black (2002). "The Fugl-Meyer Assessment of Motor Recovery after Stroke: A Critical Review of Its Measurement Properties". In: *Neurorehabilitation and Neural Repair* 16.3.

Gollee, H., D. Murray-Smith, and J. Jarvis (2001). "A nonlinear approach to modeling of electrically stimulated skeletal muscle". In: *IEEE Transactions on Biomedical Engineering* 48.4.

González-Izal, M., A. Malanda, I. Navarro-Amézqueta, E. Gorostiaga, F. Mallor, J. Ibañez, and M. Izquierdo (2010). "EMG spectral indices and muscle power fatigue during dynamic contractions". In: *Journal of Electromyography and Kinesiology* 20.2.

Gorgey, A. S., C. D. Black, C. P. Elder, and G. A. Dudley (2009). "Effects of Electrical Stimulation Parameters on Fatigue in Skeletal Muscle". In: *Journal of Orthopaedic & Sports Physical Therapy* 39.9.

Gray, V., C. L. Rice, and S. J. Garland (2012). "Factors That Influence Muscle Weakness Following Stroke and Their Clinical Implications: A Critical Review". In: *Physiotherapy Canada* 64.4.

Grigoras, A. V., D. C. Irimia, M. S. Poboroniuc, and C. D. Popescu (2016). "Testing of a Hybrid FES-Robot Assisted Hand Motor Training Program in Sub-Acute Stroke Survivors". In: *Advances in Electrical and Computer Engineering* 16.4.

Guadagnoli, M. A. and T. D. Lee (2004). "Challenge Point: A Framework for Conceptualizing the Effects of Various Practice Conditions in Motor Learning". In: *Journal of Motor Behavior* 36.2.

Gwo-Ching Chang, Jer-Junn Lub, Gon-Der Liao, Jin-Shin Lai, Cheng-Kung Cheng, Bor-Lin Kuo, and Te-Son Kuo (1997). "A neuro-control system for the knee joint position control with quadriceps stimulation". In: *IEEE Transactions on Rehabilitation Engineering* 5.1.

Hammer, A. M. and B. Lindmark (2010). "Responsiveness and validity of the Motor Activity Log in patients during the subacute phase after stroke". In: *Disability and Rehabilitation* 32.14.

Hara, Y. (2015). "Brain Plasticity and Rehabilitation in Stroke Patients". In: *Journal of Nippon Medical School* 82.1.

Hart, S. G. and L. E. Staveland (1988). "Development of NASA-TLX (Task Load Index): Results of empirical and theoretical research." In: *Advances in psychology* 52.

Hayashibe, M., Q. Zhang, D. Guiraud, and C. Fattal (2011). "Evoked EMG-based torque prediction under muscle fatigue in implanted neural stimulation". In: *Journal of Neural Engineering* 8.6.

Heasman, J., T. Scott, V. Vare, R. Flynn, C. Gschwind, J. Middleton, and S. Butkowski (2000). "Detection of fatigue in the isometric electrical activation of paralyzed hand muscles of persons with tetraplegia". In: *IEEE Transactions on Rehabilitation Engineering* 8.3.

Hebb, D. O. (2005). *The Organization of Behavior: A Neuropsychological Theory*.

Hillier, S., M. Immink, and D. Thewlis (2015). "Assessing Proprioception: A Systematic Review of Possibilities". In: *Neurorehabilitation and Neural Repair* 29.10.

Hiragami, S., Y. Inoue, and K. Harada (2019). "Minimal clinically important difference for the Fugl-Meyer assessment of the upper extremity in convalescent stroke patients with moderate to severe hemiparesis". In: *Journal of Physical Therapy Science* 31.11.

Hogan, N. and D. Sternad (2009). "Sensitivity of Smoothness Measures to Movement Duration, Amplitude, and Arrests". In: *Journal of Motor Behavior* 41.6.

Höhler, C., E. Trigili, D. Astarita, J. Hermsdörfer, K. Jahn, and C. Krewer (2024). "The efficacy of hybrid neuroprostheses in the rehabilitation of upper limb impairment after stroke, a narrative and systematic review with a meta-analysis". In: *Artificial Organs* 48.3.

Höhler, C., S. Endo, J. Hermsdörfer, L. Cazenave, H. Kavianirad, K. Jahn, and C. Krewer (2025). "Repetitive Grasping After Stroke Assisted by Functional Electrical Stimulation". In: *Artificial Organs*.

Horn, S. D., G. DeJong, R. J. Smout, J. Gassaway, and B. Conroy (2005). "Stroke Rehabilitation Patients, Practice, and Outcomes: Is Earlier and More Aggressive Therapy Better?" In: *Archives of Physical Medicine and Rehabilitation* 86.12.

Houwink, A., R. H. Nijland, A. C. Geurts, and G. Kwakkel (2013). "Functional Recovery of the Paretic Upper Limb After Stroke: Who Regains Hand Capacity?" In: *Archives of Physical Medicine and Rehabilitation* 94.5.

Howlett, O. A., N. A. Lannin, L. Ada, and C. McKinstry (2015). "Functional Electrical Stimulation Improves Activity After Stroke: A Systematic Review With Meta-Analysis". In: *Archives of Physical Medicine and Rehabilitation* 96.5.

Hu, J. S. L., J. Lu, W. B. Tan, and D. Lomanto (2016). "Training improves laparoscopic tasks performance and decreases operator workload". In: *Surgical Endoscopy* 30.5.

Hu, X. L., K. Y. Tong, R. Li, M. Chen, J. J. Xue, S. K. Ho, and P. N. Chen (2011). "Post-stroke wrist rehabilitation assisted with an intention-driven functional electrical stimulation (FES)-robot system". In: *IEEE International Conference on Rehabilitation Robotics*.

Hu, X. L., K. Y. Tong, R. Li, M. Chen, J. J. Xue, S. K. Ho, and P. Chen (2010). "Effectiveness of functional electrical stimulation (FES)-robot assisted wrist training on persons after stroke". In: *Annual International Conference of the IEEE Engineering in Medicine and Biology*.

Hu, X., K. Tong, R. Song, X. Zheng, K. Lui, W. Leung, S. Ng, and S. Au-Yeung (2009). "Quantitative evaluation of motor functional recovery process in chronic stroke patients during robot-assisted wrist training". In: *Journal of Electromyography and Kinesiology* 19.4.

Hu, X.-L., R. K.-y. Tong, N. S. K. Ho, J.-j. Xue, W. Rong, and L. S. W. Li (2015). "Wrist Rehabilitation Assisted by an Electromyography-Driven Neuromuscular Electrical Stimulation Robot After Stroke". In: *Neurorehabilitation and Neural Repair* 29.8.

Hu, X., K. Tong, V. S. Tsang, and R. Song (2006). "Joint-Angle–Dependent Neuromuscular Dysfunctions at the Wrist in Persons After Stroke". In: *Archives of Physical Medicine and Rehabilitation* 87.5.

Huang, Y., C. Nam, W. Li, W. Rong, Y. Xie, Y. Liu, Q. Qian, and X. Hu (2020). "A comparison of the rehabilitation effectiveness of neuromuscular electrical stimulation robotic hand training and pure robotic hand training after stroke: A randomized controlled trial". In: *Biomedical Signal Processing and Control* 56.

Hubel, D. H. and T. N. Wiesel (1965). "Binocular Interaction in Striate Cortex of Kittens Reared with Artificial Squint". In: *Journal of Neurophysiology* 28.6.

Hunter, S. M., L. Hammett, S. Ball, N. Smith, C. Anderson, A. Clark, R. Tallis, A. Rudd, and V. M. Pomeroy (2011). "Dose–Response Study of Mobilisation and Tactile Stimulation Therapy for the Upper Extremity Early After Stroke: A Phase I Trial". In: *Neurorehabilitation and Neural Repair* 25.4.

Huynh, B. P., J. A. DiCarlo, I. Vora, J. Ranford, P. Gochyyev, D. J. Lin, and T. J. Kimberley (2023). "Sensitivity to Change and Responsiveness of the Upper Extremity Fugl-Meyer Assessment in Individuals With Moderate to Severe Acute Stroke". In: *Neurorehabilitation and Neural Repair* 37.8.

Ibitoye, M. O., N. A. Hamzaid, N. Hasnan, A. K. Abdul Wahab, and G. M. Davis (2016). "Strategies for Rapid Muscle Fatigue Reduction during FES Exercise in Individuals with Spinal Cord Injury: A Systematic Review". In: *PLOS ONE* 11.2. Ed. by A. Lucia.

Indrawati, ., I. K. Sudiana, and M. Sajidin (2018). "Active, Passive, and Active-Assistive Range of Motion (ROM) Exercise to Improve Muscle Strength in Post Stroke Clients: A Systematic Review:" in: *Proceedings of the 9th International Nursing Conference.*

Intercollegiate Stroke Working Party (2023). "National Clinical Guideline for Stroke for the UK and Ireland". In: *Available at: www.strokeguideline.org.*

Ivanova, E., G. Carboni, J. Eden, J. Krüger, and E. Burdet (2020). "For Motion Assistance Humans Prefer to Rely on a Robot Rather Than on an Unpredictable Human". In: *IEEE Open Journal of Engineering in Medicine and Biology* 1.

Ivanova, E., J. Eden, G. Carboni, J. Krüger, and E. Burdet (2022). "Interaction with a reactive partner improves learning in contrast to passive guidance". In: *Scientific Reports* 12.1.

Jonsdottir, J., R. Thorsen, I. Aprile, S. Galeri, G. Spannocchi, E. Beghi, E. Bianchi, A. Montesano, and M. Ferrarin (2017). "Arm rehabilitation in post stroke subjects: A randomized controlled trial on the efficacy of myoelectrically driven FES applied in a task-oriented approach". In: *PLOS ONE* 12.12. Ed. by A. Martinuzzi.

Kahn, L., W. Rymer, and D. Reinkensmeyer (2004). "Adaptive assistance for guided force training in chronic stroke (2004)". In: *The 26th Annual International Conference of the IEEE Engineering in Medicine and Biology Society.* Vol. 1.

Kahn, L. E., P. S. Lum, W. Z. Rymer, and D. J. Reinkensmeyer (2006). "Robot-assisted movement training for the stroke-impaired arm: Does it matter what the robot does?" In: *The Journal of Rehabilitation Research and Development* 43.5.

Kapadia, N., V. Zivanovic, and M. Popovic (2013). "Restoring Voluntary Grasping Function in Individuals with Incomplete Chronic Spinal Cord Injury: Pilot Study". In: *Topics in Spinal Cord Injury Rehabilitation* 19.4.

Karlsson, S., Jun Yu, and M. Akay (2000). "Time-frequency analysis of myoelectric signals during dynamic contractions: a comparative study". In: *IEEE Transactions on Biomedical Engineering* 47.2.

Katrak, P., G. Bowring, P. Conroy, M. Chilvers, R. Poulos, and D. McNeil (1998). "Predicting upper limb recovery after stroke: The place of early shoulder and hand movement". In: *Archives of Physical Medicine and Rehabilitation* 79.7.

Kavianirad, H., S. Endo, T. Keller, and S. Hirche (2022). "EMG-Based Volitional Torque Estimation in Functional Electrical Stimulation Control". In: *2022 IEEE-EMBS Conference on Biomedical Engineering and Sciences (IECBES).*

Kessner, S. S. (2016). "Somatosensory deficits after stroke: a scoping review". In: *Topics in Stroke Rehabilitation.*

Kleim, J. A. and T. A. Jones (2008). "Principles of Experience-Dependent Neural Plasticity: Implications for Rehabilitation After Brain Damage". In: *Journal of Speech, Language, and Hearing Research* 51.1.

Klein, J., S. Spencer, J. Allington, J. E. Bobrow, and D. J. Reinkensmeyer (2010). "Optimization of a Parallel Shoulder Mechanism to Achieve a High-Force, Low-Mass, Robotic-Arm Exoskeleton". In: *IEEE Transactions on Robotics* 26.4.

Krakauer, J. W. (2020). "The applicability of motor learning to neurorehabilitation". In: *Oxford Textbook of Neurorehabilitation.*

Krakauer, J. W., S. T. Carmichael, D. Corbett, and G. F. Wittenberg (2012). "Getting Neurorehabilitation Right: What Can Be Learned From Animal Models?" In: *Neurorehabilitation and Neural Repair* 26.8.

Krebs, H., J. Palazzolo, L. Dipietro, M. Ferraro, J. Krol, K. Rannekleiv, B. Volpe, and N. Hogan (2003). "Rehabilitation Robotics: Performance-Based Progressive Robot-Assisted Therapy". In: *Autonomous Robots* 15.1.

Krebs, H. I., M. Ferraro, S. P. Buerger, M. J. Newbery, A. Makiyama, M. Sandmann, D. Lynch, B. T. Volpe, and N. Hogan (2004). "Rehabilitation robotics: pilot trial of a spatial extension for MIT-Manus". In: *Journal of NeuroEngineering and Rehabilitation* 1.1.

Krebs, H. I., B. T. Volpe, D. Williams, J. Celestino, S. K. Charles, D. Lynch, and N. Hogan (2007). "Robot-Aided Neurorehabilitation: A Robot for Wrist Rehabilitation". In: *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 15.3.

Kristensen, O. H., E. Stenager, and U. Dalgas (2017). "Muscle Strength and Poststroke Hemiplegia: A Systematic Review of Muscle Strength Assessment and Muscle Strength Impairment". In: *Archives of Physical Medicine and Rehabilitation* 98.2.

Kroon, J. de, M. IJzerman, J. Chae, G. Lankhorst, and G. Zilvold (2005). "Relation between stimulation characteristics and clinical outcome of the upper extremity in stroke". In: *Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine* 37.

Kwah, L. K., L. A. Harvey, J. Diong, and R. D. Herbert (2013). "Models containing age and NIHSS predict recovery of ambulation and upper limb function six months after stroke: an observational study". In: *Journal of Physiotherapy* 59.3.

Kwakkel, G. (2019). "Standardized Measurement of Quality of Upper Limb Movement After Stroke: Consensus-Based Core Recommendations From the Second Stroke Recovery and Rehabilitation Roundtable". In: *Neural Repair* 33.11.

Kwakkel, G., B. J. Kollen, and H. I. Krebs (2008). "Effects of Robot-Assisted Therapy on Upper Limb Recovery After Stroke: A Systematic Review". In: *Neurorehabilitation and Neural Repair* 22.2.

Kwakkel, G. et al. (2004). "Effects of Augmented Exercise Therapy Time After Stroke: A Meta-Analysis". In: *Stroke* 35.11.

Lambercy, O., L. Dovat, R. Gassert, E. Burdet, C. L. Teo, and T. Milner (2007). "A Haptic Knob for Rehabilitation of Hand Function". In: *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 15.3.

Lambercy, O. et al. (2009). "Exercises for rehabilitation and assessment of hand motor function with the Haptic Knob". In: *Proceedings of the 3rd International Convention on Rehabilitation Engineering & Assistive Technology - ICREATE '09*.

Lambercy, O. et al. (2011). "Effects of a robot-assisted training of grasp and pronation/supination in chronic stroke: a pilot study". In: *Journal of NeuroEngineering and Rehabilitation* 8.1.

Lance, J. W. (1980). "The control of muscle tone, reflexes, and movement: Robert Wartenbeg Lecture". In: *Neurology* 30 (12).

Lang, C. E. and J. A. Beebe (2007). "Relating Movement Control at 9 Upper Extremity Segments to Loss of Hand Function in People with Chronic Hemiparesis". In: *Neurorehabilitation and Neural Repair* 21.3.

Lang, C. E., D. F. Edwards, R. L. Birkenmeier, and A. W. Dromerick (2008). "Estimating Minimal Clinically Important Differences of Upper-Extremity Measures Early After Stroke". In: *Archives of Physical Medicine and Rehabilitation* 89.9.

Lang, C. E., K. R. Lohse, and R. L. Birkenmeier (2015). "Dose and timing in neurorehabilitation: prescribing motor therapy after stroke". In: *Current Opinion in Neurology* 28.6.

Lang, C. E., J. R. MacDonald, D. S. Reisman, L. Boyd, T. Jacobson Kimberley, S. M. Schindler-Ivens, T. G. Hornby, S. A. Ross, and P. L. Scheets (2009). "Observation of Amounts of Movement Practice Provided During Stroke Rehabilitation". In: *Archives of Physical Medicine and Rehabilitation* 90.10.

Lang, C. E., J. M. Wagner, A. W. Dromerick, and D. F. Edwards (2006). "Measurement of Upper-Extremity Function Early After Stroke: Properties of the Action Research Arm Test". In: *Archives of Physical Medicine and Rehabilitation* 87.12.

Lateva, Z. C., K. C. McGill, and C. G. Burgar (1996). "Anatomical and electrophysiological determinants of the human thenar compound muscle action potential". In: *Muscle & Nerve* 19.11.

Laubacher, M., E. A. Aksoez, A. K. Brust, M. Baumberger, R. Riener, S. Binder-Macleod, and K. J. Hunt (2019). "Stimulation of paralysed quadriceps muscles with sequentially and spatially distributed electrodes during dynamic knee extension". In: *Journal of NeuroEngineering and Rehabilitation* 16.1.

Lawrence, E. S., C. Coshall, R. Dundas, J. Stewart, A. G. Rudd, R. Howard, and C. D. A. Wolfe (2001). "Estimates of the Prevalence of Acute Stroke Impairments and Disability in a Multiethnic Population". In: *Stroke* 32.6.

Lee, S. I., C. P. Adans-Dester, A. T. OBrien, G. P. Vergara-Diaz, R. Black-Schaffer, R. Zafonte, J. G. Dy, and P. Bonato (2021). "Predicting and Monitoring Upper-Limb Rehabilitation

Outcomes Using Clinical and Wearable Sensor Data in Brain Injury Survivors". In: *IEEE Transactions on Biomedical Engineering* 68.6.

Lee, Y.-y., K.-c. Lin, H.-j. Cheng, C.-y. Wu, Y.-w. Hsieh, and C.-k. Chen (2015). "Effects of combining robot-assisted therapy with neuromuscular electrical stimulation on motor impairment, motor and daily function, and quality of life in patients with chronic stroke: a double-blinded randomized controlled trial". In: *Journal of NeuroEngineering and Rehabilitation* 12.1.

Li, S. (2015). "New insights into the pathophysiology of post-stroke spasticity". In: *Frontiers in Human Neuroscience* 9.192.

Li, Z., D. Guiraud, D. Andreu, A. Gelis, C. Fattal, and M. Hayashibe (2018). "Real-Time Closed-Loop Functional Electrical Stimulation Control of Muscle Activation with Evoked Electromyography Feedback for Spinal Cord Injured Patients". In: *International Journal of Neural Systems* 28.06.

Lincoln, N. B., J. L. Crow, J. M. Jackson, G. R. Waters, S. A. Adams, and P. Hodgson (1991). "The unreliability of sensory assessments". In: *Clinical Rehabilitation* 5.4.

Lo, J. W. et al. (2019). "Profile of and risk factors for poststroke cognitive impairment in diverse ethnoregional groups". In: *Neurology* 93.24.

Lotti, N., M. Xiloyannis, E. Ficanha, D. Chiaradia, A. Frisoli, and L. Masia (2020). "Adaptive Model-Based Myoelectric Control for a Soft Wearable Arm Exosuit: A New Generation of Wearable Robot Control". In: *IEEE Robotics and Automation Magazine* 27.1.

Lyle, R. C. (1981). "A performance test for assessment of upper limb function in physical rehabilitation treatment and research". In: *International Journal of Rehabilitation Research* 4.4.

Lynch, C. L. and M. R. Popovic (2008). "Functional Electrical Stimulation". In: *IEEE Control Systems* 28.2.

Maciejasz, P., J. Eschweiler, K. Gerlach-Hahn, A. Jansen-Troy, and S. Leonhardt (2014). "A survey on robotic devices for upper limb rehabilitation". In: *Journal of NeuroEngineering and Rehabilitation* 11.1.

Maclean, N., P. Pound, C. Wolfe, and A. Rudd (2000a). "Qualitative analysis of stroke patients' motivation for rehabilitation". In: *BMJ* 321.7268.

Maclean, N. and P. Pound (2000b). "A critical review of the concept of patient motivation in the literature on physical rehabilitation". In: *Social Science & Medicine* 50.4.

Maffiuletti, N. A. (2010). "Physiological and methodological considerations for the use of neuromuscular electrical stimulation." In: *European journal of applied physiology* 110.2.

Maffiuletti, N. A., I. Vivodtzev, M. A. Minetto, and N. Place (2014). "A new paradigm of neuromuscular electrical stimulation for the quadriceps femoris muscle". In: *European Journal of Applied Physiology* 114.6.

Mahoney, F. I. and D. W. Barthel (1965). "Functional evaluation: The Barthel Index". In: *Maryland State Medical Journal* 14.

Mangold, S., C. Schuster, T. Keller, A. Zimmermann-Schlatter, and T. Ettlin (2009). "Motor Training of Upper Extremity With Functional Electrical Stimulation in Early Stroke Rehabilitation". In: *Neurorehabilitation and Neural Repair* 23.2.

Marchal-Crespo, L. and D. J. Reinkensmeyer (2009). "Review of control strategies for robotic movement training after neurologic injury". In: *Journal of NeuroEngineering and Rehabilitation* 6.1.

Mathiowetz, V., G. Volland, N. Kashman, and K. Weber (1985). "Adult norms for the Box and Block Test of manual dexterity". In: *The American Journal of Occupational Therapy* 39.6.

Maulden, S. A., J. Gassaway, S. D. Horn, R. J. Smout, and G. DeJong (2005). "Timing of Initiation of Rehabilitation After Stroke". In: *Archives of Physical Medicine and Rehabilitation* 86.12.

Mazzoleni, S., P. Sale, M. Franceschini, S. Bigazzi, M. C. Carrozza, P. Dario, and F. Posteraro (2013). "Effects of proximal and distal robot-assisted upper limb rehabilitation on chronic stroke recovery". In: *NeuroRehabilitation* 33.1. Ed. by H. I. Krebs.

Mazzoleni, S., V.-D. Tran, P. Dario, and F. Posteraro (2018). "Wrist Robot-Assisted Rehabilitation Treatment in Subacute and Chronic Stroke Patients: From Distal-to-Proximal Motor Recovery". In: *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 26.9.

Meadmore, K. L., T. A. Exell, E. Hallewell, A.-M. Hughes, C. T. Freeman, M. Kutlu, V. Benson, E. Rogers, and J. H. Burridge (2014). "The application of precisely controlled functional electrical stimulation to the shoulder, elbow and wrist for upper limb stroke rehabilitation: a feasibility study". In: *Journal of NeuroEngineering and Rehabilitation* 11.1.

Meadmore, K. L., A.-M. Hughes, C. T. Freeman, Z. Cai, D. Tong, J. H. Burridge, and E. Rogers (2012). "Functional electrical stimulation mediated by iterative learning control and 3D robotics reduces motor impairment in chronic stroke". In: *Journal of NeuroEngineering and Rehabilitation* 9.1.

Mehrholz, J., M. Pohl, T. Platz, J. Kugler, and B. Elsner (2018). "Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke". In: *Cochrane Database of Systematic Reviews* 2018.9. Ed. by Cochrane Stroke Group.

Merletti, R. and P. Parker, eds. (2004). *Electromyography: physiology, engineering, and noninvasive applications*. IEEE Press series in biomedical engineering.

Milot, M.-H., S. J. Spencer, V. Chan, J. P. Allington, J. Klein, C. Chou, J. E. Bobrow, S. C. Cramer, and D. J. Reinkensmeyer (2013). "A crossover pilot study evaluating the functional outcomes of two different types of robotic movement training in chronic stroke survivors using the arm exoskeleton BONES". In: *Journal of NeuroEngineering and Rehabilitation* 10.1.

Miura, N. and T. Watanabe (2016). "Potential of M-Wave Elicited by Double Pulse for Muscle Fatigue Evaluation in Intermittent Muscle Activation by Functional Electrical Stimulation for Motor Rehabilitation". In: *Journal of Medical Engineering* 2016.

Miyasaka, H., A. Orand, H. Ohnishi, G. Tanino, K. Takeda, and S. Sonoda (2016). "Ability of electrical stimulation therapy to improve the effectiveness of robotic training for paretic upper limbs in patients with stroke". In: *Medical Engineering & Physics* 38.11.

Mizrahi, J., M. Levy, H. Ring, E. Isakov, and A. Liberson (1994). "EMG as an indicator of fatigue in isometrically FES-activated paralyzed muscles". In: *IEEE Transactions on Rehabilitation Engineering* 2.2.

Murphy, T. H. and D. Corbett (2009). "Plasticity during stroke recovery: from synapse to behaviour". In: *Nature Reviews Neuroscience* 10.12.

Nakayama, H., H. Stig Jørgensen, H. Otto Raaschou, and T. Skyhøj Olsen (1994). "Recovery of upper extremity function in stroke patients: The Copenhagen stroke study". In: *Archives of Physical Medicine and Rehabilitation* 75.4.

Nehrujee, A., H. Andrew, Reethajanetsurekha, A. Patricia, S. Samuelkamaleshkumar, H. Prakash, S. Sujatha, and S. Balasubramanian (2021). "Plug-and-Train Robot (PLUTO) for Hand Rehabilitation: Design and Preliminary Evaluation". In: *IEEE Access* 9.

Nieminen, H., E. .-. Takala, and E. Viikari-Juntura (1993). "Normalization of electromyogram in the neck-shoulder region". In: *European Journal of Applied Physiology and Occupational Physiology* 67.3.

Nijland, R. H., E. E. Van Wegen, B. C. Harmeling-van Der Wel, and G. Kwakkel (2010). "Presence of Finger Extension and Shoulder Abduction Within 72 Hours After Stroke Predicts Functional Recovery: Early Prediction of Functional Outcome After Stroke: The EPOS Cohort Study". In: *Stroke* 41.4.

Nudo, R. J. (2006). "Mechanisms for recovery of motor function following cortical damage". In: *Current Opinion in Neurobiology* 16.6.

Oldfield, R. C. (1971). "The assessment and analysis of handedness: the Edinburgh inventory." In: *Neuropsychologia* 9.1.

Page, S. J., G. D. Fulk, and P. Boyne (2012). "Clinically Important Differences for the Upper-Extremity Fugl-Meyer Scale in People With Minimal to Moderate Impairment Due to Chronic Stroke". In: *Physical Therapy* 92.6.

Pandyan, A., M. Gregoric, M. Barnes, D. Wood, F. V. Wijck, J. Burridge, and G. Johnson (2005). "Spasticity: Clinical perceptions, neurological realities and meaningful measurement". In: *Disability and Rehabilitation* 27.1.

Park, J. H., G. Park, H. Y. Kim, J.-Y. Lee, Y. Ham, D. Hwang, S. Kwon, and J.-H. Shin (2020). "A comparison of the effects and usability of two exoskeletal robots with and without robotic actuation for upper extremity rehabilitation among patients with stroke: a single-blinded randomised controlled pilot study". In: *Journal of NeuroEngineering and Rehabilitation* 17.1.

Patel, A., V. Berdunov, Z. Quayyum, D. King, M. Knapp, and R. Wittenberg (2020). "Estimated societal costs of stroke in the UK based on a discrete event simulation". In: *Age and Ageing* 49.2.

Prange-Lasonder, G. B. et al. (2021). "European evidence-based recommendations for clinical assessment of upper limb in neurorehabilitation (CAULIN): data synthesis from systematic reviews, clinical practice guidelines and expert consensus". In: *Journal of NeuroEngineering and Rehabilitation* 18.1.

Przewoźnik, D. A., A. Rajtar-Zembaty, and A. Starowicz-Filip (2015). "The influence of cognitive, emotional and social factors on motivation for rehabilitation in patients after stroke". In: *Neuropsychiatria i Neuropsychologia* 10.2.

Qian, Q., X. Hu, Q. Lai, S. C. Ng, Y. Zheng, and W. Poon (2017). "Early Stroke Rehabilitation of the Upper Limb Assisted with an Electromyography-Driven Neuromuscular Electrical Stimulation-Robotic Arm". In: *Frontiers in Neurology* 8.

Qian, Q., C. Nam, Z. Guo, Y. Huang, X. Hu, S. C. Ng, Y. Zheng, and W. Poon (2019). "Distal versus proximal - an investigation on different supportive strategies by robots for upper limb rehabilitation after stroke: a randomized controlled trial". In: *Journal of NeuroEngineering and Rehabilitation* 16.1.

Qiu, S., A. E. Draghici, G. Picard, and J. A. Taylor (2020). "Muscle Fatigue in Response to Electrical Stimulation Pattern and Frequency in Spinal Cord Injury". In: *PM&R* 12.7.

Qiu, T., N. Alibeji, and N. Sharma (2016). "Robust compensation of electromechanical delay during neuromuscular electrical stimulation of antagonistic muscles". In: *2016 American Control Conference (ACC)*.

Raghavan, P. (2015). "Upper Limb Motor Impairment After Stroke". In: *Physical Medicine and Rehabilitation Clinics of North America* 26.4.

Rand, D., P. L. (Tamar) Weiss, and D. Gottlieb (1999). "Does Proprioceptive Loss Influence Recovery of the Upper Extremity After Stroke?" In: *Neurorehabilitation and Neural Repair* 13.1.

Resquin, F., A. Cuesta Gomez, J. Gonzalez-Vargas, F. Brunetti, D. Torricelli, F. Molina Rueda, R. Cano de la Cuerda, J. C. Miangolarra, and J. L. Pons (2016). "Hybrid robotic systems for upper limb rehabilitation after stroke: A review". In: *Medical Engineering & Physics* 38.11.

Resquín, F., J. Gonzalez-Vargas, J. Ibáñez, F. Brunetti, and J. L. Pons (2016). "Feedback error learning controller for functional electrical stimulation assistance in a hybrid robotic system for reaching rehabilitation". In: *European Journal of Translational Myology* 26.3.

Riener, R., L. Lünenburger, I. C. Maier, G. Colombo, and V. Dietz (2010). "Locomotor Training in Subjects with Sensori-Motor Deficits: An Overview of the Robotic Gait Orthosis Lokomat". In: *Journal of Healthcare Engineering* 1.2.

Riener, R., J. Quintern, and G. Schmidt (1996). "Biomechanical model of the human knee evaluated by neuromuscular stimulation". In: *Journal of Biomechanics* 29.9.

Riener, R. and L. J. Seward (2014). "Cybathlon 2016". In: *IEEE International Conference on Systems, Man, and Cybernetics*.

Ring, H. and N. Rosenthal (2005). "Controlled study of neuroprosthetic functional electrical stimulation in sub-acute post-stroke rehabilitation". In: *Journal of Rehabilitation Medicine* 37.1.

Robinson, R. G. and R. E. Jorge (2016). "Post-Stroke Depression: A Review". In: *American Journal of Psychiatry* 173.3.

Rodgers, H. et al. (2019). "Robot assisted training for the upper limb after stroke (RATULS): a multicentre randomised controlled trial". In: *The Lancet* 394.10192.

Rodriguez-Falces, J. and N. Place (2017). "Muscle excitability during sustained maximal voluntary contractions by a separate analysis of the M-wave phases". In: *Scandinavian Journal of Medicine & Science in Sports* 27.12.

Rodriguez-Falces, J. and N. Place (2018). "Determinants, analysis and interpretation of the muscle compound action potential (M wave) in humans: implications for the study of muscle fatigue". In: *European Journal of Applied Physiology* 118.3.

Roh, J., W. Z. Rymer, and R. F. Beer (2015). "Evidence for altered upper extremity muscle synergies in chronic stroke survivors with mild and moderate impairment". In: *Frontiers in Human Neuroscience* 9.

Roh, J., W. Z. Rymer, E. J. Perreault, S. B. Yoo, and R. F. Beer (2013). "Alterations in upper limb muscle synergy structure in chronic stroke survivors". In: *Journal of Neurophysiology* 109.3.

Rohrer, B., S. Fasoli, H. I. Krebs, R. Hughes, B. Volpe, W. R. Frontera, J. Stein, and N. Hogan (2002). "Movement Smoothness Changes during Stroke Recovery". In: *The Journal of Neuroscience* 22.18.

Rong, W., K. Y. Tong, X. L. Hu, and S. K. Ho (2015). "Effects of electromyography-driven robot-aided hand training with neuromuscular electrical stimulation on hand control performance after chronic stroke". In: *Disability and Rehabilitation: Assistive Technology* 10.2.

Royal College of Physicians, L. (2015). *Party, Intercollegiate Stroke Working. "Sentinel Stroke National Audit Programme (SSNAP).".* Tech. rep.

Royal Dutch Society for Physical Therapy (2014). *KNGF Clinical Practice Guideline for Physical Therapy in patients with stroke.* Practice Guidelines. Royal Dutch Society for Physical Therapy.

Rushton, D. (2003). "Functional Electrical Stimulation and rehabilitation—an hypothesis". In: *Medical Engineering & Physics* 25.1.

Saes, M. et al. (2021). "Smoothness metric during reach-to-grasp after stroke: part 2. longitudinal association with motor impairment". In: *Journal of NeuroEngineering and Rehabilitation* 18.1.

Salbach, N. M. et al. (2022). "Canadian Stroke Best Practice Recommendations: Virtual Stroke Rehabilitation Interim Consensus Statement 2022". In: *American Journal of Physical Medicine & Rehabilitation* 101.11.

Schmidt, R. and T. Lee (2011). *Motor Control and Learning: a behavioral emphasis. 5th Edition.*

Schwarz, A., C. M. Kanzler, O. Lambercy, A. R. Luft, and J. M. Veerbeek (2019). "Systematic Review on Kinematic Assessments of Upper Limb Movements After Stroke". In: *Stroke* 50.3.

See, J., L. Dodakian, C. Chou, V. Chan, A. McKenzie, D. J. Reinkensmeyer, and S. C. Cramer (2013). "A Standardized Approach to the Fugl-Meyer Assessment and Its Implications for Clinical Trials". In: *Neurorehabilitation and Neural Repair* 27.8.

Shimodozono, M., T. Noma, S. Matsumoto, R. Miyata, S. Etoh, and K. Kawahira (2014). "Repetitive facilitative exercise under continuous electrical stimulation for severe arm impairment after sub-acute stroke: A randomized controlled pilot study". In: *Brain Injury* 28.2.

Shindo, K., T. Fujiwara, J. Hara, H. Oba, F. Hotta, T. Tsuji, K. Hase, and M. Liu (2011). "Effectiveness of Hybrid Assistive Neuromuscular Dynamic Stimulation Therapy in Patients With Subacute Stroke: A Randomized Controlled Pilot Trial". In: *Neurorehabilitation and Neural Repair* 25.9.

Shuggi, I. M., H. Oh, P. A. Shewokis, and R. J. Gentili (2017). "Mental workload and motor performance dynamics during practice of reaching movements under various levels of task difficulty". In: *Neuroscience* 360.

Song, R., K.-y. Tong, X. Hu, and W. Zhou (2013). "Myoelectrically controlled wrist robot for stroke rehabilitation". In: *Journal of NeuroEngineering and Rehabilitation* 10.1.

Squeri, V., L. Masia, P. Giannoni, G. Sandini, and P. Morasso (2014). "Wrist rehabilitation in chronic stroke patients by means of adaptive, progressive robot-aided therapy". In: *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 22.2.

Stinear, C., S. Ackerley, and W. Byblow (2013). "Rehabilitation is Initiated Early After Stroke, but Most Motor Rehabilitation Trials Are Not: A Systematic Review". In: *Stroke* 44.7.

Stinear, C. M., C. E. Lang, S. Zeiler, and W. D. Byblow (2020). "Advances and challenges in stroke rehabilitation". In: *The Lancet Neurology* 19.4.

Stinear, C. M., W. D. Byblow, S. J. Ackerley, P. A. Barber, and M.-C. Smith (2017). "Predicting Recovery Potential for Individual Stroke Patients Increases Rehabilitation Efficiency". In: *Stroke* 48.4.

Stroke Foundation (2024). *Australian and New Zealand Living Clinical Guidelines for Stroke Management.* Tech. rep. Stroke Foundation.

Stulen, F. B. and C. J. De Luca (1981). "Frequency Parameters of the Myoelectric Signal as a Measure of Muscle Conduction Velocity". In: *IEEE Transactions on Biomedical Engineering* 28.7.

Takahashi, C. D., L. Der-Yeghiaian, V. Le, R. R. Motiwala, and S. C. Cramer (2008). "Robot-based hand motor therapy after stroke". In: *Brain* 131.2.

Tepavac, D. and L. Schwirtlich (1997). "Detection and prediction of FES-induced fatigue". In: *Journal of Electromyography and Kinesiology* 7.1.

Thoroughman, K. A. and R. Shadmehr (1999). "Electromyographic Correlates of Learning an Internal Model of Reaching Movements". In: *The Journal of Neuroscience* 19.19.

Thrasher, T. A., V. Zivanovic, W. McIlroy, and M. R. Popovic (2008). "Rehabilitation of Reaching and Grasping Function in Severe Hemiplegic Patients Using Functional Electrical Stimulation Therapy". In: *Neurorehabilitation and Neural Repair* 22.6.

Ting, D. S., A. Pollock, G. N. Dutton, F. N. Doubal, D. S. Ting, M. Thompson, and B. Dhillon (2011). "Visual Neglect Following Stroke: Current Concepts and Future Focus". In: *Survey of Ophthalmology* 56.2.

Tu, Y., Z. Zhang, X. Gu, and Q. Fang (2016). "Surface electromyography based muscle fatigue analysis for stroke patients at different Brunnstrom stages". In: *Annual International Conference of the IEEE Engineering in Medicine and Biology Society.*

Twitchell, T. E. (1951). "The restoration of motor function following hemiplegia in man". In: *Brain* 74.4.

Van Der Vliet, R., R. W. Selles, E.-R. Andrinopoulou, R. Nijland, G. M. Ribbers, M. A. Frens, C. Meskers, and G. Kwakkel (2020). "Predicting Upper Limb Motor Impairment Recovery after Stroke: A Mixture Model". In: *Annals of Neurology* 87.3.

Veerbeek, J. M., A. C. Langbroek-Amersfoort, E. E. H. van Wegen, C. G. M. Meskers, and G. Kwakkel (2017). "Effects of Robot-Assisted Therapy for the Upper Limb After Stroke: A Systematic Review and Meta-analysis". In: *Neurorehabilitation and Neural Repair* 31.2.

Veerbeek, J. M., E. Van Wegen, R. Van Peppen, P. J. Van Der Wees, E. Hendriks, M. Rietberg, and G. Kwakkel (2014). "What Is the Evidence for Physical Therapy Poststroke? A Systematic Review and Meta-Analysis". In: *PLoS ONE* 9.2.

Veterans Affairs/Department of Defense, U. D. of (2024). *Management of Stroke Rehabilitation.* Tech. rep. U.S. Department of Veterans Affairs/Department of Defense.

Vidoni, E. D., N. E. Acerra, E. Dao, S. K. Meehan, and L. A. Boyd (2010). "Role of the primary somatosensory cortex in motor learning: An rTMS study". In: *Neurobiology of Learning and Memory.*

Vøllestad, N. K. (1997). "Measurement of human muscle fatigue". In: *Journal of Neuroscience Methods* 74.2.

Vromans, M. and P. D. Faghri (2018). "Functional electrical stimulation-induced muscular fatigue: Effect of fiber composition and stimulation frequency on rate of fatigue development". In: *Journal of Electromyography and Kinesiology* 38.

Ward, N. S., F. Brander, and K. Kelly (2019). "Intensive upper limb neurorehabilitation in chronic stroke: outcomes from the Queen Square programme". In: *Journal of Neurology, Neurosurgery & Psychiatry* 90.5.

Westerveld, A. J., A. C. Schouten, P. H. Veltink, and H. van der Kooij (2014). "Passive reach and grasp with functional electrical stimulation and robotic arm support". In: *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*.

Wiest, M. J., A. J. Bergquist, M. G. Heffernan, M. Popovic, and K. Masani (2019). "Fatigue and Discomfort During Spatially Distributed Sequential Stimulation of Tibialis Anterior". In: *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 27.8.

Winstein, C., R. Lewthwaite, S. R. Blanton, L. B. Wolf, and L. Wishart (2014). "Infusing Motor Learning Research Into Neurorehabilitation Practice: A Historical Perspective With Case Exemplar From the Accelerated Skill Acquisition Program". In: *Journal of Neurologic Physical Therapy* 38.3.

Winstein, C. and R. Varghese (2018). "Been there, done that, so what's next for arm and hand rehabilitation in stroke?" In: *NeuroRehabilitation* 43.1. Ed. by R. L. Harvey.

Winstein, C. J. et al. (2016). "Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association". In: *Stroke* 47.6.

Wolf, D., N. Dunkelberger, C. G. McDonald, K. Rudy, C. Beck, M. K. O'Malley, and E. Schearer (2017). "Combining functional electrical stimulation and a powered exoskeleton to control elbow flexion". In: *International Symposium on Wearable Robotics and Rehabilitation*.

World Health Organization (2001). *International Classification of Functioning, Disability and Health (ICF)*.

Woytowicz, E. J., J. C. Rietschel, R. N. Goodman, S. S. Conroy, J. D. Sorkin, J. Whitall, and S. McCombe Waller (2017). "Determining Levels of Upper Extremity Movement Impairment by Applying a Cluster Analysis to the Fugl-Meyer Assessment of the Upper Extremity in Chronic Stroke". In: *Archives of Physical Medicine and Rehabilitation* 98.3.

Wu, F.-C., Y.-T. Lin, T.-S. Kuo, J.-J. Luh, and J.-S. Lai (2011). "Clinical effects of combined bilateral arm training with functional electrical stimulation in patients with stroke". In: *IEEE International Conference on Rehabilitation Robotics*.

Zeiler, S. R. and J. W. Krakauer (2013). "The interaction between training and plasticity in the poststroke brain:" in: *Current Opinion in Neurology* 26.6.

Zhang, Q., M. Hayashibe, P. Fraisse, and D. Guiraud (2011). "FES-Induced Torque Prediction With Evoked EMG Sensing for Muscle Fatigue Tracking". In: *IEEE/ASME Transactions on Mechatronics* 16.5.

Appendix A

Associated publications

A.1 Proof of concept of hybrid robot- and FES-assisted training in unimpaired participants

Hybrid Robotic and Electrical Stimulation Assistance Can Enhance Performance and Reduce Mental Demand

Lucille Cazenave, *Member, IEEE*, Martin Einenkel, Aaron Yurkewich, *Member, IEEE*, Satoshi Endo, *Member, IEEE*, Sandra Hirche, *Fellow, IEEE*, and Etienne Burdet, *Member, IEEE*

***Abstract*— Combining functional electrical stimulation (FES) and robotics may enhance recovery after stroke, by providing neural feedback with the former while improving quality of motion and minimizing muscular fatigue with the latter. Here, we explored whether and how FES, robot assistance and their combination, affect users' performance, effort, fatigue and user experience. 15 healthy participants performed a wrist flexion/extension tracking task with FES and/or robotic assistance. Tracking performance improved during the hybrid FES-robot and the robot-only assistance conditions in comparison to no assistance, but no improvement is observed when only FES is used. Fatigue, muscular and voluntary effort are estimated from electromyographic recording. Total muscle contraction and volitional activity are lowest with robotic assistance, whereas fatigue level do not change between the conditions. The NASA-Task Load Index answers indicate that participants found the task less mentally demanding during the hybrid and robot conditions than the FES condition. The addition of robotic assistance to FES training might thus facilitate an increased user engagement compared to robot training and allow longer motor training session than with FES assistance.**

***Index Terms*— Neurorehabilitation, robotic assistance, functional electrical stimulation.**

Manuscript received 21 March 2023; revised 31 July 2023 and 11 September 2023; accepted 4 October 2023. Date of publication 10 October 2023; date of current version 20 October 2023. This work was supported in part by the United Kingdom Research and Innovation (UKRI) Centre for Doctoral Training (CDT) in Artificial Intelligence (AI) for Healthcare under Grant EP/S023283/1 and in part by the European Commission H2020 Project ReHyb under Grant ICT 871767. *(Corresponding author: Lucille Cazenave.)*

This work involved human subjects or animals in its research. Approval of all ethical and experimental procedures and protocols was granted by the Research Ethics Committee of Imperial College London under Approval No. 21IC6935, and performed in line with the Declaration of Helsinki.

Lucille Cazenave is with the Bioengineering Department and the UKRI Centre for Doctoral Training in AI for Healthcare, Imperial College of Science, Technology and Medicine, SW7 2AZ London, U.K. (e-mail: lucille.cazenave16@imperial.ac.uk).

Martin Einenkel, Satoshi Endo, and Sandra Hirche are with the Chair of Information-Oriented Control, Technical University of Munich, 80333 Munich, Germany (e-mail: martin.einenkel@tum.de; s.endo@tum.de; hirche@tum.de).

Aaron Yurkewich is with the Department of Automotive and Mechatronics Engineering, Ontario Tech University, Oshawa, ON L1G 0C5, Canada (e-mail: aaron.yurkewich@ontariotechu.ca).

Etienne Burdet is with the Bioengineering Department, Imperial College of Science, Technology and Medicine, SW7 2AZ London, U.K. (e-mail: e.burdet@imperial.ac.uk).

Digital Object Identifier 10.1109/TNSRE.2023.3323370

I. Introduction

STROKE is the most common neurological disorder in adults and results in upper-limb impairments in over 70% of post-stroke individuals [1], [2]. Rehabilitation is needed after stroke to help reduce disabilities but current services do not meet the patients' expectations in many areas, including reduction of arm impairment [3], [4] and less than 15% of them achieve complete functional recovery of the paretic arm at 6 months [5], [6]. There is thus a need to provide more efficient motor training and enhance recovery of upper-limb function. Technologies such as robotics and functional electrical stimulation (FES) have thus been introduced within the rehabilitation process to improve the outcomes.

FES has been used in this context to assist patients during training, by contracting the relevant muscles and stimulating the peripheral nerves. It can also strengthen neural pathways through orthodromic and antidromic neural activation [7]. Meta-analysis studies found that upper-limb motor function is improved after FES-based therapy in acute and chronic stroke patients [8], [9] and some studies also report improvements in activities of daily living (ADLs) [10], [11].

On the other hand, rehabilitation robots have been used to provide assistance during movement [12], [13], [14]. However, the literature suggests that upper-limb robotic-based training only slightly improves motor functions compared to conventional interventions [14], [15] and does not necessarily translate to improvement in ADLs [14], [15], [16], [17].

Although there is evidence that FES training is beneficial for upper-limb motor recovery, it can be uncomfortable, tiring, and usually does not produce strong and smooth motion [18], [19], [20], [21]. Could robotic systems be used to complement FES by providing power and mitigating discomfort and fatigue? Such hybrid system could help users perform smooth and well controlled limb motion. They would also provide a more complete sensorimotor experience than robotic training alone by eliciting additional mechanoreceptors and muscle activity through the stimulation, which may benefit functional recovery. Recently, novel hybrid controllers for upper-limb assistance have been developed, using model predictive control to distribute the actuation between both systems more optimally [22] and adaptive cooperative con-

© 2023 The Authors. This work is licensed under a Creative Commons Attribution 4.0 License.
For more information, see https://creativecommons.org/licenses/by/4.0/

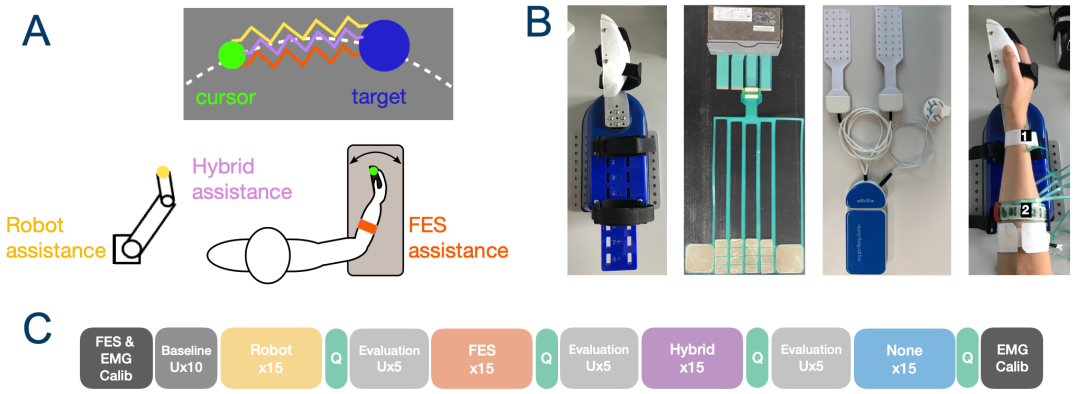


Fig. 1. Experiment description. **A.** Participants track a randomly moving target on-screen with wrist flexion/extension and receive four different assistance conditions: no assistance, robot-only assistance, FES-only assistance and hybrid (robot + FES) assistance. **B.** Hybrid robot-FES system (from left to right): HRX-1 wrist robotic device; FES device with 16-electrode array; EMG recording device with ground electrode and two high-density 32-channel electrode arrays; hybrid set-up where the FES anode electrode, shown as 1, is placed on the dorsal side of the wrist near the ulnar head and the cathode electrodes array, shown as 2, are around the arm inline with the wrist flexor and extensor muscle belly with the EMG electrodes placed distally. **C.** Overview of experimental protocol, where four assistance conditions were presented randomly to each participants: no assistance, FES-only assistance, robot-only assistance and hybrid assistance. Each block represents one trial of the target tracking task.

trol where FES-induced muscle fatigue is considered in the control loop [23], [24]. Although the results from these developments and preliminary testings are promising, most of these systems have not been tested with clinical populations and only report the effect of hybrid assistance on users' performance and motor torque reduction. Additionally, existing systems deployed in the stroke rehabilitation environment are relying on FES as the main means of assistance and using a robotic device only to promote gravitational support [25], [26], [27], [28], [29], [30], [31], [32], or to contribute to other joint motion than the one supported by FES [25], [26], [27].

To evaluate whether a system that combines robotic assistance and FES to the same joint motion can be truly useful to clinical populations, we first need to understand how each mode of assistance alters performance, motor behaviours, as well as user experience in a healthy cohort. To this end, we developed a simple one degree-of-freedom interface for wrist flexion/extension that can provide FES and robotic assistance, based on users' performance during the tracking of a moving target. The aim of this work was to explore whether and how FES, robot assistance, and their combination, alter users' performance, their physiological responses and their workload perception in a target tracking task, where continuous assistive feedback is required. More specifically, we investigated tracking performance, quality of motion, muscular and voluntary effort, fatigue and user experience. While we expected a general performance improvement with assistance, we also anticipated differences among the various modes. Here, we hypothesised that robotic assistance could lead to reduced fatigue and tracking error but also lower effort than FES. While we hypothesised that the combination of these two modalities would additively improve the tracking performance, we further explored how it would impact the resulting motor behaviours and physiological responses.

II. Methods

A. Participants

This study was approved by the Research Ethics Committee of Imperial College London (approval number: 21IC6935). 15 healthy participants (6 female) aged 27.8 ± 3.41 years old were recruited for this study. The participants signed an informed consent form and filled out a demographic questionnaire prior to participating in the experiment. 13 participants were right handed and two were left handed as was assessed using the Edinburgh Handedness Inventory [33].

B. Robotic Interface

The HRX-1 one degree-of-freedom wrist robotic interface (HumanRobotiX, UK) used in the study is shown in Fig. 1B. It is actuated by a brushless low friction motor, which delivers up to 4 Nm of torque and is controlled by the Epos4 70/15 motor controller (Maxon Motors, Switzerland). Torque measurement is provided by the embedded torque sensor (with 0.014 Nm resolution) and the user's wrist angle is recorded using the embedded optical encoder (0.01° resolution). The hand is attached to an ergonomic handle while the forearm is strapped to an adjustable arm support to ensure joint alignment. The robot is programmed in Matlab and ran at a frequency of approximately 100 Hz.

C. FES System

The CLASS V1.0 FES device 16-electrode array (Tecnalia Research & Innovation, Spain) was used (Fig. 1B), and controlled remotely via Bluetooth communication. A hydrogel layer is placed on the electrodes to improve the conductivity of the array with the skin and additional Velcro straps are positioned around the electrodes to tighten the array around the forearm. The anode electrode is positioned on the dorsal side of the wrist near the ulnar head and the cathode array is positioned around the arm inline with the belly

of the wrist flexor and extensor muscles for comfortable and effective stimulation (Fig. 1B). The frequency of the stimulation is set to 35 Hz and the pulse width to 300 μs as these values are used clinically [34]. The amplitude of the stimulation varies (with 1 mA resolution) during the experiment.

D. EMG Recording

Muscle activity is recorded using two 32-channel EMG electrode arrays (GR10MM0804, OT Bioelettronica, Italy) with a Sessantaquattro amplifier (OT Bioelettronica, Italy) (Fig. 1B). We used two electrode arrays that covered the forearm proximally to the FES electrodes (Fig. 1B), which recorded the activity in muscles such as the extensor carpi radialis longus, the extensor digitorum, the flexor carpi radialis and the flexor digitorum superficialis. The EMG data is sampled at 2000 Hz and stored on a PC for analysis.

E. Experiment Task

The participants tracked a moving target on a computer monitor placed in front of them using wrist flexion/extension movements of the right hand while being assisted by a robot or FES (Fig. 1A). The target trajectory was defined as:

$$q^*(t) = 38.6^\circ \sin\left[2.0308(t^+)\right] \sin\left[1.0927(t^+)\right] \quad (1)$$

where $t^+ = t + t_0$, t is the elapsed time and t_0 is the starting time. q^* is the target angle. The target was programmed and updated in Matlab and $t_0 \in \{0, 3.094, 14.375\}$ s was randomly selected every trial to minimise prediction of the target trajectory by the participants. Participants were instructed to track the target as accurately as possible and told that they may feel haptic interaction from the robot and/or electrical stimulation.

F. FES and EMG Calibration

An *FES calibration* was performed at the start of the experiment. Two cathode electrodes within the cathode array are selected to generate the flexion movements and two other cathode electrodes for the extension movements. The electrode location and corresponding maximum stimulation are selected individually for the flexion and extension side, such that the stimulation is comfortable and the generated movement covers the participant's full range of motion. The FES amplitude is capped at the maximum comfortable stimulation determined by the user for the flexion s_f^{max} and extension movements s_e^{max}. The torque generated by each of these stimulation amplitudes while the participant is relaxed is also recorded as τ_f^{max} and τ_e^{max}. The minimum FES amplitude is defined as the participant's sensory threshold through self-report, individually for the flexor stimulation s_f^{min} and the extensor stimulation s_e^{min}. We assume a linear mapping between the stimulation amplitude s_f and s_e and the produced torque τ_f and τ_e for amplitudes above s_f^{min} and s_e^{min} for the flexion and extension movements respectively [35] such that:

$$\tau_f(t) = \alpha_s\, s_f(t) \quad \tau_e(t) = \alpha_s\, s_e(t) \quad (2)$$

with the linear coefficient α_s defined as:

$$\alpha_s = \frac{s_f^{max} - s_f^{min}}{\tau_f^{max}} \quad (3)$$

An *EMG calibration* was then performed to obtain a measure of effort, by linearly regressing muscle activity with torque produced during isometric contraction. During this calibration, participants were asked to resist each of the four increasing torque levels: $\{0.4, 0.8, 1.2, 1.7\}$ Nm during 2.5 s in flexion and extension at the fixed angle q $= 30^\circ$. This was repeated four times with a 3 s rest in between to prevent fatigue.

G. Control of Robot-FES System

The task considered in this study is a continuous target tracking task with a pseudo-random trajectory, that requires continous assistive feedback. Therefore, the torque exerted on the wrist flexion/extension by the robot is described as:

$$u_r(t) = K_r\, e(t) \quad e(t) = q(t) - q^*(t) \quad (4)$$

where $e(t)$ is the tracking error between the participant's trajectory q and the target trajectory q^*. The robot control stiffness $K_r = 0.0097$ Nm/° corresponds to a soft-middle interaction stiffness [13]. It has been selected after preliminary testings in order to observe tracking improvement with assistance, while preventing slacking.

The stimulation amplitude provided to the wrist flexor or extensor is described as:

$$s(t) = \begin{cases} s_e(t) = -K_s\, e(t) + s_e^{min} & e(t) < 0 \\ s_f(t) = K_s\, e(t) + s_f^{min} & e(t) > 0 \end{cases} \quad (5)$$

where $s_e(t)$ refers to an extensor muscle stimulation and $s_f(t)$ a flexor muscle stimulation. K_s (in mA/°) is the FES control stiffness and is the same for the extensor and flexor stimulation in order to match the robot assistance behaviour. It is defined from the linear mapping α_s between the FES amplitude and torque ranges of the flexor as it was found to be more comfortable during preliminary tests:

$$K_s = \alpha_s\, K_r \quad (6)$$

The four assistance conditions of the experiment are defined as follows: {hybrid, robot ($s_e \equiv 0, s_f \equiv 0$), FES ($u_r \equiv 0$), no assistance ($s_e \equiv 0, s_f \equiv 0$ and $u_r \equiv 0$)}. In the hybrid condition, participants receive the same robot assistance as in the robot condition as well as the same FES assistance as in the FES condition.

H. Protocol

The experimental protocol is outlined in Fig. 1C. The experiment started with an FES and EMG calibration as detailed in Section II-F. This EMG calibration was also carried out at the end of the experiment to examine potential changes in muscle activity due to fatigue. The participants first completed ten trials of the trajectory tracking task without assistance.

They then completed four blocks of the trajectory tracking task, each block using one of four conditions of assistance: {hybrid, robot, FES and no assistance}. The conditions were presented in random order, with each block containing 15 trials consisting of 15 s of target tracking and a 3 s rest. Each block was followed by a questionnaire (see Appendix) that evaluated the workload with the NASA-TLX ten-point ordinal Likert Scale [36] and the comfort and usefulness of the stimulation and robot torques using five-point ordinal Likert Scale questions [37]. Subsequently, a block of five trajectory tracking trials with no assistance was performed, including a first washout trial and four evaluation trials.

I. Performance Analyses

Task performance was quantified by the Root Mean Square Error (RMSE) [°] between the target trajectory $q^*(t)$ and the participant's trajectory $q(t)$: $\sqrt{\frac{1}{T}\int_0^T e(t)^2\,dt}$, $T = 15\,s$. Other metrics were used to quantify the participant's performance more specifically. The time delay [s], tracking error due to a temporal shift between the target's and participant's trajectories, was calculated using the cross-correlation between the two trajectories. Smoothness, quantified with the SPARC (Spectral Arc Length) metric, was also explored as it is a marker of the quality of sensorimotor control, often impaired after stroke [38]. Understanding how each assistance condition affects motion smoothness in healthy individuals is relevant for later application to stroke rehabilitation, where smoothness is linked with functional recovery [39]. A SPARC value closer to zero corresponds to a smoother motion.

J. Effort and Fatigue

Fatigue and effort during the task were estimated using recorded EMG signals of the flexor and extensor muscles from the participants. Mains noise was attenuated using a Notch filter (Matlab function $iirnotch$ with notch at 50 Hz). A low-pass and high-pass second order Butterworth filters (with cut-off frequencies $f_c = 10$ Hz and $f_c = 500$ Hz, respectively) were applied in the forward and reverse directions. The EMG signal was rectified and the envelope was obtained using a low-pass second order Butterworth filter with cut-off frequency $f_c = 5$ Hz. The channel on the extensor and flexor arrays with the highest envelope amplitude during the EMG calibration were used for the following analyses. For both time-domain effort metrics, the torque-normalised EMG signal was used. The torque-muscle activity relationship was obtained by linearly regressing the envelope of the fully-rectified EMG during the EMG calibration procedure with the corresponding torque.

Fatigue was estimated by computing the median frequency of the filtered EMG signal [40]. A decrease in EMG median frequency corresponds to an increase in fatigue. The EMG frequency during the EMG calibration at the start and end of the experiment, and across conditions were compared. For the latter, the median frequency was averaged for the last four trials of the previous and following evaluation blocks and their difference was taken to quantify fatigue changes.

For the muscular effort metric, the EMG signal containing both the FES-induced muscle activity, i.e. the evoked M-wave, and the volitional activity were considered. Although the evoked M-wave is not a voluntary contribution, it is resulting in the recruitment of motor units leading to muscle contraction, as with volition. We used a Hampel filter, where outliers away by 1.5 standard deviations from the median of 30 surrounding samples are replaced by that median; this filtered the FES artefacts. The envelope of the signal was obtained and the total effort was evaluated from the mean amplitude of the envelope of the torque-normalised EMG signal, averaged across trials. Muscular effort levels during the EMG calibration at the start and end of the experiment were compared as well as during each training condition.

The volitional contribution was also considered as it can inform about the effect of each modality on user engagement, which is relevant for stroke rehabilitation. Adaptive filters can be used to filter the EMG corrupted by the FES artifact and the M-wave contribution [35], [41], [42]. In this work, we used an adaptive filter designed for EMG-based torque estimation under stimulation of wrist flexor and extensor with the same setup as here [35]. The torque-normalised EMG was obtained from the envelope of this signal, and averaged across trials.

K. Statistical Analysis

For the comparison of performance metrics, effort, fatigue levels and questionnaire answers between the conditions, we used a one-way repeated measures ANOVA or a non-parametric Friedman test when the data was not normally distributed. A one-sample Shapiro-Wilk test was used to test the null hypothesis that the data comes from a normal distribution. Post-hoc paired sample t-tests or paired Wilcoxon sign-rank tests were used for comparisons of performance metrics, effort and fatigue levels and questionnaire answers between each condition, controlling for the family-wise error rate with Bonferroni-Holm correction. For the comparison of the fatigue level before and after the experiment, a paired Wilcoxon sign-rank test was used as data was not normally distributed. Similarly, for questions comparing the FES and hybrid conditions, and the hybrid and robot conditions, paired Wilcoxon sign-rank tests were used. For the statistical analysis of performance, effort and fatigue metrics, the average across trials in one condition was calculated for each participant. In the box plot figures, the whisker lines above and below the box indicate the 1.5 interquartile range. Outliers are displayed by a red + sign. Comparisons not shown are not significant.

III. Results

A. Performance Results

The assistance condition affects participants' tracking performance ($F(3, 56) = 20.38$, $p < 0.001$). RMSE is smaller with hybrid or robot assistance relative to the no assistance and FES conditions (all $p < 0.001$) (Fig. 2A). There is no significant difference between hybrid assistance and robot assistance

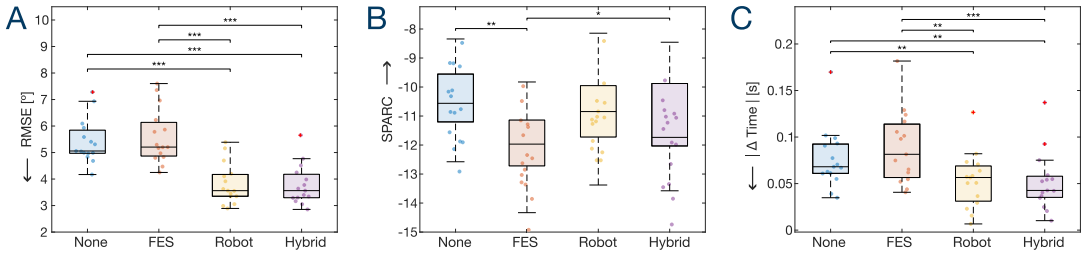


Fig. 2. Performance, motor adaptation and quality of motion metrics during the tracking task with four different assistance conditions. (A) Tracking performance indicated by the Root Mean Square Error (RMSE). (B) Smoothness of participant's trajectory, evaluated using Spectral Arc Length (SPARC) [38]. A SPARC value closer to zero corresponds to a smoother motion. (C) Time Delay indicates the temporal shift between the target's and participant's trajectories. $*: p < 0.05, **: p < 0.01, ***: p < 0.001$. Comparisons not shown are not significant.

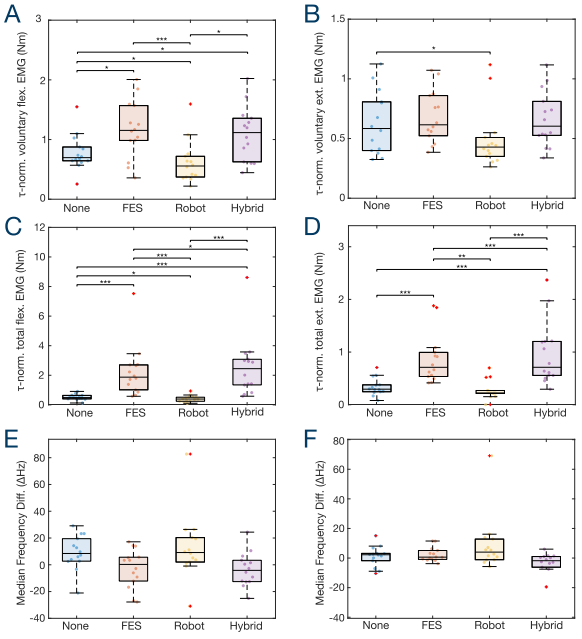


Fig. 3. Voluntary effort (A,B), muscular effort (C,D) and changes in muscle fatigue (E,F) during the tracking task assisted with four different assistance conditions. The effort metrics are estimated as the mean envelope amplitude of the torque-normalised EMG signal. Fatigue is obtained from the median frequency of the EMG signal, a decrease in frequency indicates increased fatigue. (A) Voluntary effort in the flexor muscles. (B) Voluntary effort in the extensor muscles. (C) Total muscular effort in the flexor muscles (including M-wave contribution). (D) Total muscular effort in the extensor muscles (including M-wave contribution). (E) Fatigue changes in the flexor muscles. (F) Fatigue changes in the extensor muscles. $*: p < 0.05, **: p < 0.01, ***: p < 0.001$. Comparisons not shown are not significant.

($p = 0.74$). The effect of assistance condition on smoothness was also investigated ($F(3, 56) = 3.82$, $p = 0.015$) and results indicate that FES assistance leads to decreased smoothness compared to the hybrid condition ($p < 0.05$) but other differences are not significant (all $p > 0.075$) (Fig. 2B). The hybrid and robot assistance also reduce time delays compared to none and FES conditions (all $p < 0.01$) and there is no statistical difference between the hybrid and the robot conditions ($p = 0.93$) (Fig. 2C). When investigating performance improvement on evaluation trials before and after each assistance condition, we do not find statistical differences ($F(3, 56) = 0.37$, $p = 0.77$) (Appendix, Fig. 6).

B. Effort and Fatigue

The EMG recording for one participant was corrupted and thus EMG-based metrics are reported as $N = 14$. When comparing the total level of muscle activity in the flexor muscles during the assisted tracking task ($\chi^2(3) = 37.46$, $p < 0.001$) (Fig. 3C), we find that it is lower with robot assistance compared to all other assistance conditions ($p < 0.001$ with FES and hybrid and $p < 0.05$ with none). Higher muscular effort is observed in the FES and hybrid assistance compared to no assistance, with higher muscle activity in the hybrid condition ($p < 0.05$ with FES). Similar trends are found for the extensor muscles ($\chi^2(3) = 24.26$, $p < 0.001$) (Fig. 3D), although there is no statistical difference between the robot and no assistance conditions ($p = 0.90$) and total muscle activity is highest in the hybrid condition ($p < 0.001$ with FES).

Regarding the voluntary effort (Fig. 3A, B), similar trends are found in the flexor muscle ($\chi^2(3) = 25.00$, $p < 0.001$), where higher volition is observed in the FES and hybrid assistance conditions, while these differences are not present in the extensor muscle ($\chi^2(3) = 16.54$, $p < 0.001$). The voluntary contribution is similar in the FES and hybrid conditions for both flexor ($p = 0.46$) and extensor muscles ($p = 0.53$). In the robot condition, the volitional contraction is lowest ($p < 0.05$ with none in flexor and extensor muscles).

Regarding fatigue, we observe that the median frequency of the flexor muscle activity increases in the none and robot conditions, suggesting muscle recovery and does not change after the FES and hybrid condition when looking at the mean (Fig. 3E). These differences are not as clear in the extensor muscles (Fig. 3F). The comparison of the change in muscle fatigue between conditions is not statistically different for the flexor ($\chi^2(3) = 5.40$, $p = 0.15$) or the extensor ($\chi^2(3) = 7.71$, $p = 0.052$)). No statistical differences are found when comparing muscle fatigue before and after the experiment during the EMG calibration (Appendix, Fig. 7).

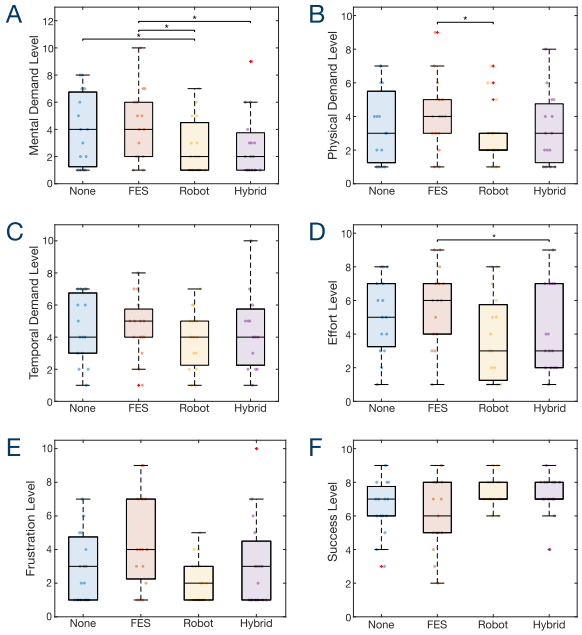


Fig. 4. Answers to the 10-point NASA-TLX questionnaires on perceived workload after the trajectory tracking task with four different assistance conditions, with answers from very low (1) to very high (10). $*: p < 0.05$. Comparisons not shown are not significant.

C. Questionnaire Answers

The answers to the NASA-TLX questions are shown in Fig. 4. The assistance type affected participants' mental demand ($\chi^2(3) = 16.18$, $p = 0.001$) (Fig. 4A). It is lower in the robot and the hybrid conditions in comparison with the no assistance and FES assistance conditions ($p < 0.05$). Participants also perceived the lowest physical demand in the robot condition, but this difference is statistically significant only with respect to the FES condition ($p < 0.05$) (Fig. 4B). Moreover, participants indicated that their effort was lowest in the robot and hybrid conditions and the latter is significantly different from the FES condition ($p < 0.05$) (Fig. 4D). Their frustration level during the assisted task was lower in the hybrid and robot assistance conditions than in the FES condition but differences are not statistically significant ($\chi^2(3) = 7.68$, $p = 0.053$) (Fig. 4E). The responses to the statement "The electrical stimulation was comfortable" are similar in the hybrid and FES conditions ($p = 0.94$) but participants thought that their performance increased thanks to the stimulation with the hybrid assistance but not with FES only, although this difference is not statistically significant ($p = 0.57$) (Fig. 5). The robotic forces were rated as comfortable and useful in both the hybrid and robot conditions.

IV. Discussion

Literature suggests that adding FES to robotic assistance could improve motor recovery during stroke rehabilitation. However, there is a need to understand how FES and robotic assistance alter performance, physiological measures and subjective experience, such that the benefits of these modalities can be fully exploited for clinical applications. This work thus used a simple wrist flexion/extension interface to explore these aspects in healthy participants in a target tracking task, requiring continuous assistance FES and robot assistance proportional to the tracking error.

Performance and quality of motion increases when robotic assistance is present. Tracking performance is higher when participants receive hybrid and robot assistance compared to no assistance or FES assistance. Hybrid assistance does not improve tracking performance more than robot assistance. We find that the assistance modes improve tracking performance except the FES assistance alone. However, it is not disturbing participants' performance, even though we used a simple controller. On the other hand, we expected that the additive effect of FES and robotic assistance would further improve performance, even though the goal of the hybrid controller was not focused on improving tracking performance but rather made simple to investigate the effects of assistance. The stimulation thus does not seem to contribute to performance improvement in the hybrid condition. These observations could be extended to the use of more advanced strategies, where the goal is to optimise for control objectives such as tracking performance or learning. However, few studies have tested other strategies to assist users in ADLs, such as shared control approaches, where the action of one modality has knowledge of the other, and similarly they did not always find performance improvements in the hybrid compared to the robot-only condition [22], [23].

In this work, we additionally investigated the effect of each modality and their combination on various quality of motion metrics. We found that participants' movements are smoother with the hybrid assistance than with the FES assistance and there is no significant difference in movement smoothness in the hybrid, robot and no assistance conditions. We see similar trends for other objective metrics, such as time delay and under/overshoot. Adding FES to a robotic-based assistive device thus does not impede motion quality in our experiment, even though the controller used is simple and does not account for the delay between the trigger of the stimulation and the resulting muscle contraction (e.g. 10-140ms [7], [43]). It is useful to understand how smoothness is affected by different assistive modalities as it captures motor control abilities which are affected in stroke population, and is linked with functional recovery [39], [44]. Furthermore, this analysis can then be used as a reference to later interpret data from stroke patients performing similar tasks with these assistance modes. In the hybrid context, it can also be used to inform on the assisted motion quality and as an indicator of possible counteracting effects between the stimulation and robot torque [45]. As no difference was found in participants' smoothness during the no-assistance and hybrid conditions, it seems that the electromechanical delay did not affect participants' motion.

Total muscular effort is higher when stimulation is applied while it does not induce more fatigue, and voluntary effort is lowest in the robot-only condition. The amount of muscular effort, quantified by the total level of muscle activity, both from the stimulation-induced M-wave and the voluntary

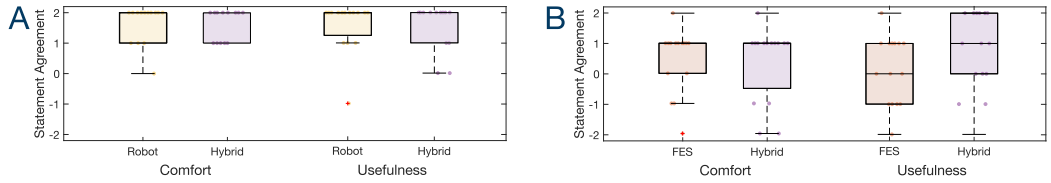


Fig. 5. Answers from a 5-point ordinal Likert scale questionnaire on comfort (**A** and **C**) and usefulness (**B** and **D**) of robotic force (top row) and electrical stimulation (bottom row) after trajectory tracking with four different assistance conditions. Agreement level from 'Strongly Agree' (2) to 'Strongly Disagree' (−2) was provided for each statement.

contribution, is generally higher in the conditions with electrical stimulation (FES and hybrid) compared to the other two conditions; this is due to the M-wave contribution of the stimulation. Although it is common to disregard the M-wave and only investigate the voluntary contribution, we chose to also explore the total EMG activity as the stimulation also leads to the activation of motor units and thus affects the characteristics of the muscles [46].

We also observe that voluntary effort is lowest in the robot condition. This suggests the potential value of integrating FES assistance into robotic-based therapy as it leads to increased total muscle contraction but also higher voluntary contribution, thus enhancing user engagement which could potentially promote recovery in stroke patients. Additionally it could prevent slacking that seems to occur here when robot-only assistance is provided. On the other hand, we find that the total muscular effort is higher in the hybrid than in the FES condition. This could be due to the electromechanical delay between the stimulation and the resulting muscle contraction, which is not present when a robotic torque is applied to the handle. In some cases the stimulation could lead to overshooting of the trajectory although the target is already moving towards the other direction. Although we do not see a difference in performance and smoothness between the robot and hybrid condition, it might be that the two assisting systems are counteracting each other, which could cause increased muscle activity level for the user to drive the handle in the desired direction. Similarly, the higher voluntary contribution of the flexor muscles in the hybrid and FES conditions could be a consequence of a counteraction between the user's intention and the delayed contraction resulting from the stimulation. These trends were observed in another hybrid training study with stroke patients where EMG activation levels in the flexors and extensors were lower with FES compared to hybrid assistance [47]. Models of the muscle response to electrical stimulation are available and could be incorporated as a feedforward element to the existing controller to ensure muscle contraction resulting from FES occurs in a similar time range as the robotic torque assistance for the motion to be produced [48], [49], [50], [51]. Recent works have also targeted the development of controllers to reduce the effect of the electromechanical delay of the stimulation [52], [53], which would lead to a better alignment of the motion resulting from the two actuation systems. However, these approaches for delay compensation are not considering the time-varying nature of the electromechanical delay [43], and are applied to cyclic gait motion or to the tracking of pre-determined trajectories, hence they would not be suitable for this pseudo-random tracking task.

Regarding fatigue, there are no significant changes before and after the experiment in the flexor and extensor muscles. Neither do we find that the FES and hybrid conditions lead to higher fatigue than the other conditions when investigating fatigue changes for each condition individually. Although FES is commonly described as fatiguing, we do not find such trends in these healthy participants who performed a task that is not physically demanding – average rating below 4 for all conditions in the 10-point NASA-TLX questionnaire. This could be in part due to the dynamic nature of the task, which did not require sustained stimulation, as well as the relatively short duration of each trial and training block. FES is also mostly used and evaluated in clinical populations, where rehabilitation activities that make use of FES assistance can require higher stimulation amplitudes and training duration than these able-bodied individuals were prescribed. Moreover, the response to stimulation amplitudes and duration might be different in healthy participants who already have the capacity to move and stroke patients who may have weakness and lack the ability to contract their muscles as intended.

Mental demand is rated as lowest in the hybrid and robot conditions. The NASA-TLX questionnaire answers also indicate that in this study, participants did not feel more frustrated when training with FES or hybrid assistance compared to robot or no assistance. The electrical stimulation was rated as comfortable on average but participants perceived that the stimulation in the hybrid assistance was more useful in improving their performance than in the FES condition. This finding resonates with the tracking error results, where performance in the hybrid condition is higher than in the FES condition, although this increase might not be due to the stimulation directly. Robot-assisted training is perceived as the least physically demanding, but is only significantly different to FES-assisted training, whereas the effort is perceived significantly lower in hybrid than FES conditions. Indeed, the effort rating could be considered by users as a compound of mental and physical demand [54], and here mental demand is rated lower in the hybrid and robot conditions.

These answers only partly translate to the physiological differences on voluntary effort that we observe, where in the flexor muscles, we do find differences between most conditions. Although previous studies have found relationships between task difficulty, NASA-TLX ratings and muscle activity amplitude, these were investigated in more demanding

and tiring tasks such as repairing a pump gearbox [55], controlling traffic density [56], and performing surgical procedures [57]. For instance in the repair task, the complex task resulted in significantly higher physical demand ratings and EMG levels compared to the simple task, with a significant correlation between these two metrics [55]. The average physical demand rating of this task was higher than 6, whereas our target tracking task was rated below 4 on average in all conditions. The absence of consistent findings between physical demand ratings and EMG levels in our work could be explained by the low demand of the target tracking task we investigated. The results from the subjective workload assessment motivate the use of hybrid assistance for motor training: although total muscle activity level is higher than with FES assistance, perceived effort is lower, which could lead to longer and more enjoyable training. On the other hand, hybrid and robot assistance are rated as less mentally demanding than FES and they are not significantly different from each other. The trends observed in these answers seem to follow those of the tracking performance, which suggests that they could be related. This is in agreement with previous motor task studies investigating the relationship between mental load and motor performance [58], [59]. This indicates that using hybrid assistance could reduce mental demand, thus enhancing user experience.

V. Conclusion

The present study explores how FES and robot assistance and their combination affects performance, effort, fatigue and user experience in a wrist target tracking task. The results suggest that the addition of the two modalities in a hybrid device reduces mental demand while increases performance compared to FES assistance only and could prevent slacking, occuring during robot-only training. Future work will aim at testing the efficacy of this hybrid device in stroke patients, where training benefits of hybrid rehabilitation technologies could be observed.

Appendix I
Additional Figures

See Figs. Fig. 6 and Fig. 7

Appendix II
Questionnaire

- What is your level of muscle fatigue? (1 = fatigued; 10 = not fatigued)
- What is your level of mental fatigue? (1 = fatigued; 10 = not fatigued)
- How mentally demanding was the task? (1 = very low; 10 = very high)
- How physically demanding was the task? (1 = very low; 10 = very high)
- How hurried or rushed was the pace of the task? (1 = very low; 10 = very high)
- How successful were you in accomplishing what you were asked to do? (1 = very bad; 10 = very good)

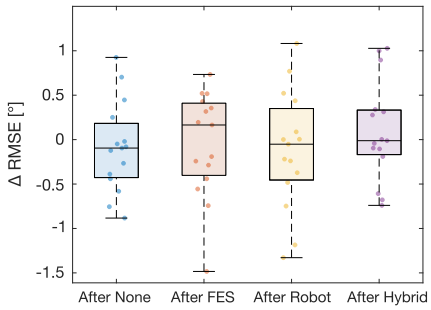


Fig. 6. Motor adaptation during the tracking task with four different assistance conditions. Tracking performance improvement indicates the difference in participant's tracking performance before and after training; a positive result indicates that they are performing better after training.

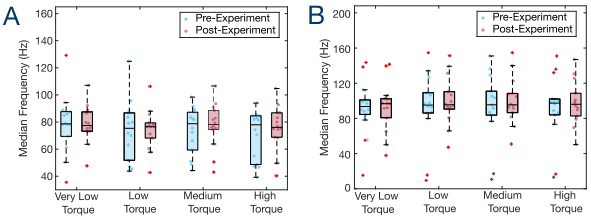


Fig. 7. Muscle fatigue was evaluated during the EMG calibration at the start and end of the experiment, where participants had to track four different levels of torque. Fatigue is calculated as the median frequency of the EMG signal, a decrease in frequency indicates an increased fatigue. Level of fatigue for (A) the flexor muscles and (B) the extensor muscles.

- How hard did you have to work to accomplish your level of performance? (1 = very low; 10 = very high)
- How insecure, discouraged, irritated, stressed, and annoyed were you? (1 = very low; 10 = very high)
- The forces were comfortable. (from 'strongly disagree' to 'strongly agree')
- The forces improved my performance. (from 'strongly disagree' to 'strongly agree')
- The electrical stimulation was comfortable. (from 'strongly disagree' to 'strongly agree')
- The electrical stimulation improved my performance. (from 'strongly disagree' to 'strongly agree').

Acknowledgment

The authors would like to thank Thierry Keller and Igone Idigoras Leibar and their team in the Neuroengineering Department of TECNALIA Research & Innovation for developing the electrical stimulator and electrodes and their assistance during the implementation of the FES control algorithm and also would like to thank Nuria Peña-Pérez and Dr. Hristo Dimitrov for their advice on EMG set-up and analysis.

References

[1] H. Nakayama, H. S. Jørgensen, H. O. Raaschou, and T. S. Olsen, "Recovery of upper extremity function in stroke patients: The Copenhagen stroke study," *Arch. Phys. Med. Rehabil.*, vol. 75, no. 4, pp. 394–398, Apr. 1994.

[2] E. S. Lawrence et al., "Estimates of the prevalence of acute stroke impairments and disability in a multiethnic population," *Stroke*, vol. 32, no. 6, pp. 1279–1284, Jun. 2001.

[3] T. Chen, B. Zhang, Y. Deng, J.-C. Fan, L. Zhang, and F. Song, "Long-term unmet needs after stroke: Systematic review of evidence from survey studies," *BMJ Open*, vol. 9, no. 5, May 2019, Art. no. e028137.

[4] A. Cieza, K. Causey, K. Kamenov, S. W. Hanson, S. Chatterji, and T. Vos, "Global estimates of the need for rehabilitation based on the global burden of disease study 2019: A systematic analysis for the global burden of disease study 2019," *Lancet*, vol. 396, no. 10267, pp. 2006–2017, Dec. 2020.

[5] D. T. Wade, R. Langton-Hewer, V. A. Wood, C. E. Skilbeck, and H. M. Ismail, "The hemiplegic arm after stroke: Measurement and recovery," *J. Neurol., Neurosurgery Psychiatry*, vol. 46, no. 6, pp. 521–524, Jun. 1983.

[6] G. Kwakkel, B. J. Kollen, J. van der Grond, and A. J. H. Prevo, "Probability of regaining dexterity in the flaccid upper limb: Impact of severity of paresis and time since onset in acute stroke," *Stroke*, vol. 34, no. 9, pp. 2181–2186, Sep. 2003.

[7] C. L. Lynch and M. R. Popovic, "Functional electrical stimulation," *IEEE Control Syst. Mag.*, vol. 28, no. 2, pp. 40–50, Apr. 2008.

[8] O. A. Howlett, N. A. Lannin, L. Ada, and C. McKinstry, "Functional electrical stimulation improves activity after stroke: A systematic review with meta-analysis," *Arch. Phys. Med. Rehabil.*, vol. 96, no. 5, pp. 934–943, May 2015.

[9] J. Eraifej, W. Clark, B. France, S. Desando, and D. Moore, "Effectiveness of upper limb functional electrical stimulation after stroke for the improvement of activities of daily living and motor function: A systematic review and meta-analysis," *Systematic Rev.*, vol. 6, no. 1, p. 40, Feb. 2017.

[10] T. A. Thrasher, V. Zivanovic, W. McIlroy, and M. R. Popovic, "Rehabilitation of reaching and grasping function in severe hemiplegic patients using functional electrical stimulation therapy," *Neurorehabilitation Neural Repair*, vol. 22, no. 6, pp. 706–714, Nov. 2008.

[11] M. B. Popovic, D. B. Popovic, T. Sinkjær, A. Stefanovic, and L. Schwirtlich, "Restitution of reaching and grasping promoted by functional electrical therapy," *Artif. Organs*, vol. 26, no. 3, pp. 271–275, Mar. 2002.

[12] G. Ganesh, A. Takagi, R. Osu, T. Yoshioka, M. Kawato, and E. Burdet, "Two is better than one: Physical interactions improve motor performance in humans," *Sci. Rep.*, vol. 4, no. 1, p. 3824, Jan. 2014.

[13] E. Ivanova, G. Carboni, J. Eden, J. Krüger, and E. Burdet, "For motion assistance humans prefer to rely on a robot rather than on an unpredictable human," *IEEE Open J. Eng. Med. Biol.*, vol. 1, pp. 133–139, 2020.

[14] R. Bertani, C. Melegari, M. C. De Cola, A. Bramanti, P. Bramanti, and R. S. Calabrò, "Effects of robot-assisted upper limb rehabilitation in stroke patients: A systematic review with meta-analysis," *Neurological Sci.*, vol. 38, no. 9, pp. 1561–1569, Sep. 2017.

[15] J. M. Veerbeek et al., "Effects of robot-assisted therapy for the upper limb after stroke: A systematic review and meta-analysis," *Neurorehabil. Neural Repair*, vol. 31, no. 2, pp. 107–121, 2017.

[16] H. Rodgers et al., "Robot assisted training for the upper limb after stroke (RATULS): A multicentre randomised controlled trial," *Lancet*, vol. 394, no. 10192, pp. 51–62, Jul. 2019.

[17] J. Mehrholz, A. Pollock, M. Pohl, J. Kugler, and B. Elsner, "Systematic review with network meta-analysis of randomized controlled trials of robotic-assisted arm training for improving activities of daily living and upper limb function after stroke," *J. NeuroEngineering Rehabil.*, vol. 17, no. 1, p. 83, Dec. 2020.

[18] A. S. Gorgey, C. D. Black, C. P. Elder, and G. A. Dudley, "Effects of electrical stimulation parameters on fatigue in skeletal muscle," *J. Orthopaedic Sports Phys. Therapy*, vol. 39, no. 9, pp. 684–692, Sep. 2009.

[19] N. A. Maffiuletti, "Physiological and methodological considerations for the use of neuromuscular electrical stimulation," *Eur. J. Appl. Physiol.*, vol. 110, no. 2, pp. 223–234, Sep. 2010.

[20] N. Miura and T. Watanabe, "Potential of M-wave elicited by double pulse for muscle fatigue evaluation in intermittent muscle activation by functional electrical stimulation for motor rehabilitation," *J. Med. Eng.*, vol. 2016, Mar. 2016, Art. no. 6957287.

[21] Q. Zhang, M. Hayashibe, P. Fraisse, and D. Guiraud, "FES-induced torque prediction with evoked EMG sensing for muscle fatigue tracking," *IEEE/ASME Trans. Mechatronics*, vol. 16, no. 5, pp. 816–826, Oct. 2011.

[22] N. Dunkelberger, J. Berning, E. M. Schearer, and M. K. O'Malley, "Hybrid FES-exoskeleton control: Using MPC to distribute actuation for elbow and wrist movements," *Frontiers Neurorobotics*, vol. 17, Apr. 2023, Art. no. 1127783.

[23] D. Burchielli et al., "Adaptive hybrid FES-force controller for arm exosuit," in *Proc. Int. Conf. Rehabil. Robot. (ICORR)*, Jul. 2022, pp. 1–6.

[24] E. Bardi et al., "Adaptive cooperative control for hybrid FES-robotic upper limb devices: A simulation study," in *Proc. EMBC*, 2021, pp. 6398–6401.

[25] F. Resquín et al., "Hybrid robotic systems for upper limb rehabilitation after stroke: A review," *Med. Eng. Phys.*, vol. 38, no. 11, pp. 1279–1288, Nov. 2016.

[26] G. Alon, K. Sunnerhagen, A. Geurts, and A. Ohry, "A home-based, self-administered stimulation program to improve selected hand functions of chronic stroke," *NeuroRehabilitation*, vol. 18, pp. 25–215, Sep. 2003.

[27] K. L. Meadmore et al., "Functional electrical stimulation mediated by iterative learning control and 3D robotics reduces motor impairment in chronic stroke," *J. NeuroEngineering Rehabil.*, vol. 9, no. 1, p. 32, 2012.

[28] T. Fujiwara et al., "Motor improvement and corticospinal modulation induced by hybrid assistive neuromuscular dynamic stimulation (HANDS) therapy in patients with chronic stroke," *Neurorehabilitation Neural Repair*, vol. 23, no. 2, pp. 125–132, Feb. 2009.

[29] R. N. Barker, S. G. Brauer, and R. G. Carson, "Training of reaching in stroke survivors with severe and chronic upper limb paresis using a novel nonrobotic device," *Stroke*, vol. 39, no. 6, pp. 1800–1807, Jun. 2008.

[30] E. Ambrosini et al., "A robotic system with EMG-triggered functional eletrical stimulation for restoring arm functions in stroke survivors," *Neurorehabilitation Neural Repair*, vol. 35, no. 4, pp. 334–345, Apr. 2021.

[31] F.-C. Wu, Y.-T. Lin, T.-S. Kuo, J.-J. Luh, and J.-S. Lai, "Clinical effects of combined bilateral arm training with functional electrical stimulation in patients with stroke," in *Proc. IEEE Int. Conf. Rehabil. Robot.*, Jun. 2011, pp. 1–7.

[32] F. Resquín, J. Gonzalez-Vargas, J. Ibáñez, F. Brunetti, and J. L. Pons, "Feedback error learning controller for functional electrical stimulation assistance in a hybrid robotic system for reaching rehabilitation," *Eur. J. Translational Myology*, vol. 26, no. 3, p. 6164, Jul. 2016.

[33] R. C. Oldfield, "The assessment and analysis of handedness: The Edinburgh inventory," *Neuropsychologia*, vol. 9, no. 1, pp. 97–113, Mar. 1971.

[34] N. Kapadia, V. Zivanovic, and M. Popovic, "Restoring voluntary grasping function in individuals with incomplete chronic spinal cord injury: Pilot study," *Topics Spinal Cord Injury Rehabil.*, vol. 19, no. 4, pp. 279–287, Oct. 2013.

[35] H. Kavianirad, S. Endo, T. Keller, and S. Hirche, "EMG-based volitional torque estimation in functional electrical stimulation control," in *Proc. IEEE-EMBS Conf. Biomed. Eng. Sci. (IECBES)*, Dec. 2022, pp. 171–176.

[36] S. G. Hart and L. E. Staveland, "Development of NASA-TLX (task load index): Results of empirical and theoretical research," *Adv. Psychol.*, vol. 52, pp. 139–183, Apr. 1988.

[37] I. E. Allen and C. A. Seaman, "Likert scales and data analyses," *Qual. Prog.*, vol. 40, no. 7, pp. 64–65, 2007.

[38] S. Balasubramanian, A. Melendez-Calderon, A. Roby-Brami, and E. Burdet, "On the analysis of movement smoothness," *J. NeuroEngineering Rehabil.*, vol. 12, no. 1, p. 112, Dec. 2015.

[39] B. Rohrer et al., "Movement smoothness changes during stroke recovery," *J. Neurosci.*, vol. 22, no. 18, pp. 8297–8304, Sep. 2002.

[40] Y. Tu, Z. Zhang, X. Gu, and Q. Fang, "Surface electromyography based muscle fatigue analysis for stroke patients at different Brunnstrom stages," in *Proc. 38th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. (EMBC)*, Aug. 2016, pp. 3781–3784.

[41] E. Ambrosini et al., "A myocontrolled neuroprosthesis integrated with a passive exoskeleton to support upper limb activities," *J. Electromyogr. Kinesiol.*, vol. 24, no. 2, pp. 307–317, Apr. 2014.

[42] B. A. C. Osuagwu, E. Whicher, and R. Shirley, "Active proportional electromyogram controlled functional electrical stimulation system," *Sci. Rep.*, vol. 10, no. 1, p. 21242, Dec. 2020. [Online]. Available: https://www.nature.com/articles/s41598-020-77664-0

[43] R. J. Downey, M. Merad, E. J. Gonzalez, and W. E. Dixon, "The time-varying nature of electromechanical delay and muscle control effectiveness in response to stimulation-induced fatigue," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 25, no. 9, pp. 1397–1408, Sep. 2017.

[44] M. Saes et al., "Smoothness metric during reach-to-grasp after stroke: Part 2. Longitudinal association with motor impairment," *J. NeuroEngineering Rehabil.*, vol. 18, no. 1, p. 144, Dec. 2021.

[45] N. Dunkelberger, E. M. Schearer, and M. K. O'Malley, "A review of methods for achieving upper limb movement following spinal cord injury through hybrid muscle stimulation and robotic assistance," *Experim. Neurol.*, vol. 328, Jun. 2020, Art. no. 113274.

[46] J. Rodriguez-Falces and N. Place, "Determinants, analysis and interpretation of the muscle compound action potential (M wave) in humans: Implications for the study of muscle fatigue," *Eur. J. Appl. Physiol.*, vol. 118, no. 3, pp. 501–521, Mar. 2018.

[47] X. L. Hu et al., "Post-stroke wrist rehabilitation assisted with an intention-driven functional electrical stimulation (FES)-robot system," in *Proc. IEEE Int. Conf. Rehabil. Robot.*, Jun. 2011, pp. 1–6.

[48] R. Riener, J. Quintern, and G. Schmidt, "Biomechanical model of the human knee evaluated by neuromuscular stimulation," *J. Biomechanics*, vol. 29, no. 9, pp. 1157–1167, Sep. 1996.

[49] M. Ferrarin and A. Pedotti, "The relationship between electrical stimulus and joint torque: A dynamic model," *IEEE Trans. Rehabil. Eng.*, vol. 8, no. 3, pp. 342–352, Sep. 2000.

[50] H. Gollee, D. J. Murray-Smith, and J. C. Jarvis, "A nonlinear approach to modeling of electrically stimulated skeletal muscle," *IEEE Trans. Biomed. Eng.*, vol. 48, no. 4, pp. 406–415, Apr. 2001.

[51] G.-C. Chang et al., "A neuro-control system for the knee joint position control with quadriceps stimulation," *IEEE Trans. Rehabil. Eng.*, vol. 5, no. 1, pp. 2–11, Mar. 1997.

[52] A. J. Del-Ama, Á. Gil-Agudo, J. L. Pons, and J. C. Moreno, "Hybrid FES-robot cooperative control of ambulatory gait rehabilitation exoskeleton," *J. NeuroEngineering Rehabil.*, vol. 11, no. 1, p. 27, 2014.

[53] T. Qiu, N. Alibeji, and N. Sharma, "Robust compensation of electromechanical delay during neuromuscular electrical stimulation of antagonistic muscles," in *Proc. Amer. Control Conf. (ACC)*, Jul. 2016, pp. 4871–4876.

[54] K. Akizuki and Y. Ohashi, "Measurement of functional task difficulty during motor learning: What level of difficulty corresponds to the optimal challenge point?" *Human Movement Sci.*, vol. 43, pp. 107–117, Oct. 2015. [Online]. Available: https://linkinghub.elsevier.com/retrieve/pii/S0167945715300105

[55] M. H. Alhaag et al., "Determining the fatigue associated with different task complexity during maintenance operations in males using electromyography features," *Int. J. Ind. Ergonom.*, vol. 88, Mar. 2022, Art. no. 103273.

[56] M. Fallahi, M. Motamedzade, R. Heidarimoghadam, A. R. Soltanian, and S. Miyake, "Effects of mental workload on physiological and subjective responses during traffic density monitoring: A field study," *Appl. Ergonom.*, vol. 52, pp. 95–103, Jan. 2016.

[57] D. Caldiroli et al., "Upper limb muscular activity and perceived workload during laryngoscopy: Comparison of Glidescope® and macintosh laryngoscopy in manikin: An observational study," *Brit. J. Anaesthesia*, vol. 112, no. 3, pp. 563–569, Mar. 2014.

[58] J. S. L. Hu, J. Lu, W. B. Tan, and D. Lomanto, "Training improves laparoscopic tasks performance and decreases operator workload," *Surgical Endoscopy*, vol. 30, no. 5, pp. 1742–1746, May 2016.

[59] I. M. Shuggi, H. Oh, P. A. Shewokis, and R. J. Gentili, "Mental workload and motor performance dynamics during practice of reaching movements under various levels of task difficulty," *Neuroscience*, vol. 360, pp. 166–179, Sep. 2017.

A.2 Feasibility of hybrid robot-FES system with subacute stroke patients in a clinical setting

Hybrid Functional Electrical Stimulation and Robotic Assistance for Wrist Motion Training after Stroke: Preliminary Results

Lucille Cazenave[1,2], Aaron Yurkewich[3], Chiara Höhler[4,5], Thierry Keller[6], Carmen Krewer[4,5], Klaus Jahn[4,7], Sandra Hirche[8], Satoshi Endo[8] and Etienne Burdet[2]

2023 International Conference on Rehabilitation Robotics (ICORR) | 979-8-3503-4275-8/23/$31.00 ©2023 IEEE | DOI: 10.1109/ICORR58425.2023.10304736

***Abstract*— This work presents preliminary results of a clinical study with sub-acute stroke patients using a hybrid system for wrist rehabilitation. The patients trained their wrist flexion/extension motion through a target tracking task, where electrical stimulation and robotic torque assisted them proportionally to their tracking error. Five sub-acute stroke patients have completed the training for 3 sessions on separate days. The preliminary results show hybrid assistance improves tracking performance and motion smoothness in most participants. In each session, patients' tracking performances before and after training were evaluated in unassisted tracking trials, without assistance. Their unassisted performance was compared across sessions and the results suggest that moderately to severely impaired patients might benefit more from hybrid training with our system than mildly impaired patients. Subjective assessments from all sessions show that the patients found the use of the device very comfortable and the training enjoyable. More data is being collected and future work will aim at verifying these trends.**

I. INTRODUCTION

Hybrid technology combining FES with active or passive robotics has been developed for upper-limb stroke rehabilitation in order to provide optimal assistance and improve functional recovery. In comparison to conventional therapy and robot-only rehabilitation, studies found greater improvements in the Box & Block test [1]–[3] and the Wolf Motor Function Test [4] with the hybrid system. However, due to the technical complexity of combining two active devices in a stroke rehabilitation scenario, some of the current systems have used robots only to provide support on other joint motions, thus not exploiting the full potential of hybrid system for rehabilitation [5]. Moreover, simple solutions such as push-buttons have been used to trigger assistance [5], which can limit the therapeutic benefits as the patient might not be engaged in the task [6]–[9].

On the other hand, advanced controllers have been introduced recently to provide more optimal combinations of FES and robotic assistance, and have been successfully tested in healthy participants [10]–[12] and simulations [13]. Results show that the use of these controllers could delay the onset of fatigue, [12], [13], reduce power requirements [10], [11], [13] and improve tracking accuracy [10], compared to FES or robot alone. However, they have not yet been tested in a rehabilitation scenario with stroke patients. Moreover, other studies that have investigated the use of a simple hybrid controller in stroke populations, such as Hu and colleagues [3] have not reported qualitative data. The goal of this work is thus to collect quantitative and qualitative data during the use of simple hybrid systems in the context of stroke rehabilitation, which is said to be crucial to achieve successful rehabilitation outcomes [14]. This patient-centred approach will allow us to gather further evidence towards the use of active robotic and FES assistance on the same joint motion to inform the development of controllers for stroke rehabilitation, where adaptive and optimal shared control can be used where beneficial.

This work presents preliminary results from a stroke study, where patients trained their wrist flexion/extension during a target tracking task with assistance from a hybrid system. In this work, a simple proportional control algorithm is used, where the intensity of FES and the amount of robotic torque provided to a patient is proportional to their tracking error. We investigated (i) how hybrid assistance affects patients' performance and quality of motion, (ii) how hybrid training affects these metrics over time and (iii) patients' experience of hybrid assistance and training.

II. METHODS

A. Participants

The study is run at the Schoen Clinic Bad Aibling and was approved by the Ethics Committee of the Ludwig-Maximilians University (LMU) Munich, Germany (registration number: 22-0297). All participants or their legal representatives signed an informed consent form prior to participating in the experiment. The study participants are subacute stroke patients staying at the inpatient rehabilitation hospital after an ischemic or hemorrhagic infarction.

The inclusion criteria are as follows: age >18 years old, cognitively able to follow instructions, with functional impairments in the wrist or fingers as assessed by the Medical

This work was supported by the UKRI CDT in AI for Healthcare EP/S023283/1 and the European Commission H2020 project ReHyb (ICT 871767).

[1]L.C. is with the AI for Healthcare Centre for Doctoral Training, Imperial College London, UK. lucille.cazenave16@imperial.ac.uk

[2]L.C. and E.B. are with the Bioengineering department, Imperial College London, UK. e.burdet@imperial.ac.uk

[3]A.Y. is with the Department of Mechatronics Engineering, Ontario Tech University, Oshawa, Canada. aaron.yurkewich@ontariotechu.ca

[4]C.H., C.K. and K.J are with the Research Department of Schoen Clinic Bad Aibling, Bad Aibling, Germany. {CHoehler, CKrewer, kljahn}@schoen-klinik.de

[5]C.H. and C.K. are with the Chair of Human Movement Science, Faculty of Sport and Health Science, Technical University Munich, Germany

[6]T.K. is with the Tecnalia Research and Innovation, San Sebastian, Spain

[7]K.J is with the German Center for Vertigo and Balance Disorders, Ludwig-Maximilians University of Munich, Germany

[8]S.E. and S.H. are with the Chair of Information-oriented Control, Technical University of Munich, Germany. {s.endo, hirche}@tum.de

Authorized licensed use limited to: Imperial College London. Downloaded on September 11,2025 at 08:42:15 UTC from IEEE Xplore. Restrictions apply.

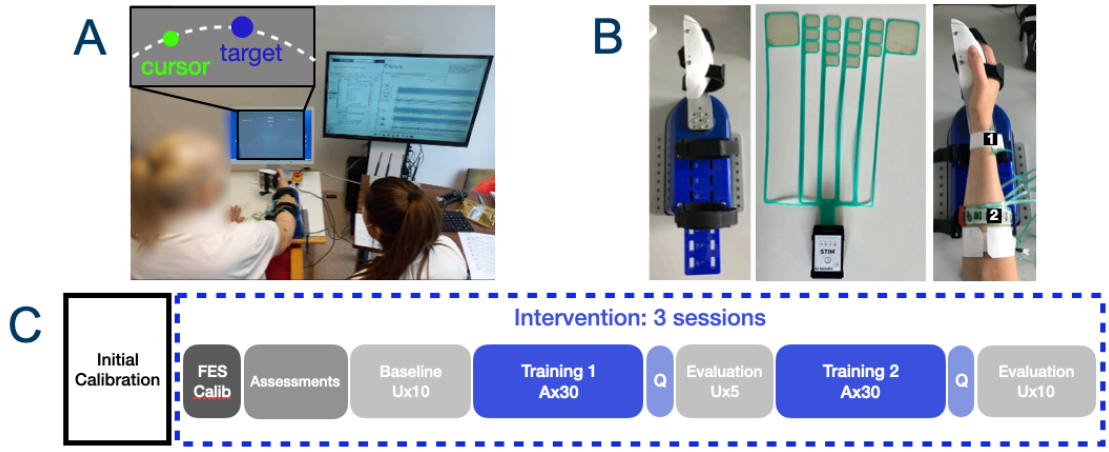


Fig. 1. Experiment description. **A.** A patient tracks a randomly moving target on-screen with wrist flexion/extension. **B.** Hybrid system (from left to right): HRX-1 wrist robotic device; FES device with 16-electrode array; hybrid set-up where the FES anode electrodes, shown as 1, are placed on the dorsal and ventral side of the wrist near the ulnar head and the cathode electrodes array, shown as 2, are placed inline with the wrist flexor and extensor muscle belly. **C.** Overview of experimental protocol, where a patient performs a series of calibration and assessment steps followed by unassisted trials (U), where no stimulation or robotic assistance are provided, and assisted training trials (A), where patients receive hybrid assistance. 'x10' refers to the number of trials for each block, here ten. 'Q' refers to the questionnaire step.

Research Council score (MRC ≤ 3) and low level or no pain in the wrist or fingers (Numeric Rating Scale < 4). Exclusion criteria can be divided in robot-related and FES-related exclusion criteria. Robot-related exclusion criteria are: severe contractures or muscle tone resulting in the operator's inability to position the patient's arm in the device and flex or extend the wrist more than 20°. FES-related exclusion criteria are: pregnancy, presence of implantable devices or other metal implants in the stimulated area, no motion or muscle contraction resulting from FES, patients with severe epilepsy and cancer or wounds in the stimulated area. Patients were also excluded if they had a severe psychiatric disorder or had no function as well as no deep sensitivity in the fingers or wrists.

Preliminary data from five patients (Table I) is presented in this work. Two patients are severely impaired (Fugl-Meyer Upper-Extremity score (FM-UE)$\leq$25), two are moderately impaired (25$\leq$FM-UE$\leq$40) and one is mildly impaired (FM-UE$>$40) [15].

TABLE I
PATIENT DEMOGRAPHICS

Patient ID	Sex	Age (years)	Side of paresis	Time since stroke (weeks)	FM-UE
1	Female	78	Right	14	29
2	Male	68	Left	5	2
3	Female	81	Right	7	38
4	Male	73	Left	8	13
5	Male	59	Right	4	45

FM-UE: Fugl-Meyer Upper-Extremity score, maximum score: 66.

B. Protocol

The experimental protocol is outlined in Fig. 1C. Once recruited, an initial calibration session was scheduled for the patients to familiarise themselves with the system and to perform the first FES calibration. Two cathode electrodes within the cathode array are selected to generate the flexion movements and two other cathode electrodes for the extension movements. The electrode location and corresponding maximum stimulation are selected individually for the flexion and extension side, such that the stimulation is comfortable and the generated movement covers as much of the participant's ROM as possible. The FES amplitude is capped at the maximum comfortable stimulation determined by the user for the flexion s_f^{max} and extension movements s_e^{max}. The minimum FES amplitude is defined as the participant's sensory threshold through self-report, calibrated individually for the flexor stimulation s_f^{min} and the extensor stimulation s_e^{min}. Once found, the electrode locations were marked on the patient's skin if there were no counter-indications and the minimum and maximum amplitudes were noted down for the next sessions. After that, the patient was asked to relax while the stimulation amplitude was increased from s_{min} to s_{max}, with a resolution of 1 mA, and the generated torque was recorded. This was done in order to empirically identify the coefficients of the mapping between the stimulation amplitudes s_f and s_e and the produced torques τ_f and τ_e (Eq. 1) in each session. Preliminary testing indicated that the relationship between stimulation amplitude and torque could be approximated by a second order exponential for the flexion and extension movements respectively, such that:

$$\begin{aligned} s_f(t) &= f(\tau_f(t)) = \alpha_f\, e^{\beta_f\, \tau_f(t)} + \delta_f\, e^{\gamma_f\, \tau_f(t)} \\ s_e(t) &= f(\tau_e(t)) = \alpha_e\, e^{\beta_e\, \tau_e(t)} + \delta_e\, e^{\gamma_e\, \tau_e(t)} \end{aligned} \tag{1}$$

with α, β, γ and δ coefficients of the exponential terms. This mapping is used to determine the required FES amplitude when the patients are assisted by the hybrid system, to ensure that the FES and robot assistance provide the same amount of torque.

Following this initial calibration session, the patients participated in three intervention sessions of around one hour

Authorized licensed use limited to: Imperial College London. Downloaded on September 11,2025 at 08:42:15 UTC from IEEE Xplore. Restrictions apply.

each, separated by at least one break day. Each session was identical: it started with the FES calibration described above, followed by a ROM calibration.

The ROM calibration was performed as an assessment of patient's progress but also to adjust the target trajectory amplitude to each patient's capability. It started with a passive calibration, where the experimenter moved the handle of the robot in the flexion direction until they felt a resistance or a discomfort reported by the patient. This was also done in the extension direction and the cycle was repeated three times. After that, an active calibration, where patients were asked to move their wrist as far as they could in flexion and then extension was repeated three times.

In the remaining parts of the session, the patients performed a target tracking task with the wrist flexion/extension movements of their impaired hand, either unassisted (baseline and evaluation trials in Fig. 1C) where no FES or robotic assistance is provided, or assisted by the hybrid system (two training blocks), where the patient received both FES and robotic assistance. Ten unassisted trials were first completed by the patient as a baseline. The first training block consisted of 30 assisted trials, and was followed by five unassisted trials as intermediate evaluation. A second training block of 30 assisted trials was performed and followed by the final evaluation block of ten unassisted trials. Each trial lasted 12 seconds with a 3 second break. The rest time could be prolonged as desired by the patient. After the first training block and the first evaluation block, the patients answered a set of questions.

The patients tracked a moving target on a computer monitor placed in front of them. The target trajectory was defined as the product of two sinusoids, as it has been extensively used in human-robot interaction with healthy participants [16]–[18]. Here the frequencies have been adapted to the stroke population, following preliminary testings with clinicians and patients, for the target to be slower. We used:

$$q^*(t) = q^*_{mid} + q^*_{max}\,\sin\big(0.2586\,t^+\big)\,\sin\big(0.1860\,t^+\big) \quad (2)$$

where $t^+ = t + t_0$, t is the elapsed time and t_0 is the starting time. q^* is the target angle. q^*_{mid} is the middle point of the target range and the amplitude from that point to the maximum range is q^*_{max}. These are determined from the maximum target amplitude in flexion q_f^{max} and in extension q_e^{max}, where the target was defined to go up to 30% beyond the active ROM of the patient but capped by their passive ROM:

$$q^*_{max} = \frac{|q_f^{max} - q_e^{max}|}{2} \qquad q^*_{mid} = \frac{q_f^{max} + q_e^{max}}{2} \quad (3)$$

The target was programmed and updated in Matlab and t_0 is randomly selected to disrupt prediction. The patients were instructed to track the target as accurately as possible and told that they may feel haptic interaction from the robotic device and/or electrical stimulation.

C. Hybrid Robot-FES system

The robot used in the study is the HRX-1 one degree-of-freedom wrist robotic interface (HumanRobotiX, UK [19]) (Fig. 1B). It is actuated by a brushless low friction motor, located below the metal plate of the handle, which delivers up to 4 Nm of torque and is controlled by the Epos4 70/15 motor controller (Maxon Motors, Switzerland). Torque measurement is provided by the embedded torque sensor (with 0.014 Nm resolution), connected between the metal handle plate and the motor shaft using a shaft collar. The user's wrist angle is recorded using the embedded optical encoder (0.01° resolution). The hand is attached to an ergonomic handle while the forearm is strapped to an adjustable arm support to ensure joint alignment. To maintain hygiene standards, device-specific cleaning protocols were followed. The robot is programmed in Matlab and ran at a frequency of approximately 75 Hz.

The stimulation device used in this study is the STIM 2.0 FES device 16-electrode array (Tecnalia Research & Innovation, Spain) (Fig. 1B), controlled remotely via Bluetooth communication. A hydrogel layer is placed on the electrodes to improve the conductivity of the array with the skin and straps are used to tighten the array around the forearm. Each patient uses an individual set of electrodes throughout the study. The pulse frequency of the stimulation is set to 35 Hz and the pulse width to 300 μs as these values have been used clinically [20]. The amplitude of the stimulation varies (with 0.1 mA resolution) during the experiment.

The control of the hybrid system determines the torque required from the robot and the FES, during assisted training, where both systems are concurrently providing torque $\tau(t)$ to the patient:

$$\tau(t) = K\,e(t) \qquad e(t) = q(t) - q^*(t) \quad (4)$$

where $e(t)$ is the tracking error between the participant's trajectory q and the target trajectory q^*. A negative/positive error indicates that the target position is further in extension/flexion than the patient's position. The control stiffness $K = 0.42$ Nm/rad corresponds to a soft-medium interaction stiffness [16]. It has been selected after preliminary testings with clinicians and patients to assist them in the task while preventing slacking. The robot torque $u_r(t)$ exerted on the wrist flexion/extension and the stimulation amplitude provided to the wrist flexor $s_f(t)$ or extensor $s_e(t)$ are defined as:

$$u_r(t) = \tau(t) \qquad s(t) = \begin{cases} s_e(t) = f(\tau_e(t)), & e(t) < 0 \\ s_f(t) = f(\tau_f(t)), & e(t) > 0 \end{cases} \quad (5)$$

where $s_e(t)$ and $s_f(t)$ are a function of $\tau_e(t)$ and $\tau_f(t)$, as defined in Eq. 1.

D. Data Analysis

The Root Mean Square Error (RMSE) [°] between the target trajectory $q^*(t)$ and the patient's trajectory $q(t)$ was used to evaluate the tracking performance: $\sqrt{\frac{1}{T}\int_0^T e(t)^2\,dt}$, $T = 12\,s$. It has been used previously to characterize the sensorimotor control strategies of stroke patients during target tracking tasks [21] and as an indicator of their motor recovery [22]. The Pearson's linear correlation between the

Authorized licensed use limited to: Imperial College London. Downloaded on September 11,2025 at 08:42:15 UTC from IEEE Xplore. Restrictions apply.

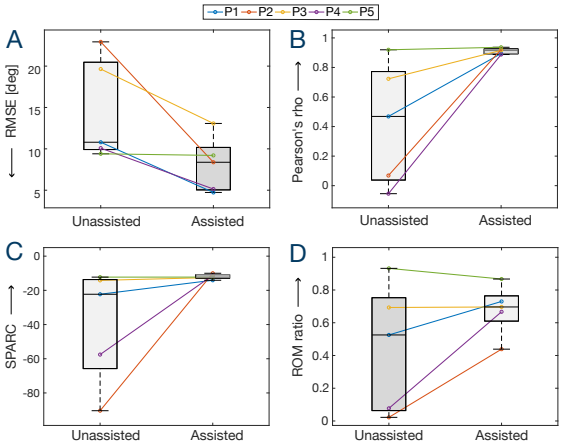


Fig. 2. Performance metrics during the tracking task while patients are receiving hybrid assistance, with arrows indicating score improvement direction. (**A**) Tracking performance. (**B**) Pearson's correlation. (**C**) Motion smoothness. (**D**) Tracking ROM ratio. The whisker lines above and below the box extend beyond the 25th or 75th percentiles of the data to the maximum or minimum value within the 1.5 interquartile range.

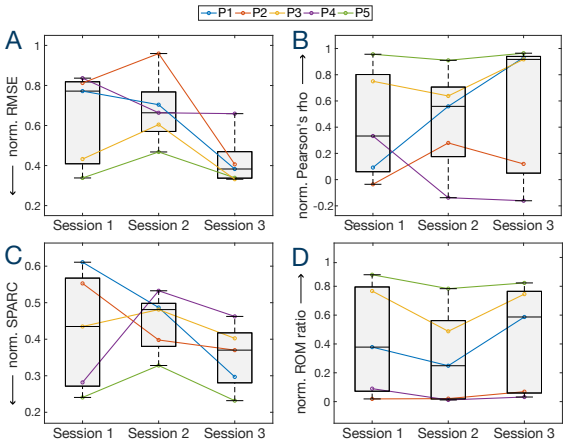


Fig. 3. Normalised performance metrics during the tracking task in the three sessions, with arrows indicating score improvement direction. (**A**) Tracking performance. (**B**) Pearson's correlation. (**C**) Motion Smooothness. (**D**) Tracking ROM ratio. The whisker lines above and below the box extend beyond the 25th or 75th percentiles of the data to the maximum or minimum value within the 1.5 interquartile range.

target and the patient's trajectory was also used. Correlation metrics between a target and patient's trajectories have previously been used in wrist tracking task and have shown to be associated with patients' functional scores [23]. Additionally, we investigated patient's motion smoothness, as there is evidence that it could be linked with motor recovery [24]. SPARC is used for this purpose [25], as it has been shown to be the most valid to investigate motion smoothness [26]. Finally, the ratio of the patients' ROM over the corresponding target ROM was used to quantify amplitude-related tracking performance. All metrics were calculated for each trial during the ten baseline trials and the 30 trials of the first training block. The average across the baseline trials and the training trials were obtained and compared across the three sessions. To allow for comparisons across patients, patient's metrics were normalised by their maximum metric value across all trials from the baseline and the first training block.

The answers of questions about the comfort and usefulness of the assistance and of two questions taken from the enjoyment section of the Intrinsic Motivation Index, are qualitatively analysed for each session.

III. RESULTS

A. Hybrid assistance

When comparing performance metrics during the assisted and unassisted trials (Fig. 2), we observe that hybrid assistance leads to increased performance for severely and moderately affected patients (i.e. FM-UE 2-38). The improvement is clear with the RMSE (Fig. 2A), subject-target correlation (Fig. 2B) and motion smoothness (Fig. 2C). The hybrid assistance only leads to an increase in ROM ratio during the tracking task for patients who are able to reach less than half of the target amplitude in the unassisted trials, i.e. two severely impaired patients, P2 and P4, and one moderately impaired patient, P1. However, even with assistance, most patients were not able to reach the target's full range.

B. Hybrid training

Patients repeated the training over three sessions and their baseline performance during the ten unassisted trials was recorded at the start of every session. The evolution of each performance metric, normalised within-patient by their maximum score for that metric, can be seen in Fig. 3. The tracking error has decreased for most patients from the first to last session and the median of session 3 is lower, with smaller interquartile range (Fig. 3A). P5, who has a high score in the first session and mild impairment, did not improve their performance with training, and this was the case for all metrics. The correlation between the patient's and target trajectory has improved for some patients (Fig. 3B). It has improved greatly from session 1 to 3 for P1 (ratio of 10.11) and slightly for P2 (ratio of 3.36) and P3 (ratio of 1.22). Similarly, P5, who has a large ROM ratio in session 1 already, did not improve (Fig. 3D). Severely impaired patients who have a low ROM ratio also did not improve their score. Regarding motion smoothness, all patients' performance improved from session 2 to session 3 (Fig. 3C). Although the median is lower in session 3 than in session 1, patients with a low normalised SPARC value did not improve, similarly as the other metrics.

C. User experience

All patients found that the use of the device and hence the assistance provided by the FES and the robot was comfortable in most sessions (Fig. 4). They also felt assistance in the majority of cases but did not always find this assistance useful for improving their performance in the target tracking task. All patients found the activity highly enjoyable and fun.

Authorized licensed use limited to: Imperial College London. Downloaded on September 11,2025 at 08:42:15 UTC from IEEE Xplore. Restrictions apply.

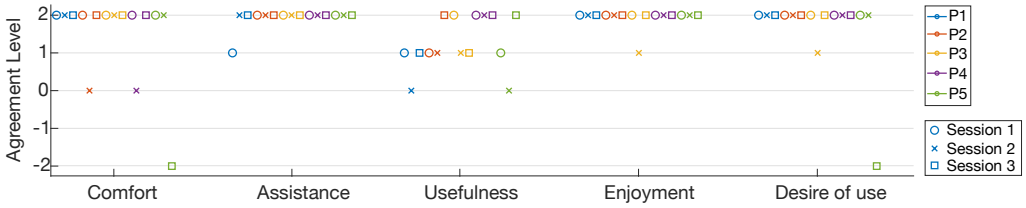


Fig. 4. Answers to 5-point Likert Scale questionnaire. Patients answered from 'Strongly disagree' to 'Strongly agree' to the following questions (figure from left to right): 'The use of the device was comfortable', 'During the experiment, I felt assistance', 'The use of the device improved my performance', 'I enjoyed doing this activity very much', 'I would like to use this sustem for my upper-limb therapy in the clinic'.

IV. DISCUSSION

This work presents preliminary results from a study investigating the use of a hybrid robotic and FES device for wrist flexion/extension in a rehabilitation setting. This device assists patients proportionally to their performance when tracking a target.

We first investigated the effect of hybrid assistance on performance and quality of motion. We found that both task-related metrics, the subject-target RMSE and correlation, improved when assistance was provided to the patients. Although patients reached high correlation scores, this metric only captures gross ability to follow the target rhythm and does not encompass finer differences such as in amplitude. For the RMSE, the variability remains higher even in the assisted case but severe patients who cannot move can have a lower RMSE than other patients who are intending to follow the target and are out of phase with it. Investigating additional metrics to get a clearer understanding is thus necessary. Some data-driven approaches have previously been used in order to mitigate this issue. A new score, that is a standard deviation away from the worst existing score can be assigned to paralysed patients, ensuring the metric is properly floored [27]. Motion smoothness and ROM ratio increased for patients with moderate to severe impairments. With assistance, patients still did not reach 80% of the target amplitude. This might be due to the stiffness values chosen for the strength of the robot and FES assistance. Indeed a soft-medium stiffness has been chosen in order to promote patient engagement and avoid slacking. A greater connection stiffness in the FES controller could also induce discomfort by providing strong stimulation in alternating directions. P5 who is mildly impaired rated the assistance as uncomfortable in the last session for this reason. Furthermore, the current data does not allow us to disentangle the impact of the FES and the robot assistance on the improvement in performance and quality of motion. To do so, additional intervention groups where patients train with each modality separately should be included, in order to understand, e.g. whether the performance improvement is due to the robot action alone.

Second, we investigated how training with the hybrid system could improve unassisted task performance and motion quality over time. Some patients' performance decreased in session 2 and increased again in session 3, this change might be due to spontaneous recovery, hence the need to collect data from a control group and more participants. The limited number of sessions also restricts the possibility to generalise about the effect of hybrid training. Additionally, results show RMSE decreased from session 1 to 3 in all patients but P5 who has the highest FM-UE score and highest tracking performance in the first session. Although the task difficulty was individually tuned as the target trajectory is based on a patient's own ROM, the least affected patient did not improve in any of the metrics, thus suggesting that the task difficulty should be further adapted to each patient. One approach used in many serious games is to adapt the difficulty of the task (e.g. robot and FES assistance, target speed and ROM) based on the challenge point framework or the 'flow channel' where users' scores should be maintained at a certain level to keep them optimally engaged [28], [29]. Similar results were found with other metrics, hence suggesting that moderately to severely impaired patients benefit from the training while the performance of mildly impaired patients do not change. Other studies explored the effect of hybrid rehabilitation on moderate to severe stroke patients and found positive training effects [1], [3], [30], [31]. These studies have investigated the effect of hybrid rehabilitation on FM-UE and have used controllers where the FES is triggered at the start of the task and the robot is passive [1], or with EMG-driven controllers [3], [30], [31]. On the other hand, recent research aims at implementing more optimal control algorithms. In this work, task performance and clinically-relevant quality of motion metrics are evaluated during hybrid training, where the results could inform the development of new patient-centred hybrid controllers. We would suggest to include adaptive stiffness gains, based on patients' abilities and preferences, as some may find FES more uncomfortable over time, as observed here. We also found that patients had a smooth motion when the same amount of FES and robot assistance is provided. Controllers providing less robotic assistance than FES could thus be tested in stroke population, as they could maintain high motion smoothness while increasing the benefits of FES.

Results from subjective assessments indicate that regardless of their impairment severity, patients highly enjoyed using this system, found it comfortable and would like to use it further for their upper-limb rehabilitation. Most studies did not consider subjective assessment of the assistance as part of their system evaluation, but a few investigated its usability [2], [32]. In a study where electrical stimulation was applied and a passive robotic system was used for support, patients found the stimulation comfortable and the

Authorized licensed use limited to: Imperial College London. Downloaded on September 11,2025 at 08:42:15 UTC from IEEE Xplore. Restrictions apply.

training enjoyable [32], while patients training with another passive exoskeleton with FES assistance found this system only moderately usable [2]. Our qualitative results thus complement existing work and are promising for the field. However, the answers to the statement 'The use of the device improved my performance' are mixed, even within subjects across sessions. Although patients found they felt assistance during the assisted trials, they did not evaluate it as useful. It is possible that the assistance did not match patients' intended motion as it was controlled to follow the target. This has been reported previously in a robot rehabilitation study where patients found that the robot was resisting their voluntary movement [33].

In summary, this hybrid robot-FES device has been used in five patients in a clinical setting for wrist flexion/extension training. Overall, patients found the device very comfortable and enjoyable to use. Additional patients are recruited and further analysis with a larger population size and in comparison to a control group is required to investigate the trends observed here and provide further recommendations for the development of hybrid controllers.

ACKNOWLEDGMENT

We would like to thank Roxana Wüchner for her help in collecting the data and Alexandra de Crignis for her assistance on the ethics application and the study preparation.

REFERENCES

[1] H. Ring and N. Rosenthal, "Controlled study of neuroprosthetic functional electrical stimulation in sub-acute post-stroke rehabilitation," *JRM*, vol. 37, no. 1, pp. 32–36, 2005.

[2] E. Ambrosini *et al.*, "A Robotic System with EMG-Triggered Functional Eletrical Stimulation for Restoring Arm Functions in Stroke Survivors," *NNR*, vol. 35, no. 4, pp. 334–345, 2021.

[3] X.-L. Hu *et al.*, "Wrist Rehabilitation Assisted by an Electromyography-Driven Neuromuscular Electrical Stimulation Robot After Stroke," *NNR*, vol. 29, no. 8, pp. 767–776, 2015.

[4] Y.-y. Lee *et al.*, "Effects of combining robot-assisted therapy with neuromuscular electrical stimulation on motor impairment, motor and daily function, and quality of life in patients with chronic stroke: a double-blinded randomized controlled trial," *JNER*, vol. 12, no. 1, p. 96, 2015.

[5] F. Resquin *et al.*, "Hybrid robotic systems for upper limb rehabilitation after stroke: A review," *Med Eng Phys*, vol. 38, no. 11, pp. 1279–1288, 2016.

[6] J. de Kroon *et al.*, "Relation between stimulation characteristics and clinical outcome of the upper extremity in stroke," *JRM*, vol. 37, pp. 65–74, 2005.

[7] D. Rushton, "Functional Electrical Stimulation and rehabilitation—an hypothesis," *Med Eng Phys*, vol. 25, no. 1, pp. 75–78, 2003.

[8] L. E. Kahn *et al.*, "Robot-assisted movement training for the stroke-impaired arm: Does it matter what the robot does?" *JRRD*, vol. 43, no. 5, p. 619, 2006.

[9] A. A. Blank *et al.*, "Current Trends in Robot-Assisted Upper-Limb Stroke Rehabilitation: Promoting Patient Engagement in Therapy," *Curr Phys Med Rehabil*, vol. 2, no. 3, pp. 184–195, 2014.

[10] D. Wolf *et al.*, "Combining functional electrical stimulation and a powered exoskeleton to control elbow flexion," in *WeRob*. IEEE, 2017, pp. 1–2.

[11] N. Dunkelberger *et al.*, "Shared Control of Elbow Movements with Functional Electrical Stimulation and Exoskeleton Assistance," in *ICORR*. IEEE, 2022, pp. 1–6.

[12] D. Burchielli, N. Lotti, F. Missiroli, C. Bokranz, A. Pedrocchi, E. Ambrosini, and L. Masia, "Adaptive Hybrid FES-Force Controller for Arm Exosuit," in *ICORR*. IEEE, 2022, pp. 1–6.

[13] E. Bardi *et al.*, "Adaptive Cooperative Control for Hybrid FES-Robotic Upper Limb Devices: a Simulation Study," in *EMBC*. IEEE, 2021, pp. 6398–6401.

[14] C. Winstein *et al.*, "Been there, done that, so what's next for arm and hand rehabilitation in stroke?" *NeuroRehabilitation*, vol. 43, no. 1, pp. 3–18, 2018.

[15] E. J. Woytowicz *et al.*, "Determining Levels of Upper Extremity Movement Impairment by Applying a Cluster Analysis to the Fugl-Meyer Assessment of the Upper Extremity in Chronic Stroke," *Arch Phys Med Rehabil*, vol. 98, no. 3, pp. 456–462, 2017.

[16] E. Ivanova *et al.*, "For Motion Assistance Humans Prefer to Rely on a Robot Rather Than on an Unpredictable Human," *IEEE EMBS*, vol. 1, pp. 133–139, 2020.

[17] E. Ivanova, J. Eden, G. Carboni, J. Krüger, and E. Burdet, "Interaction with a reactive partner improves learning in contrast to passive guidance," *Sci. Rep.*, vol. 12, no. 1, p. 15821, 2022.

[18] H. Börner *et al.*, "Physically interacting humans regulate muscle coactivation to improve visuo-haptic perception," *J. Neurophysiol.*, vol. 129, no. 2, pp. 494–499, 2023.

[19] "Hrx-1 robot." [Online]. Available: www.humanrobotix.co.uk

[20] N. Kapadia *et al.*, "Restoring Voluntary Grasping Function in Individuals with Incomplete Chronic Spinal Cord Injury: Pilot Study," *TSCIR*, vol. 19, no. 4, pp. 279–287, 2013.

[21] D. Ao *et al.*, "Sensorimotor Control of Tracking Movements at Various Speeds for Stroke Patients as Well as Age-Matched and Young Healthy Subjects," *PLOS ONE*, vol. 10, no. 6, 2015.

[22] X. Hu *et al.*, "Quantitative evaluation of motor functional recovery process in chronic stroke patients during robot-assisted wrist training," *J Electromyogr Kinesiol*, vol. 19, no. 4, pp. 639–650, 2009.

[23] J. H. Burridge *et al.*, "The relationship between upper limb activity and impairment in post-stroke hemiplegia," *Disabil. Rehabil.*, vol. 31, no. 2, pp. 109–117, 2009.

[24] B. Rohrer, S. Fasoli, H. I. Krebs, R. Hughes, B. Volpe, W. R. Frontera, J. Stein, and N. Hogan, "Movement Smoothness Changes during Stroke Recovery," *JNR*, vol. 22, no. 18, pp. 8297–8304, Sep. 2002.

[25] S. Balasubramanian *et al.*, "On the analysis of movement smoothness," *JNER*, p. 112, 2015.

[26] M. I. Mohamed Refai *et al.*, "Smoothness metrics for reaching performance after stroke. Part 1: which one to choose?" *JNER*, vol. 18, no. 1, p. 154, 2021.

[27] J. A. Semrau *et al.*, "Robotic Characterization of Ipsilesional Motor Function in Subacute Stroke," *NNR*, vol. 31, no. 6, pp. 571–582, 2017.

[28] M. A. Guadagnoli and T. D. Lee, "Challenge Point: A Framework for Conceptualizing the Effects of Various Practice Conditions in Motor Learning," *J Mot Behav*, vol. 36, no. 2, pp. 212–224, 2004.

[29] R. Lotay *et al.*, "Optimizing self-exercise scheduling in motor stroke using Challenge Point Framework theory," in *ICORR*. IEEE, 2019, pp. 435–440.

[30] Q. Qian *et al.*, "Early Stroke Rehabilitation of the Upper Limb Assisted with an Electromyography-Driven Neuromuscular Electrical Stimulation-Robotic Arm," *Front. Neurol.*, vol. 8, p. 447, 2017.

[31] Y. Huang *et al.*, "A comparison of the rehabilitation effectiveness of neuromuscular electrical stimulation robotic hand training and pure robotic hand training after stroke: A randomized controlled trial," *Biomed Signal Proces*, vol. 56, p. 101723, 2020.

[32] K. Meadmore *et al.*, "The application of precisely controlled functional electrical stimulation to the shoulder, elbow and wrist for upper limb stroke rehabilitation: a feasibility study," *JNER*, vol. 11, no. 1, p. 105, 2014.

[33] J. H. Park *et al.*, "A comparison of the effects and usability of two exoskeletal robots with and without robotic actuation for upper extremity rehabilitation among patients with stroke: a single-blinded randomised controlled pilot study," *JNER*, vol. 17, no. 1, p. 137, 2020.

Authorized licensed use limited to: Imperial College London. Downloaded on September 11,2025 at 08:42:15 UTC from IEEE Xplore. Restrictions apply.

A.3 Fatigue induced by FES and voluntary movements in unimpaired and stroke participants

2025 International Conference On Rehabilitation Robotics (ICORR)
May 12-16, 2025. Chicago, IL, USA

FES-induced and voluntary-induced fatigue in a rehabilitation-like task

Lucille Cazenave[1, 2], Nuria Peña-Pérez[3], Aaron Yurkewich[4], and Etienne Burdet[1]

***Abstract*— In the context of FES-based rehabilitation and assistance tasks, there is a growing interest in managing the induced fatigue, which is an obvious limiting factor in training duration. However, it is unclear whether and how fatigue may develop in tasks commonly used in stroke rehabilitation. This work explored the effect of FES- or volition- induced movements on EMG-based effort and M-wave metrics that characterise fatigue, during a continuous wrist target-tracking task completed by 22 unimpaired participants. We found no significant changes in the mechanical and electrical responses of the muscles during the Volition-only, FES-only, and Volition-FES conditions, suggesting that during this task, FES did not induce muscular fatigue, while both mental and physical demands were reported as low. Our results thus suggest that it may not be necessary to consider FES-induced fatigue during such continuous FES-assisted tasks, that can be used in post-stroke motor rehabilitation training.**

2025 International Conference On Rehabilitation Robotics (ICORR) | 979-8-3503-8068-2/25/$31.00 ©2025 IEEE | DOI: 10.1109/ICORR66766.2025.11063107

I. Introduction

Functional electrical stimulation (FES) training often leads to rapid muscle fatigue due to the constant motor unit recruitment, unlike the naturally varying recruitment pattern seen in voluntary movements [1]–[5]. This fatigue is evident in tasks like the Cybathlon cycling race [6], where pilots with spinal cord injuries experience a decline in pedal power over time. Physical rehabilitation after stroke commonly uses FES and might thus be affected by muscle fatigue, however it is usually applied as an assistive device, in conjunction with voluntary movement, and involves frequent breaks [7]. To explore how fatigue develops during such activities, we investigated the effects of FES-induced and voluntary motion in a simple target-tracking task designed to simulate motor rehabilitation training [8], [9].

Various metrics have been employed to characterise muscle fatigue during specific volitional or FES-induced contractions. Traditionally, EMG-based effort and fatigue metrics include time-domain measures such as EMG envelope amplitude, reciprocal activation, and cocontraction. In the frequency domain, metrics such as mean and median frequency are commonly used to assess muscle fatigue [10], [11]. On the other hand, the muscle's response to electrical stimulation can be used to estimate muscle fatigue. This so-called M-wave represents the total electrical activity of all motor units depolarized within the stimulation electrodes' range [12], where its amplitude, duration, and area can be used as fatigue measures [12]–[15]. However, the literature presents discrepancies regarding which M-wave parameters best quantify muscle fatigue, as the underlying mechanisms are not fully understood. Some studies report a decrease in M-wave peak-to-peak amplitude with fatigue [13], [14], [16], and the extent of this change may be influenced by stimulation parameters and muscle type [15], [17]. Conversely, other research highlights an increase in M-wave duration (or a decrease in frequency) or area with fatigue [13], [18]–[20].

In light of these inconsistent findings, some researchers have focused on the biphasic characteristic of the M-wave, extracting parameters from each of the two phases separately. It is believed that these phases are differently affected by the physiological processes of fatigue [12], [19], [21], [22]. Studies suggest that the second phase of the M-wave may be influenced by changes in muscle architecture, such as shortening muscle length or relative positional changes between the muscle and recording electrodes, making it less suitable for fatigue analysis [12], [21]. However, recent findings indicate that the first phase of the M-wave may remain unaffected by such structural changes and may reflect more accurately fatigue-related mechanisms [22]. Thus, separate analysis of the two M-wave phases is recommended [12].

However, most studies using fatiguing protocols have focused on isometric contractions induced by voluntary or FES input [12]. These are not typically used in a stroke rehabilitation scenario where continuous movements, through the patient's range of motion, are often preferred. To investigate how fatigue develops in such a task, we investigated these EMG-based effort and M-wave metrics during FES and/or volitionally induced muscle contractions, both in an isometric and dynamic (target-tracking) scenario. We recorded kinematic data to assess tracking performance, EMG data to extract effort and fatigue metrics, and NASA-TLX questionnaire responses, with a focus on mental and physical demand. We hypothesised that muscle fatigue would be more prominent in the presence of FES compared to the volition-only condition.

II. Methods

A. Experimental design

Twenty-two unimpaired individuals (11 female, 3 left-handed), aged 21-30 years old, participated in this experiment, approved by the Research Ethics Committee of Imperial College London (approval number: 21IC6935). Participants completed three block conditions of 25 trials of target-tracking task (Fig. 1 B). In each 30 s-trial they tracked a target moving pseudo-randomly along the horizontal axis with their right wrist flexion/exte?ZXx'nsion motions [23]. The

This work was supported in part by the UKRI CDT in AI for Healthcare EP/S023283/1 and the EC H2020 project ReHyb (ICT 871767).

[1] LC and EB are with Imperial College of Science, Technology and Medicine, London, UK. {lucille.cazenave16, e.burdet}@imperial.ac.uk.
[2] LC is with the AI for Healthcare CDT of Imperial College London.
[3] NPP is with Institute of Automatic Control, RWTH Aachen, Germany.
[4] AY is with Mechatronics Engineering dept, Ontario Tech U, Canada.

Authorized licensed use limited to: Imperial College London. Downloaded on September 11,2025 at 08:42:20 UTC from IEEE Xplore. Restrictions apply.

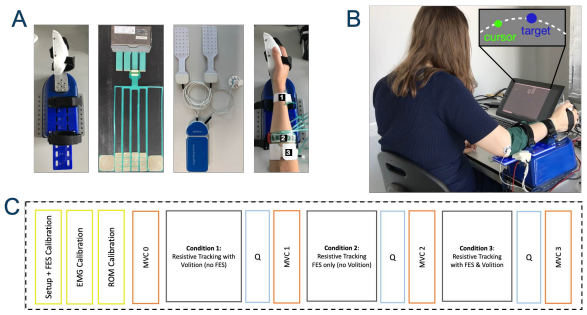


Fig. 1: Experiment description. **A.** Wrist robot-FES interface (left to right): HRX-1 wrist robotic device; FES device with 16-electrode array; EMG recording device with ground electrode and two high-density 32-channel electrode arrays; Device set-up, where the FES anode electrode (1), was placed on the dorsal side of the wrist near the ulnar head and the cathode electrodes array (2), were around the arm inline with the wrist flexor and extensor muscle belly with the EMG electrodes placed distally (3). **B.** Unimpaired individuals track a randomly moving target on-screen with wrist flexion/extension. **C.** Experimental protocol for the study on fatigue with unimpaired participants. The three conditions were presented in random order for each participant and consisted of 25 trials of a 30-second wrist target-tracking task. MVC refers to three repetitions of maximum voluntary wrist flexion and extension, followed by three repetitions of maximum flexor and extensor stimulation while participants were instructed to relax.

conditions, presented in a random order, required participants to: (i) track the target as accurately as possible, (ii) remain relaxed while FES was applied to their wrist flexor/extensor muscles to track the target, and (iii) track the target as accurately as possible while they received the same FES assistance as in (ii). The randomisation was designed to ensure that all six possible sequences of experimental conditions were presented, with each sequence carried out by at least three participants to maintain balanced exposure across conditions. The general difficulty of the task was increased by adding damping to the robot ($D = 0.0068\,Nm\,s/°$).

The FES assistance was implemented with stimulation intensity proportional to the difference between the target position and the participant's wrist position $e(t)$. Prior to carrying out these experimental conditions, an FES calibration was conducted to determine the optimal location for the stimulation electrodes and the maximum comfortable amplitude for the flexor (s_f^{max}) and extensor (s_e^{max}) muscle stimulation, and the sensory thresholds s_f^{min} and s_e^{min}, which altogether provided the stimulation range to use throughout the experiment. This was followed by a range of motion (ROM) calibration, used to determine the amplitude range of the target, set to 85% of the participants' ROM.

The amplitudes of the stimulation provided to the wrist flexor $s_f(t)$ and extensor $s_e(t)$ muscles were computed as:

$$\begin{cases} s_e(t) = -\kappa\, e(t) \;+\; s_e^{min} & e(t) < 0 \\ s_f(t) = \kappa\, e(t) \;+\; s_f^{min} & e(t) \geq 0 \end{cases} \tag{1}$$

Here, κ is the FES control stiffness (in mA/°) for the flexor and extensor stimulation and (after calibration) is equivalent to a robot control stiffness $K = 0.0097\,Nm/°$ [24].

After completion of each condition, participants filled the NASA-TLX questionnaire and performed a maximum voluntary contraction (MVC) exercise, where they were asked to flex and extend their wrist for 3.5 s as forcefully as possible three times on each side. Following this, they were instructed to relax while the maximum calibrated FES was applied for 3.5 s to their wrist flexor (s_f^{max}), followed by their wrist extensor (s_e^{max}), three times as well. For this step, the same calibrated FES intensity was used throughout the experiment.

B. FES and robotic device

The electrical stimulation device used was a 16-electrode array (Tecnalia Research & Innovation, Spain), where the anode was placed on the dorsal side of the wrist near the ulnar head and the cathode on the wrist flexor and extensor muscle belly to ensure comfortable and effective muscle contraction (Fig. 1 A). The frequency of the stimulation was set to 35 Hz, the pulse width to 300 μs and the amplitude of the stimulation varied during the experiment (with 1 mA resolution) (see Eq. 1). The robotic interface used was the HRX-1 one degree-of-freedom wrist robotic interface (HumanRobotiX, UK), which is actuated by a brushless low-friction motor and contains an embedded optical encoder (0.01 ° resolution) recorded the wrist angle (Fig. 1 A). Muscle activity was recorded using two 32-channel EMG electrode arrays (GR10MM0804, OT Bioelettronica, Italy) with a Sessantaquattro amplifier (OT Bioelettronica, Italy).

C. Data analysis

To analyse whether the target-tracking task induced fatigue, either with or without FES, we focused on five key aspects: i) the perceived mental and physical demand, ii) changes in EMG envelope amplitude during MVC, iii) changes in FES-induced torque and M-wave characteristics during continuous maximum stimulation, iv) tracking error, and v) cocontraction, and reciprocal activation of the flexor and extensor muscles during the condition trials. For evaluating metrics within each condition block, the first three trials used for familiarisation were excluded from the analysis, hence the remaining 22 trials were considered.

EMG pre-processing: EMG was recorded from the participants' wrist flexor and extensor muscles at a frequency of 2000 Hz. Mains noise was attenuated using a notch filter (Matlab function *iirnotch* with a notch at 50 Hz). A band-pass second order Butterworth filters (cut-off frequencies of 10 Hz and 500 Hz) were applied in the forward and reverse directions, so without inducing delay. An adaptive filter designed for EMG-based torque estimation under stimulation of wrist flexor and extensor with the same setup as here [25] was used to filter out the FES artifact and M-wave contribution for the in-trial EMG. The EMG signal was then rectified, and the envelope was obtained using a low-pass second-order Butterworth filter with a cut-off frequency of 5 Hz. The amplitude of the EMG envelope was normalised by the mean EMG envelope during the first MVC in flexion/extension (MVC0 condition in Fig. 1 C), so muscle activity is reported as a ratio of this maximum MVC amplitude. For subsequent analyses, the channel on the extensor and flexor arrays with the highest envelope amplitude during the EMG calibration

Authorized licensed use limited to: Imperial College London. Downloaded on September 11,2025 at 08:42:20 UTC from IEEE Xplore. Restrictions apply.

was selected. EMG metrics are reported for N = 21, as the EMG data for one participant were corrupted.

Metrics computation: Perceived effort was assessed based on the mental and physical demand items from the TLX-NASA questionnaire. To evaluate a potential decrease in MVC, we calculated the difference in muscle activity during the MVC performed before and after each condition. The average EMG value over the peak 1 s window of the 3.5 s MVC was used to characterize the MVC and the normalization value [26]–[28].

Similarly, to assess changes in FES-induced torque and M-wave characteristics, we computed the difference in mean torque and M-wave metrics during 3 s of continuous stimulation performed before and after each condition. The first 0.5 s of stimulation were excluded from the analysis to account for the delay between stimulation onset and muscle contraction. For M-wave analysis, the 3 s EMG signal was divided into pulse windows, each containing a stimulus artifact that marked the start of the window, followed by the corresponding M-wave. Within each window, we extracted the amplitude, area, and duration of each M-wave phase, averaging these metrics across the 3 s stimulation period for each M-wave phase separately [22]. Since this task is dynamic and can thus induce changes in muscle length and in the relative position of the recording and stimulating electrodes, the two M-wave phases were analysed separately (as previous work found that the first M-wave phase may be less affected by these structural changes [22]). We also analysed these metrics for the full M-wave by summing the parameters extracted from each phase to obtain the overall M-wave amplitude, duration, and area, as these are also commonly used to assess muscular fatigue [12]–[15].

We evaluated effort within trials using the cocontraction and the reciprocal activation of the wrist flexor and extensor normalised EMG envelope as described above, where cocontraction was defined as the minimum envelope amplitude between the flexor and extensor and the reciprocal activation as their difference. The tracking performance in each trial was evaluated using the Root Mean Square Error (RMSE) between the participant's and target trajectories.

Statistics: To compare perceived mental and physical demands, MVC levels, FES-induced torque, M-wave parameters, performance metrics, and EMG-based metrics during conditions, we used a one-way repeated measures ANOVA, or a non-parametric Friedman test when data were not normally distributed. Normality was assessed using the Shapiro-Wilk test. For pairwise comparisons of these metrics between conditions, we used paired sample t-tests or paired Wilcoxon signed-rank tests, controlling for the family-wise error rate using the Bonferroni-Holm correction. To determine whether differences in MVC torque, FES-induced torque, and M-wave parameters before and after each condition differed from a distribution with a mean of zero, we applied one-sample t-tests or Wilcoxon signed-rank tests for each condition individually. Moreover, for these differences, we performed this statistical analysis on the metrics distributions based on the chronological order in which the conditions were presented, regardless of their types, to identify any temporal changes in the metrics. We also conducted the same analysis after categorising the data by condition labels (FES, Volition, Volition-FES) to investigate differences associated with the specific condition types.

To explore whether tracking performance and EMG changed over time, we (i) explored trends within conditions using a linear mixed-effects model (LME) with restricted maximum likelihood, with the trial number as a fixed effect (slope) and a random intercept for each participant; and (ii) examined differences between the first and last three trials of each condition (excluding familiarisation trials), both across and within conditions. We used a one-way ANOVA or Friedman test and corresponding post-hoc tests to compare across conditions, and we used a one-sample t-test or Wilcoxon signed-rank test to compare the distribution of the metric within one condition, to one with a zero mean.

III. Results

A. Perceived mental and physical demand

We observed a significant effect of the condition on the NASA-TLX responses for the questions: "How physically demanding was this task?" ($\chi^2(2)$ = 26.66, $p < 0.001$) and "How mentally demanding was this task?" ($\chi^2(2)$ = 30.34, $p < 0.001$), where the mean for the Volition and Volition-FES conditions is below 6/10, and for the FES condition below 3/10, for both items. When participants were asked to relax while FES was applied, the task was perceived as the least demanding. In contrast, no differences were observed between the Volition and Volition-FES conditions in physical ($p = 0.73$) or mental demand ratings ($p = 0.45$).

B. MVC differences

Changes in MVC during the condition (a negative difference indicates a decrease in MVC) are reported in Fig. 2. No significant differences in MVC change across conditions were observed (MVC EMG flexor: $\chi^2(2)$ = 1.52, $p = 0.467$; MVC EMG extensor: $\chi^2(2)$ = 0.10, $p = 0.954$). Additionally, none of the conditions induced a significant change in MVC compared to zero (all $p > 0.1924$). We also investigated the chronological evolution of the MVC throughout the experiment by computing the difference between the current MVC and the previous one, independently of the condition order, and found a significant effect of the condition for the flexor MVC ($\chi^2(2)$ = 9.09, $p = 0.0106$), but no significant pairwise comparisons between conditions (all $p > 0.276$). There was no effect of the condition on the extensor MVC ($\chi^2(2)$ = 0.09, $p = 0.956$).

C. FES-induced torque differences

Similarly, we explored changes in the torque generated under maximum comfortable stimulation intensity (calibrated at the start of the experiment) while participants were at rest, across conditions. Fig. 2 shows the difference between FES-induced torque before and after each condition to assess potential decreases in this induced torque (where a negative difference indicates a decrease). No significant differences

Authorized licensed use limited to: Imperial College London. Downloaded on September 11,2025 at 08:42:20 UTC from IEEE Xplore. Restrictions apply.

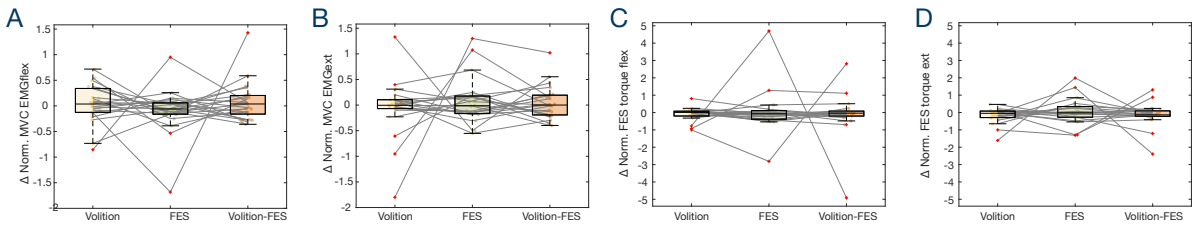


Fig. 2: Difference in mean normalised EMG during MVC trials for the flexor MVC (A) and extensor MVC (B), and in mean normalised FES-induced torque for the flexor stimulation (C) and extensor stimulation (D), for each condition. A negative difference indicates a decrease in MVC or FES-induced torque after the condition compared to before the condition.

in FES-induced torque changes across conditions were observed (FES torque flexor: $\chi^2(2)$ = 4.11, $p = 0.1284$; FES torque extensor: $\chi^2(2)$ = 0.42, $p = 0.8102$). Additionally, there were no significant changes (different from zero) in FES-induced torque within any condition (all $p > 0.1842$). When investigating chronological evolution of this metric, where conditions are considered in the order they were presented to the participants, we did not find an effect of the condition either (FES torque flexor: $\chi^2(2)$ = 3.26, $p = 0.1956$; FES torque extensor: $\chi^2(2)$ = 0.74, $p = 0.6918$).

D. M-wave parameters differences

Additionally, we evaluated the changes of various parameters characterising the M-wave recorded during maximum comfortable stimulation intensity while participants were at rest. We explored differences between the current M-wave peak-to-peak amplitude, duration and area, before and after each condition to assess potential changes in these metrics. There was no significant effect of the condition type on these metrics (MW amplitude flexor: $\chi^2(2)$ = 0.4, $p = 0.8187$; MW amplitude extensor: $\chi^2(2)$ = 0.11, $p = 0.9487$; MW duration flexor: $\chi^2(2)$ = 0.7, $p = 0.7047$; MW duration extensor: $\chi^2(2)$ = 5.05, $p = 0.08$; MW area flexor: $\chi^2(2)$ = 0.7, $p = 0.7047$; MW area extensor: $\chi^2(2)$ = 2.63, $p = 0.2683$). We also examined changes in parameters for each phase of the M-wave separately but found no significant effect of the condition (all $p > 0.0648$). When assessing whether changes within each condition differed from zero, no significant results were found for any full M-wave parameters across conditions (all $p > 0.062$). However, in the Volition-FES condition, significant changes were observed in the MW2 amplitude ($p = 0.0442$) and MW2 area ($p = 0.0329$) during extensor stimulation. Similarly when considering the data chronologically, regardless of the condition type, no effect of the condition was observed (MW amplitude flexor: $\chi^2(2)$ = 0.3, $p = 0.8607$; MW amplitude extensor: $\chi^2(2)$ = 2.63, $p = 0.2683$; MW duration flexor: $F(2)$ = 1.94, $p = 0.1536$; MW duration extensor: $\chi^2(2)$ = 0.95, $p = 0.6227$; MW area flexor: $\chi^2(2)$ = 1.3, $p = 0.5220$; MW area extensor: $F(2)$ = 0.15, $p = 0.8648$).

E. Changes in performance metrics across conditions

Fig. 3 A shows the changes in RMSE across trials for each condition. In the Volition and FES conditions, we observed a significant effect of trial number on RMSE, with a positive slope indicating a slight decrease in tracking performance (Volition: slope = 0.0275, $t(461) = 2.282$, $p = 0.023$; FES: slope = 0.0278, $t(461) = 5.171$, $p < 0.001$). In contrast, the Volition-FES condition showed no significant slope (slope = 0.0027, $t(461) = 0.245$, $p = 0.806$). When investigating the difference in RMSE between the last three trials and the first three trials for each condition, we found no significant effect of condition ($\chi^2(2)$ = 0.27, $p = 0.87$). We also considered each condition individually and evaluated whether the change in RMSE across each condition is significantly different from zero. There, we found that RMSE change during the FES condition is significantly different from zero ($p = 0.0112$), with a positive median, indicating a decrease in tracking performance throughout the condition.

F. Changes in effort across conditions

We examined how the mean cocontraction (CC) and reciprocal activation (RA) of the wrist flexor and extensor varied over trials in each condition, to measure voluntary effort (Fig. 3 B, C). For the CC, we observed a significant negative effect of the trial number on the FES (slope = -0.0004, $t(437) = -2.125$, $p = 0.0341$) and Volition-FES (slope = -0.0016, $t(437) = -4.344$, $p < 0.001$) conditions, suggesting adaptation and learning. However, the slope was not significant in the Volition condition (slope = -0.0003, $t(440) = -0.991$, $p = 0.322$). For RA, a significant positive slope was observed in the Volition-FES condition (slope = 0.0004, $t(437) = 2.811$, $p < 0.0052$), while non-significant effects were found in the other two conditions (Volition: slope = -0.0005, $t(440) = -1.491$, $p = 0.137$; FES: slope = 0.0002, $t(437) = 1.931$, $p = 0.0541$). Additionally, in the (relaxed) FES condition, the median of the normalised RA and CC was lower compared to the other two conditions, where participants actively followed the target (Fig. 3 B, C). We also investigated whether changes in mean CC and RA, over trials differed across conditions by computing the difference between the last three and first three trials and did not find a significant effect of condition type (CC: $\chi^2(2)$ = 2.67, $p = 0.264$; RA: $\chi^2(2)$ = 0.38, $p = 0.827$).

IV. Discussion

The aim of this study was to determine whether FES-assisted tasks, similar to those used in rehabilitation, induce muscular fatigue, and how this should inform the design of FES-based motor rehabilitation systems. We explored the effects of FES-induced and voluntary motion on perceived and muscular fatigue, performance, and effort during a continuous target-tracking task.

Authorized licensed use limited to: Imperial College London. Downloaded on September 11,2025 at 08:42:20 UTC from IEEE Xplore. Restrictions apply.

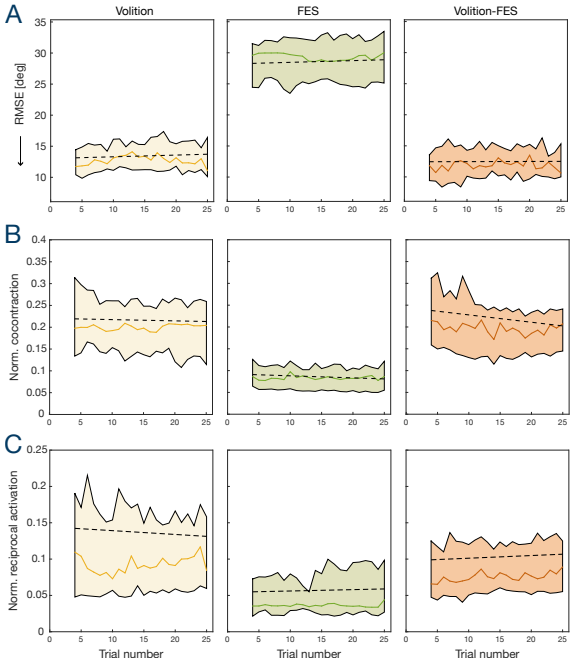


Fig. 3: Evolution of performance metrics across trials for each condition: RMSE between the participant's and target positions (A), cocontraction of the wrist flexor and extensor (B), reciprocal activation of the wrist flexor and extensor (C). The lines represent the median of each metric computed over all participants and the shaded areas represents the data from the first to third quartile of the metric. The first three trials are excluded as they were used as familiarisation trials.

A. Subjective, mechanical and electrical responses after condition

We did not observe significant changes in mechanical responses following each training block involving FES-induced and/or voluntary wrist motion aimed at tracking a continuously moving target, as was indicated by consistent MVC torque output across all conditions (Fig. 2 A, B). Similarly, no significant changes were detected in the electrical response, as assessed by the M-wave response to maximum stimulation and the constant FES-induced torque across conditions (Fig. 2 C, D). Since fatigue is typically characterised by a reduction in maximal power or force output [29], the absence of changes in MVC before and after each condition suggests that fatigue did not develop over time in this study. The M-wave parameters measured under maximum comfortable stimulation after each condition also remained stable, indicating that the muscle's electrical response was unaffected by the tracking task conditions. Even when separating the M-wave phases to compute these parameters—which has been found to be more suitable for fatigue estimation during tasks involving changes in muscle architecture—we did not find any changes across conditions [12], [21]. These findings contradict our initial hypothesis that the Volition-FES condition would result in greater fatigue compared to the Volition condition.

Indeed, previous research has shown that fatigue tends to be greater in conditions involving electrical stimulation, potentially due to the unnatural recruitment patterns and the early recruitment of fast and fatigable muscle fibres under FES [3]. However, despite the task being designed to simulate an FES-assisted rehabilitation scenario, and involving continuous stimulation for 25 trials of 30 seconds each, it did not induce noticeable muscular fatigue. This may be attributed to the task not being sufficiently challenging or tiring for participants. The mean questionnaire ratings indeed suggest that the task was not physically demanding, with ratings consistently lower than or equal to 6/10 across conditions. Literature on fatiguing protocols typically involves more intense conditions, such as 1-5 minutes of MVC or 1-3 minutes of tetanic stimulations [12]. This may also be related to the electrode configuration used for stimulation in this experiment, which may not have been optimal for extracting parameters from the M-wave, as a monopolar (belly-tendon) configuration is typically recommended. In this study, we used the FES electrode placement recommended by our clinical collaborators and employed in our clinical studies [23]. This choice may have made the recordings more susceptible to crosstalk and positional shifts, particularly since the wrist flexor and extensor muscles of interest are relatively small [12]. On the other hand, the aim of this study was to explore whether FES-assisted motor training, relevant for post-stroke rehabilitation, induces fatigue, and while muscle fatigue might manifest differently in stroke patients, it was not observed in the unimpaired participants in this scenario. The mechanical and electrical response of stroke patients' muscles following FES-based rehabilitation exercise should be further investigated to confirm whether these findings translate to the target clinical population.

B. Performance and effort across conditions

We also investigated the evolution of metrics potentially associated with muscle fatigue over time, including tracking performance, cocontraction, and reciprocal activation (Fig. 3). Tracking performance decreased over trials in both the Volition and FES conditions (Fig. 3 A). This was also confirmed by the increase in tracking error between the first three and last three trials in the FES condition. This suggests that, over time, the stimulation became less effective at contracting the muscles to follow the target trajectory, consistent with previous studies on FES during continuous tasks [30]. It is also possible that the decrease in tracking performance is related to variations in the electromechanical delay between stimulation and motion onset [31], resulting in a delayed motion response relative to the target. This decrease in performance may thus be in part due to fatigue and could be used as a marker of fatigue in a closed-loop control system.

In contrast, the EMG metrics did not show significant performance degradation. A decrease in cocontraction over trials was found in the Volition-FES and FES conditions, together with an increase in reciprocal activation in the Volition-FES condition (Fig. 3). This decrease in cocontraction suggests learning and adaptation, where participants reduce their muscle activation over time and learn to interact

Authorized licensed use limited to: Imperial College London. Downloaded on September 11,2025 at 08:42:20 UTC from IEEE Xplore. Restrictions apply.

with FES assistance [32], [33]. The increased reciprocal activation could suggest that muscle usage became more efficient and movement directionality more pronounced. On the other hand, although no significant decrease in performance and MVC was observed in the Volition-FES condition, the slight increase in reciprocal activation could constitute an early sign of muscle fatigue or a fatigue management mechanism [34].

When further examining the effect of condition on changes in tracking performance and effort from the first to the last trials, we found no significant differences across conditions. This suggests that no single condition led to greater performance reduction or effort alteration compared to others. This outcome was unexpected given the differing physiological processes underlying voluntary and FES-induced muscle contractions [3]. Despite observing higher tracking error and lower muscle activity in the relaxed FES condition, no significant difference in performance or effort changes was found across conditions. This discrepancy may be due to the experimental task design, which did not involve long-duration MVCs or tetanic stimulations as seen in studies reporting fatigue [3], [12]. Overall, these results suggest that continuous FES-assisted tasks, which could be used in post-stroke motor rehabilitation, may be suitable and may not induce significant muscular fatigue.

V. Conclusion

We investigated the impact of FES-induced and/or voluntary movement during a continuous target-tracking task on perceived fatigue, performance, effort, and muscular fatigue in unimpaired participants. Our findings revealed no significant changes in the mechanical and electrical responses of the muscles across any of the three conditions, suggesting that the task did not induce muscular fatigue, although we observed a larger decline in tracking performance in the FES condition, which may indicate that the movement resulting from stimulation could be altered over time without necessarily leading to fatigue. Together, these findings suggest that for this type of continuous FES-assisted task, that can be used in post-stroke rehabilitation, FES-induced fatigue may not be a major factor to be considered.

References

[1] A. S. Gorgey *et al.*, "Effects of Electrical Stimulation Parameters on Fatigue in Skeletal Muscle," *J Orthop Sports Phys Ther*, 2009.

[2] N. A. Maffiuletti, "Physiological and methodological considerations for the use of neuromuscular electrical stimulation." *Eur J App Physiol*, 2010.

[3] C. S. Bickel, C. M. Gregory, and J. C. Dean, "Motor unit recruitment during neuromuscular electrical stimulation: a critical appraisal," *Eur J Appl Physiol*, 2011.

[4] N. Miura and T. Watanabe, "Potential of M-Wave Elicited by Double Pulse for Muscle Fatigue Evaluation in Intermittent Muscle Activation by Functional Electrical Stimulation for Motor Rehabilitation," *J Med Eng*, 2016.

[5] Q. Zhang *et al.*, "FES-Induced Torque Prediction With Evoked EMG Sensing for Muscle Fatigue Tracking," *IEEE/ASME Trans Mechatronics*, 2011.

[6] R. Riener and L. J. Seward, "Cybathlon 2016," in *IEEE Int Conf Syst Man Cybern*, 2014.

[7] J. Eraifej *et al.*, "Effectiveness of upper limb functional electrical stimulation after stroke for the improvement of activities of daily living and motor function: a systematic review and meta-analysis," *Sys Reviews*, 2017.

[8] G. Alon, "Functional Electrical Stimulation (FES): Transforming Clinical Trials to Neuro-Rehabilitation Clinical Practice- A Forward Perspective," 2013.

[9] A. Nehrujee *et al.*, "Long-term Usability and Feasibility of Home-Based Hand Therapy With the Plug-And-Train Hand Rehabilitation Robot(PLUTO)," *Arch Phys Med Rehab*, 2023.

[10] F. B. Stulen and C. J. De Luca, "Frequency Parameters of the Myoelectric Signal as a Measure of Muscle Conduction Velocity," *IEEE Trans Biomed Eng*, 1981.

[11] L. Arendt-Nielsen *et al.*, "Changes in muscle fiber conduction velocity, mean power frequency, and mean EMG voltage during prolonged submaximal contractions," *Muscle & Nerve*, 1989.

[12] J. Rodriguez-Falces and N. Place, "Determinants, analysis and interpretation of the muscle compound action potential (M wave) in humans: implications for the study of muscle fatigue," *Eur J App Physiol*, 2018.

[13] N. C. Chesler and W. K. Durfee, "Surface EMG as a fatigue indicator during FES-induced isometric muscle contractions," *JEK*, 1997.

[14] D. Tepavac and L. Schwirtlich, "Detection and prediction of FES-induced fatigue," *JEK*, 1997.

[15] M. Badier *et al.*, "M-wave changes after high- and low-frequency electrically induced fatigue in different muscles," *Muscle & Nerve*, 1999.

[16] J. Mizrahi *et al.*, "EMG as an indicator of fatigue in isometrically FES-activated paralyzed muscles," *IEEE Trans Rehab Eng*, 1994.

[17] M. Vromans and P. D. Faghri, "Functional electrical stimulation-induced muscular fatigue: Effect of fiber composition and stimulation frequency on rate of fatigue development," *JEK*, 2018.

[18] N. Dimitrova *et al.*, "Estimate of M-wave changes in human biceps brachii during continuous stimulation," *JEK*, 2005.

[19] J. Heasman *et al.*, "Detection of fatigue in the isometric electrical activation of paralyzed hand muscles of persons with tetraplegia," *IEEE Trans Rehab Eng*, 2000.

[20] M. Hayashibe *et al.*, "Evoked EMG-based torque prediction under muscle fatigue in implanted neural stimulation," *JNER*, 2011.

[21] Z. C. Lateva *et al.*, "Anatomical and electrophysiological determinants of the human thenar compound muscle action potential," *Muscle & Nerve*, 1996.

[22] J. Rodriguez-Falces and N. Place, "Muscle excitability during sustained maximal voluntary contractions by a separate analysis of the M-wave phases," *Scand J Med Sci Sports*, 2017.

[23] L. Cazenave *et al.*, "Hybrid Functional Electrical Stimulation and Robotic Assistance for Wrist Motion Training After Stroke: Preliminary Results," in *IEEE ICORR*, 2023.

[24] E. Ivanova *et al.*, "For Motion Assistance Humans Prefer to Rely on a Robot Rather Than on an Unpredictable Human," *IEEE Open J Eng Med Biol*, 2020.

[25] H. Kavianirad *et al.*, "EMG-Based Volitional Torque Estimation in Functional Electrical Stimulation Control," in *IEEE EMBS*, 2022.

[26] H. Nieminen *et al.*, "Normalization of electromyogram in the neck-shoulder region," *Eur J Appl Physiol*, 1993.

[27] B. Castelein *et al.*, "Optimal Normalization Tests for Muscle Activation of the Levator Scapulae, Pectoralis Minor, and Rhomboid Major: An Electromyography Study Using Maximum Voluntary Isometric Contractions," *Arch Phys Med Rehab*, 2015.

[28] R. A. Ekstrom *et al.*, "Normalization procedures using maximum voluntary isometric contractions for the serratus anterior and trapezius muscles during surface EMG analysis," *JEK*, 2005.

[29] N. K. Vøllestad, "Measurement of human muscle fatigue," *J Neurosci Methods*, 1997.

[30] B. C. Allen *et al.*, "Characterization of the Time-Varying Nature of Electromechanical Delay During FES-Cycling," *IEEE TNSRE*, 2020.

[31] R. J. Downey *et al.*, "The Time-Varying Nature of Electromechanical Delay and Muscle Control Effectiveness in Response to Stimulation-Induced Fatigue," *IEEE TNSRE*, 2017.

[32] K. A. Thoroughman *et al.*, "Electromyographic Correlates of Learning an Internal Model of Reaching Movements," *J Neurosci*, 1999.

[33] D. W. Franklin *et al.*, "Adaptation to Stable and Unstable Dynamics Achieved By Combined Impedance Control and Inverse Dynamics Model," *J Neurophysiol*, 2003.

[34] B. Prilutsky and R. Gregor, "Analysis of muscle coordination strategies in cycling," *IEEE TRE*, 2000.

Authorized licensed use limited to: Imperial College London. Downloaded on September 11,2025 at 08:42:20 UTC from IEEE Xplore. Restrictions apply.