Are there brain-based predictors of the ability to learn a new skill in healthy ageing and can they help in the design of effective therapy after stroke?

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Abstract

This thesis aimed at looking for neural correlates of motor adaptation as a model of rehabilitation after brain injury. Healthy adults across the lifespan and stroke patients were tested in a force-field learning paradigm. This thesis focuses on EEG analysis and the complex relationship of brain-derived measures with observed behaviour.

To describe each domain in detail, the focus was first on finding group differences between older and younger healthy adults in a similar manner as it was later between stroke patients versus healthy controls. The analyses were finalised by looking for relationships between the EEG and motor performance data in a multiple linear regression approach.

As candidate EEG biomarkers of motor adaptation, error related event related potential around movement onset in the frontocentral electrodes was chosen in time domain. In the time-frequency domain, the focus was on movement related beta band spectral perturbation, looking at the electrodes over the primary motor cortex and the frontocentral ROI found significant in the time domain. Finally, functional connectivity was analysed focusing first on electrode over the primary motor cortex contralateral to the movement as a seed region, to narrow down the analysis to bilateral motor cortex connectivity and connectivity between primary motor cortex contralateral to the movement and the frontocentral region identified as important in the time domain analysis. The crucial part of the project was analysing the relationship between the neural and kinematic measures.

The most important predictor of summed error in motor adaptation was the connectivity between C3 and C4 electrode at the baseline prestimulus period in motor

adaptation condition and pinch asymmetry. Higher prestimulus interhemispheric connectivity was associated with bigger deviation from the optimal trajectory. When looking at summed error dynamic derivative as a dependent variable - performance index - it was the ERP at the central error-related ROI that explained the most variance. It can be concluded that higher baseline interhemispheric connectivity can be a reflection of a maladaptive process, perhaps related to increased interhemispheric inhibition. It is important to also note that the same connectivity at different timepoints in the movement can be of different significance - differences between stroke patients and controls were present in the postmovement period.

In conclusion, brain information could be helpful for e.g. stratifying patients into different intensity programs based on their predicted potential to recover. Moreover, brain information could be utilised to apply closed-loop systems modulating the intensity of tasks to reach the optimal brain state that facilitates learning. I believe this work will help incorporating brain-derived measures in informing neurorehabilitation programmes in the future.

Declaration

I declare that the work reported in this thesis was carried out in accordance with the regulations of the University of East London. The work is novel except where indicated by special reference in the text and no part of this thesis has been submitted for any other degrees. Any views expressed in the dissertation are those of the author and in no way represent those of the University of East London.

The thesis has not been presented to any other University for examination either in the United Kingdom either overseas.

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Abbreviations

ACC	anterior cingulate cortex
EEG	electroencephalography
EMG	electromyography
ERP	event related potential
ERSP	event related spectral perturbation
Fam	familiarization
Fam_l	late familiarization
FC	functional connectivity
fMRI	functional magnetic resonance imaging
M1	primary motor cortex
MA	motor adaptation
MA_e	early motor adaptation
MA_l	late motor adaptation
MRI	magnetic resonance imaging
PLV	phase locking value
PM	premotor cortex
PPC	posterior parietal cortex
ROI	region of interest
SMA	supplementary motor area
TOI	time of interest

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1. Introduction

The notion of neuroplasticity is defined both as a developmental or epigenetic process in a healthy brain and as recovery in an injured brain. Brain injured patients, often with similar levels of disability, can show very different responses to rehabilitation (Juenger et al., 2013) and the cause of this is probably linked to the potential for neuroplasticity to take place. Whereas recovery outcomes can be easily observed, it is still uncertain what internal mechanisms promote good recovery. It has been postulated that it is the inclusion of brain derived measures that can promote development of better rehabilitation programmes (Ward, 2017) and the search for recovery biomarkers is an ongoing effort in many different research groups (Triccas et al., 2019; Boyd et al., 2017; Stinear, 2017).

In hope of a better understanding of recovery from acquired brain injury, in this thesis, I search for internal neural correlates of the differences in the ability to adapt motor behaviour in a new environment in different populations that vary in their potential for neuroplasticity. It is known that changes not only in brain activity, but also in brain volume can be observed following new motor skills learning both in young and older adults (Bezzola, Merillat, Gaser, & Jancke, 2011; Boyke, Driemeyer, Gaser, Büchel, & May, 2008). In the case of brain injured patients, the learning process may be disrupted or different to that observed in the healthy population (Scheidt & Stoeckmann, 2007).

The following questions arise: Can we predict the ability to adapt the motor activity to a novel environment based on a brain-based measure? Can it help us decide

whether a patient after a brain injury will be able to undertake a training programme with success? Can it lead us to design a tailor-made rehabilitation programme?

The purpose of the thesis is to analyse the neuroplasticity processes accompanying motor skill learning. This purpose will be addressed in a force-field learning paradigm, measuring EEG correlates of motor adaptation in healthy participants across the lifespan and in stroke patients.

1.1. What is motor adaptation

Motor skill learning is a blanket term encompassing different motor skill acquisition processes. The ones that have been identified as the most pertinent to neurorehabilitation are motor adaptation and motor learning. They have been defined as distinct processes (Krakauer & Mazzoni, 2011).

Motor adaptation is defined as learning of a previously known motor skill in presence of a perturbation. It is characterized by a gradual improvement of performance, but contrary to motor learning, the skill fades quickly after the perturbation is no longer in place. It is typically studied with error-based experimental paradigms, such as visuomotor rotation and force-field tasks (Krakauer & Mazzoni, 2011).

It is important to discern the difference between motor adaptation and more complex motor learning, which involves acquisition of a completely new motor skill. Applying either the model of motor adaptation or motor learning to motor rehabilitation in brain injury has different implications (Dipietro et al., 2012). More specific differences between the two processes are discussed in Table 1.

	Motor adaptation	Motor skill learning
Definition	Adjustment of an existing motor skill to different environmental conditions	Acquisition of new motor skill
Perturbation	Movement perturbation is present	No perturbation
Level of performance	Skill is improved to the level previously acquired	Improvement present
Potential for generalization	No generalization	Allows limited generalization
Stability of effects	After-effects short lived	Improvements maintained over time
Sleep dependency	Not sleep dependent	Sleep dependent
Neural substrates	Corticocerebellar system	Corticostriatal system
Implications of the model for rehabilitation	Train exhaustive set of tasks	Train through more sparse set of tasks

Table 1.1. Differences between motor adaptation and motor learning.

Adapted from details given in several reviews (Debas et al., 2010; Dipietro et al., 2012; Krakauer & Mazzoni, 2011; Winstein, Merians, & Sullivan, 1999).

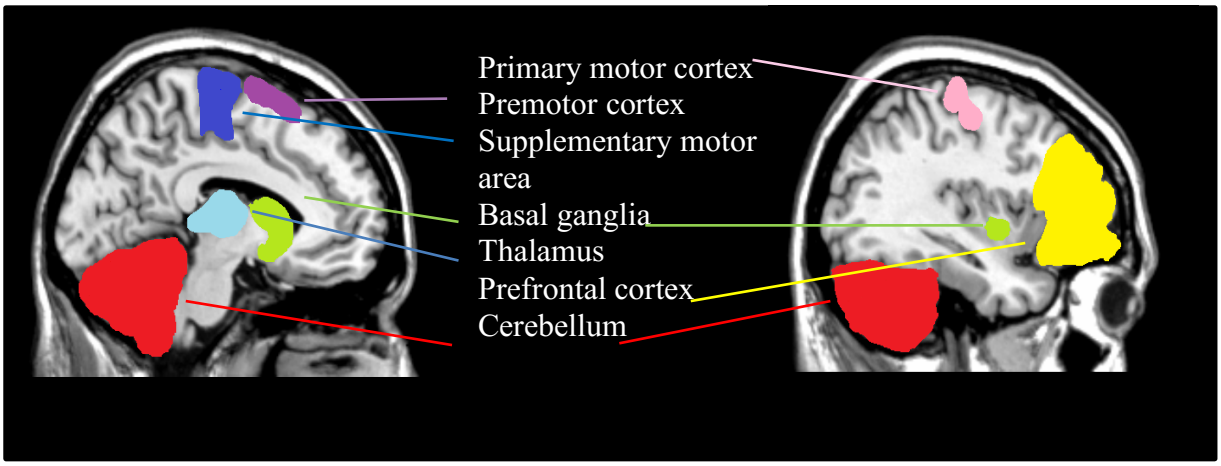
1.2. Neural structures supporting motor adaptation

The effects of adaptation have been observed both in the periphery (kinematic data, muscle activity) and in the central nervous system (Shadmehr & Holcomb, 1997). A typical target skill in force field tasks is upper limb movement adaptation. In the periphery, motor adaptation is expressed by decreasing errors in movement (e.g. Hunter et al., 2009) and accompanied by a typical muscle activation pattern, with an initial increase of muscle activity and followed by a reduction thereafter (Pizzamiglio, Desowska, Shojaii, Taga, & Turner, 2017; Pizzamiglio, De Lillo, Naeem, Abdalla, & Turner, 2016; Darainy & Ostry, 2008; Thoroughman & Shadmehr, 1999).

At the neural mechanism level, it is a predictive model formation process that is responsible for successful adaptation. The mechanism explaining that behaviour is trial-to-trial updating of the internal model of the future movement based on the previous movement feedback, and motor to sensory mapping (Krakauer & Mazzoni, 2011; Wolpert & Miall, 1996). There is substantial evidence on predictive forward modelling in the sensorimotor system, allowing fast feedback control of reaching movements (Desmurget & Grafton, 2000). These powerful computations happen online in the central nervous system.

The anatomic areas consequently found to be associated with motor skill acquisition in fMRI studies are (figure 1): primary motor cortex (M1, Brodmann Area(BA) 4), premotor cortex (PM, BA6), supplementary motor area (SMA, medial BA6), dorsolateral prefrontal cortex (PFC, BA 9,10), basal ganglia, cerebellum, and sensory cortex (S1, BA 1,2,3) (Ghilardi et al., 2000; Tomassini et al., 2011).

Of these, two systems supporting motor skill learning emerge including the cortico-thalamic-cerebellar and the cortico-thalamic-striatal circuits (Debas et al., 2010; Hikosaka, Nakamura, Sakai, & Nakahara, 2002; Krebs et al., 1998; Lohse, Wadden, Boyd, & Hodges, 2014).



Medial view (more) lateral view

Figure 1.1. Neural correlates of motor skill learning.

Based on Ghilardi et al. (2000), Hardwick, Rottschy, Miall, and Eickhoff (2013); images based on MRIcron template (Rorden & Brett, 2000).

It has been suggested that motor adaptation is associated more with the corticocerebellar system activity, whereas the more effective motor learning relies on the corticostriatial system (Debas et al., 2010). Also Krebs and colleagues (1998) distinguish the role of these two neural systems in the learning process, connecting the right cortico-striatal system with early phases of learning whereas the cortico-cerebellar loop becomes more involved with late learning. The role of the prefrontal cortex seems to be more generally connected to cognitive control over actions (Miller & Cohen, 2001) but recently was demonstrated to be involved in motor adaptation mechanisms possibly through an 'active inference' process (Faiman et al., 2018). A structure especially important for motor planning and execution is the SMA and pre-SMA (Nachev, Kennard, & Husain, 2008; Picard & Strick, 2003; Tanji, 1996). The signal from this region recorded by EEG, due to low spatial resolution related to the volume conduction problem (see Chapter 2), can come also from a deeper structure - anterior cingulate cortex (ACC), important in the dopaminergic system responsible for error processing (Krigolson & Holroyd, 2006). Another element of that system is the posterior parietal cortex (PPC), which is also responsible for integration of visual sensory information and motor sensory feedback (Krigolson & Holroyd, 2006).

In experiments on long-term motor adaptation, a shift between the activation in the prefrontal areas and frontal eye fields in early phases of adaptation to the cerebellum and sensorimotor and parietal cortex activation has been observed (Della-Maggiore & McIntosh, 2005; Shadmehr & Holcomb, 1997), also suggesting a different role of the frontal attentiona and parietal sensorimotor systems in the adaptation process.

1.3 Ageing and motor adaptation

It is known that the ageing process influences the integrity of white matter structure (Salat et al., 2005). Older adults compensate less white matter integrity with more task-related brain activation, ('less-wiring-more-firing' hypothesis (Daselaar et al., 2015)). During motor tasks, there is age-related increase in brain activation in older adults (Hutchinson et al., 2002; Ward & Frackowiak, 2003). During performance of a unilateral hand motor task, older adults exhibit more brain activation and it is more bilateral, even if their performance is matched to that of young adults (Hutchinson et al., 2002; Wu & Hallett, 2005).

During a motor task, beta oscillations over the primary motor cortex are changed in older adults, with greater resting baseline beta power and greater movement related beta desynchronisation during the movement in ipsilateral M1, suggesting greater inhibitory activity (Rossiter, Davis, Clark, Boudrias, & Ward, 2014). During a continuous motor control task, a neural signature of error processing was diminished in older adults, which was accompanied by more error commission (Colino et al., 2017). Whole-brain networks seem to be characterised by increased functional connectivity in ageing during a motor task, and it is hypothesised that this hyperactivation of task-specific networks facilitates the maintenance of motor performance in older adults (Larivière et al., 2019). In all domains there are changes in brain functioning noted in older adults during motor execution tasks, however changes during specifically motor adaptation tasks still need to be uncovered (Huang & Ahmed, 2014).

Both motor adaptation and skill learning are impaired in older adults (Hardwick & Celnik, 2014). Implicit skill learning peaks at the age of 12, declining steadily

afterwards (Janacsek, Fiser, & Nemeth, 2012). Both motor adaptation and skill learning are less accurate in older adults (Hardwick & Celnik, 2014), however older adults are still able to reach the optimal adaptation outcome in prism adaptation paradigm (Fernández-Ruiz, Hall, Vergara, & Díiaz, 2000). It seems that it is not the mechanism of updating internal model that is responsible for this decline, but decline in cognitive resources (Seidler, 2006; Vandevoorde & Orban de Xivry, 2019).

1.4 Stroke and motor adaptation

[This section is adapted from our published systematic literature review (Desowska & Turner, 2019). See Appendix 5 for full publication and all referenced work from other groups that are summarised in the following section]

According to the Global Burden of Disease Study, stroke is the second most common cause of death and the third most common cause of disability worldwide with 25.7 million stroke survivors and 10.3 million new strokes in 2013 (Feigin, Norrving, & Mensah, 2017). In the UK, there are around 1.2 million stroke survivors and half of them are left with an impairment, which makes stroke the largest cause of complex disability (Adamson, Beswick, & Ebrahim, 2004). The most frequent type of disability is upper limb weakness, which is found in 77% of disabled stroke survivors (Lawrence et al., 2001).

The number of stroke survivors and people with incident stroke have increased by 50% to 100% during the last 25 years due to improved stroke care, aging and growth of the population alongside increased prevalence of stroke risk factors, leaving growing numbers of stroke survivors in need for effective rehabilitation (Feigin et al., 2017). The

original insult resulting in motor disability occurs in the brain, so there is need for understanding brain processes underlying recovery. Recovery is a dynamic process with neural system reorganizing structurally and functionally to accommodate for the change caused by stroke. The insight into that process is best achieved by longitudinal studies tracking the change in the system. Ultimately it is the change of the functional architecture in the brain after an insult that can shed more light on the behaviour of this system, how it adapts to the change, and the functional meaning of these adaptations.

Motor dysfunction of the upper extremity has been extensively studied in stroke as it is one that is genuinely debilitating in every-day life. Many innovative interventions have been designed to specifically target this problem including robot-assisted training (Rodgers et al., 2017; Rodgers et al., 2019), constrained-induced movement therapy (Wolf et al., 2010), brain stimulation techniques (Fregni et al., 2006), neurofeedback (Mihara et al., 2013; Mottaz et al., 2015) and training with a brain-machine-interface (Bundy et al., 2017; Ramos-Murguialday et al., 2013). The effects of some of the therapies seem promising and hand function may show signs of recovery even in the chronic phase of recovery, although not in every patient (Ward, 2017). However, it has remained a mystery why patients with similar initial levels of motor impairment after a stroke can recover hand function to markedly different degrees (Boyd et al., 2017; Turner, Tang, Winterbotham, & Kmetova, 2012). Since the original insult happened in the brain, answering that question taking into account only the musculoskeletal system is impossible.

As a result of high variability in recovery of motor function, more recent effort has focussed on not only recovery in terms of behavioural motor output, but also on

possible recovery of affected brain networks (Ward, 2017). In terms of brain structure, the lesion location is an important factor that predicts motor function outcome (Park, Kou, & Ward, 2016; Rondina, Filippone, Girolami, & Ward, 2016). The corticospinal tract, connecting the primary motor cortex (M1) with the motor effectors, is one of the most crucial structures for hand function and thus corticospinal tract damage can lead to further changes in structural connectivity (Koch, Schulz, & Hummel, 2016) even in the contralesional hemisphere (Lin et al., 2015), however there is still need for more large-scale longitudinal studies on that subject (Koch et al., 2016).

When analysed from the perspective of neural activation, the brain shows compensatory activity within the contralesional motor cortex in the days and weeks following a stroke that has affected hand function (Bajaj et al., 2016). During recovery, a return to the ipsilesional M1 activation pattern is a typical result in classic fMRI activation studies utilising simple motor tasks (Ward & Frackowiak, 2006). However, brain activation accompanying other motor-related functions can still remain altered. For example, during the process of acquiring a new motor skill over time, a decrease of activation after training is present in healthy controls, whereas no change or increase in activation occurs in stroke patients, notably in the areas that seem structurally disconnected before learning (Bosnell et al., 2011).

However, even if the basic neural activation pattern related to hand movement may appear normal, there might still be changes of the network functional architecture during recovery following a stroke (Pellegrino et al., 2012; Sharma et al., 2009). Studies analysing correlations between activations in different regions employ typically two approaches: functional and effective connectivity. The first focuses on observing non-

directional temporal associations between brain systems usually based on correlation or phase synchrony measures, the latter focuses on tracking the causal influence one region exerts on another, utilising different modelling measures like Granger's causality or Dynamic Causal Modelling to name the most popular (Friston, Moran, & Seth, 2013).

A typical finding in stroke connectivity studies is decreased functional connectivity (FC) in the perilesional area observed shortly after the insult that slowly resolves with time; a process predicting recovery (Westlake et al., 2012). On the other hand, increased FC was observed after stroke expressed as an increase in small-world network efficiency in the gamma frequency band and an increase in the interhemispheric connectivity in stroke patients during a simple finger extension task (Fallani et al., 2017). There may be complex relationships between structural connectivity and FC following a stroke such as reduced M1 fractional anisotropy (structural connectivity) in the anatomical connection between M1 of both hemispheres (Liu, Qin, Zhang, Zhang, & Yu, 2015). This may be accompanied by increased resting state FC between the same two structures, suggesting that the activity is somewhat compensatory to structural damage (Liu et al., 2015). Further, there can be an increased activation *and* resting state FC in an intact ipsilesional M1 region, accompanied by reduced ipsilesional M1 cortical thickness (Zhang et al., 2014).

In case of stroke affecting the hand function, there is visible compensatory activity within the unaffected motor cortex in the days and weeks following the insult. Return to the ipsilesional primary motor cortex activation pattern with recovery is a typical result observed in classic fMRI studies (Ward & Frackowiak, 2006).

Connectivity studies suggest the lesioned hemisphere plays an important role in the process of recovery, with underconnectivity in the perilesional area observed shortly after stroke and reducing with time, which is a predictor of recovery (Grefkes & Ward, 2014; Westlake et al., 2012). However, even in well recovered stroke patients, the contralesional hemisphere may still play a role in supporting the hand function (Grefkes & Ward, 2014; Simis et al., 2015). This process however can be also maladaptive, since the increase in connectivity can be actually an expression of an inhibitory connection coming from the unaffected hemisphere that is related with worse hand function (Rehme, Eickhoff, Wang, Fink, & Grefkes, 2011).

Recovering from a cardiovascular episode, in which motor functions are initially affected, is argued to be a specific case of motor learning (Dipietro et al., 2012; Lefebvre et al., 2015), thus applying the mechanisms of motor skill learning to motor recovery from stroke could promote recovery (Matthews, Johansen-Berg, & Reddy, 2004).

What happens to the motor learning process itself after stroke remains still uncertain. Stroke patients are still able to learn new motor skills (Meehan, Randhawa, Wessel, & Boyd, 2011). Winstein and colleagues (1999) argue that it is rather motor execution and control that are affected in hemiplegia rather than the learning ability itself. Dipietro and colleagues (2012) argue that it is learning, not adaptation, that drives recovery in stroke.

Scheidt and Stoeckmann (2007) analysed the strategy of motor learning in stroke patients. Their finding suggested that although the strategy is the same both in stroke

and in healthy adults, stroke patients rely on sensory feedback from the previous task to a lesser extent than healthy participants.

There is scarce fMRI evidence on neural correlates of motor learning. Carey et al. (2002) found that chronic stroke patients show a bilaterally reorganized pattern of fMRI activation, relying more on the contralesional hemisphere during motor performance, which shifts to the ipsilesional hemisphere after training. Similarly, Boyd and colleagues (2010) found that motor training induces reduction in the volume of contralesional fMRI activity. Bosnell et al. (2011) showed that although stroke patients show less activation in the ipsilesional hemisphere during a motor task, this activation fails to reduce with training, as it is the case in healthy participants.

The activation in dorsal premotor cortex in the affected hemisphere has been found to correlate with motor learning in stroke patients. Premotor cortex has been previously found to play a role in both motor recovery from brain insult (Carey et al., 2002; Lefebvre et al., 2015) and motor learning in healthy participants (Meehan et al., 2013). Meehan et al. (2011) found that stroke patients compensate for their motor deficits with more activation in dorsolateral PFC during motor skill learning as compared with healthy adults.

To sum up, motor learning processes are a promising model of recovery from a brain injury. These processes have been traditionally researched in the musculoskeletal effector system and the body of knowledge about the underlying brain processes is only emerging. Moreover, brain related studies were mostly conducted using fMRI technique and for a dynamic process as learning, EEG offers more optimal – superior to fMRI –

temporal resolution. The evidence of EEG correlates of motor adaptation is scarce and to our knowledge there has been no EEG studies on motor adaptation in stroke population.

1.5. Research questions

Stroke patients seem to be able to adapt their motor behaviour to a new environment. However, performance data suggest that they do it in a different way compared to healthy adults (Scheidt & Stoeckmann, 2007). It is argued that recovery of motor function post brain injury is a specific example of motor learning (Dipietro et al., 2012), but can we model the recovery process on healthy motor learning? Or is there a specific, different pattern of learning, when the potential for the neuroplasticity is lower than in healthy adults? The answer to that question lies in the brain activity, yet there is little knowledge on the neural correlates of motor learning when the plasticity potential is diminished.

The aim of the thesis was to better understand the process of motor adaptation over the healthy lifespan and apply that knowledge to find out more about motor recovery after a stroke. I was interested specifically in understanding what happens in the brain during motor adaptation, since brain injury is where the behavioural changes originate after a stroke. I was hoping to use that knowledge to formulate future directions on how to use the results in designing better rehabilitation strategies.

As a technique electroencephalography (EEG) was chosen due to its superior temporal resolution crucial for capturing fast-paced neural changes in a dynamic process of learning. Even though the EEG technique appears optimal for the process, there has

been a very limited body of research using EEG accompanying dynamic movement in force field motor adaptation. Faiman et al. (2018) and Ozdenici et al. (2017) used force field learning paradigm to analyse only resting state data, and Tan et al. (2014) and Torrecillos et al. (2015) analysed only post and premovement oscillations utilising different combination of adaptation paradigm, utilising rotational, force-field and target displacement errors. Another great advantage of the EEG technique is portability, that can allow to gather data on the bedside or in the move and cost effectiveness that facilitates using the technique in clinics (see chapter 2).

To meet the aims of the project, EEG was recorded during a robot mediated force-field learning task, where the participants adapted their arm movements. I set out to first identify EEG correlates of a motor adaptation process and to see if it is affected by ageing, and to finally investigate the mechanisms of plastic changes in an injured brain.

The approach was exploratory, assuming that specific patterns of EEG activation that accompany motor adaptation can be uncovered. To explore it, the data in the time and time frequency domain were analysed, looking at event related potentials (ERP, chapter 4), event related spectral perturbation (ERSP, chapter 5) and in terms of connectivity using phase locking value (PLV, chapter 6).

The general framework of the hypotheses involved three steps. In the first step, the classical movement-related characteristics of brain activity was sought, such as the motor potential expressed as negative deflection in ERP with a peak around the movement onset (chapter 4), movement related beta desynchronisation in the time

frequency domain (chapter 5) as well as an increase in functional connectivity of electrodes over the primary motor cortex around movement onset (chapter 6). These well research movement related patterns were found as expected.

The second step involved hypotheses there about the differences between simple robot assisted reaching and reaching in a force field to establish how the neural signatures of motor execution change with motor adaptation. The specific hypotheses were based on error processing literature, with most studies reporting error related negativity ERP (chapter 4) and increased functional connectivity related to training (chapter 6), however task-related measures were very scarce in literature. Indeed, the neural signatures of motor adaptation expressed as differences between the familiarization and motor adaptation stages of the paradigm were found in ERP and PLV.

In a third step of analyses, it was sought to understand how neural correlates of motor adaptation change in stroke. More wide-spread and less specific activation was expected, with stroke patients using more resources to maintain motor performance and decrease of functional connectivity after stroke, but this step was the most exploratory in nature since there is no literature on EEG correlates of motor adaptation after stroke. ERP and PLV analysis showed significant differences in motor adaptation related activity between stroke and healthy participants.

Finally, I looked for relationships between kinematic and brain measures in the hope of building a consistent view of neural correlates of motor adaptation that could inform therapeutic interventions and found two measures that show potential to be

clinically useful – premovement PLV for stratification of the patients and ERP for modulation of the learning process.

Based on literature, the regions of interest were built over two regions crucial for motor execution and planning - primary motor cortex (M1) and supplementary motor area (SMA). Another region of interest that emerged from literature search was the anterior cingulate cortex (ACC), related to dopaminergic-based system of error processing. Due to the nature of EEG, the signal from this area overlaps with the SMA signal.

I focused on dynamic changes accompanying movement, so as a start of each analysis, I looked at the time of interest around the movement onset to understand the pre- versus post-movement initiation change. I then expanded out times of interest to seek out changes over the span of whole trials or to seek out EEG signal change in further specific time periods.

To summarise thusfar, I used EEG in a robot-mediated force-field learning paradigm to identify neural correlates of motor adaptation and their changes in stroke in hope to find biomarkers that could inform designing neuroscience-based rehabilitation programmes in the future.

2. General methods

2.1. The EEG signal origin

EEG is a neurophysiology technique known for a century. It allows to measure brain electric activity as a difference between electrical potentials between the recording electrode and a set reference electrode on the scalp level.

The electric activity is generated by open field neural cells, mostly populations of pyramidal cell positioned in parallel alignment and the actual signal is generated by their postsynaptic potential. The postsynaptic potential is created as a result of influx of ions of positive valence through the cell membrane to the cell, leading to membrane repolarization and creation of source and sink dynamics surrounding the neurons (Nunez & Srinivasan, 2006). The signal can be detected by EEG when 10000 - 50000 cells are synchronously active (Murakami & Okada, 2006). To reach the sensor, the electrical signal travels through tissue with different conductive properties, scalp, skull and cerebrospinal fluid, and gets attenuated and distorted. Due to the nature of volume conduction, it travels in different directions and can be detected from different positions on the scalp.

Because of the volume conduction problem, meaning that many electrodes in different locations can pick up a signal coming from the same neural source, EEG is characterised by poor spatial resolution, but its main advantage is high temporal resolution, with data recorded in miliseconds.

The key to link the physics of electrical current flow in the neural tissue to cognitive processes in human mind seem to be the neural oscillations - a prominent

feature of EEG data, with characteristic associated with characteristic of studied behaviour (Cohen, 2017).

The brain signal is grouped in specific frequency bands: delta (1-4Hz), theta (4-7Hz), alpha (8-13Hz), beta (13-30Hz) and gamma (30-80Hz) of different functional meaning (Engel & Fries, 2010).

Alpha oscillations expressing the inhibition of neural networks are probably produced by rhythmically firing pyramidal cells, thalamocortical loops, local interneurons among other potential apha generators (Wang, 2010). Alpha oscillations characteristics vary with different cognitive tasks or regions (Cohen, 2017). Generally, it is hypothesized to be responsible for inhibition (Jensen & Mazaheri, 2010) and together with beta they seem to be responsible for more top-down processes (Fries, 2009a), whereas theta has been linked to attentive exploration routines (Fries, 2009b).

Their faster counterparts - gamma oscillations - seem to be the medium for neuron communication, according to the communication through coherence hypothesis (Fries, 2015), but because of the fact that gamma band activity happens in the same frequency band as muscle activity, it is much more difficult to obtain a clear view of these from scalp electrode recordings. According to the author of that concept, it is the gamma rhythm that expresses the most directly the rapid excitation and inhibition between pre-and postsynaptic neuronal groups.

Another advantage of EEG is a relative mobility of the setup, that allows testing in clinics by the bedside or mobile setups and relative cost effectiveness. Which all make it a useful tool in clinical settings.

The choice of neuroimaging method in research settings is not however driven by cost effectiveness only, but rather by the nature of the task or behaviour that is under investigation. In case of the present study that investigates fast-paced changes accompanying motor control and learning, EEG was the best choice.

2.2. Quality of the signal

In an extremely sensitive recording and extremely technical setup, EEG is prone to be contaminated by noise that can be a real challenge in the initial stages of data analysis. The noise is generated by participant per se - mostly originating from contamination of the brain signal with other signal, like movement related muscle signature, heart signal, but also bad EEG cap fit related to individual differences in skull shape or interaction with hair, eye movements or sweating. Also the external environment is a source of noise, like line noise at 50 Hz (in the UK) or bad contact of the electrode with the scalp, and the more electrical equipment is used in the experimental setup, the more risk for noise contamination.

To account for the noisy nature of EEG data, many sophisticated signal pre-processing techniques have been developed to allow obtaining the best quality for further analysis. The techniques in general involve filtering data in a specific band, rejection of bad channels and epochs and identification and rejection of artifactual signal from the data. Also offline choice of the reference electrode can influence the final results (Trujillo, Stanfield, & Vela, 2017). There are many options for performing the preprocessing steps and it is by no means a complete discussion (de Cheveigné & Arzounian, 2018; Gabard-Durnam, Mendez Leal, Wilkinson, & Levin, 2018).

2.3. EEG measures

Once the data is clean, there are next steps to obtain the form of data that could undergo standard statistical analysis.

For the time domain data, event related potentials (ERP) are used, which are simple arithmetic averages of the obtained potentials for a certain number of trials for each participant per each experimental condition. Averaging over a number of trials allows for additional control of inter trial variability seen in brain signals, but removes the multidimensional and dynamic aspects of the signals (Luck, 2005; Makeig et al., 2004) .

To understand the brain signal further, analysis moves into the frequency domain. By decomposing the signal by different techniques, most popular being Fourier of Hilbert transform (Gabor, 1946); (Lyons, 2010), the signal's different frequency components are extracted, bearing now information of phase and amplitude of the oscillations at each frequency point. In case of event related data, a time-frequency approach is utilised, that allows frequency decomposition at each timepoint, result being a matrix of time by frequency data. This decomposition is usually performed using wavelets of different properties, most popular being Morlet wavelets in gaussian shape multiplied by a sine wave at a specific frequency (Mallat, 1989). The data in time-frequency domain are interpreted as a reflection of neural synchrony, with event related synchronisation and desynchronisation as main concepts for analysis (Pfurtscheller & da Silva, 1999). Finally, to understand the communication between different regions of the brain, an approach of analysis of phase locking or synchrony is assumed, that still operates in the frequency domain, adding however the complexity of different locations of the signal and their associations (Lachaux, Rodriguez, Martinerie, & Varela, 1999;

Mallat, 1989). In this work, I will analyse the obtained data using all above approaches, trying to grasp different aspects of neural correlates of motor adaptation.

2.3. Example of different domain EEG measures in motor control

In the time domain, a voluntary movement elicits a characteristic sequence of ERP components including a slow negative Bereitschaftspotential (BP) at first, a steeper Negative Slope (NS) preceding the movement and the Motor Potential (MP) – a negativity appearing around the movement onset (Wiese et al., 2005). Further subcomponents have been identified during finger movements and include a peak of negative slope of BP, an initial slope of MP, a parietal peak of MP and the frontal peak of MP (fpMP)(Tarkka & Hallett, 1991a) which is located over the frontocentral supplementary motor area (SMA). The fpMP has been interpreted as crucial for feedback processing in simple movement trials without error processing (Tarkka & Hallett, 1991b).In arm reaching ERP studies, the crucial time window for movement preparation has been identified around 300 ms after the visual cue over the midline electrodes (Naranjo et al., 2007). Frontocentral and parietal ERPs have been found crucial for identification of robot-mediated arm movement in an online correction of movement study (Dipietro, Poizner, & Krebs, 2014).

In the time-frequency domain, beta event related spectral perturbation (ERSP) is the most characteristic neural correlate of movement and a part of a complex of spectral changes in the brain involving the faster waves: a self-paced movement is accompanied by contralateral alpha and beta desynchronisation starting before the movement onset, bilateral alpha and beta desynchronisation during the movement, followed by a contralateral beta synchronisation after the movement offset (Crone, Miglioretti,

Gordon, & Lesser, 1998; Pfurtscheller & da Silva, 1999; van Wijk, Beek, & Daffertshofer, 2012), with bursts of gamma synchronisation during the duration of the movement as seen in subdural recordings (Pfurtscheller, Graimann, Huggins, Levine, & Schuh, 2003). Since scalp recording is heavily contaminated by muscle activity in the gamma band, it is not possible to disentangle the movement-related gamma brain signal from the electomyography using scalp electrodes. Besides beta, alpha rhythm in the motor cortex is also crucial - interpreted as a specific motor mu rhythm, responsible for information processing function that modulates motor cortex activity during perception of movement (Pineda, 2005; van Wijk, Beek, & Daffertshofer, 2012).

Movement execution studies have revealed a robust pattern of phase locking in delta-theta frequency bands over the primary motor cortex contralateral to the movement, regardless of the moving hand laterality or whether the movement was cued or self initiated (Popovych et al., 2016). The phase locking index in this study was distinct of time-frequency and time domain results, which led the authors to think that it is the phase-locked motor cortex oscillations that are crucial for movement preparation and execution. There were studies in EEG functional connectivity role in motor learning, emphasizing the role of beta band coherence involving C3 electrode over primary motor cortex, however they all focused on resting state and not task-related connectivity (Faiman, Pizzamiglio, & Turner, 2018; Wu, Srinivasan, Kaur, & Cramer, 2014).

Having in mind all the advantages and disadvantages of what EEG technique has to offer, the experimental design was planned to maximise the potential of analysing the

movement related signal in the high temporal resolution, analysing in depth each aspect of motor adaptation related signal in all domains.

2.4. Experimental design

To understand motor adaptation, a classical robot-assisted force field learning paradigm was employed, recording simultaneously EEG as the participants adapted. The participants were screened for the level of ability in their hand function, verbal and general cognitive ability in a separate session and invited to the lab for the EEG motor adaptation recording.

2.4.1. Motor adaptation task

The participant's task was to perform a straight reaching movement (15 cm of linear trajectory length, northwest direction) from a central starting point to a peripheral target (1 cm diameter on the screen both) within an instructed period of 1.0 – 1.2 seconds. A vertical screen situated at eye-level gave online feedback regarding the position of the displaced robot handle. After each movement, the participant relaxed the arm as the robot repositioned it to the central point. A single trial started with a visual cue prompting the participant to perform the reaching movement and ended with the passive return to the central position.

The experimental protocol was based on 3 conditions, each composed of 96 reaching trials. The familiarization condition (Fam) was performed in a null force-field to familiarize the participant with the reaching task and served as a baseline for comparisons. During the motor adaptation condition (MA), the robot applied a velocity-

dependent force-field in the clockwise direction of 25 Ns/m absolute intensity, perpendicular to the trajectory of the end-effector joystick. The wash out condition was performed in a null force-field once again. As this condition tends not to differ to familiarization, further analyses focused on differences between Fam and MA condition for clarity. For further detailed wash out analyses please refer to the paper that in part describes the young adults group described here (Pizzamiglio, Desowska, Shojaii, Taga, & Turner, 2017). Resting periods were scheduled at the beginning of the experiment, between conditions and at the end of the experiment. Figure 2.1. presents a photo of the actual setup (A), a schema of the motor adaptation task procedure (B), and a task screen visible to the participant (C).

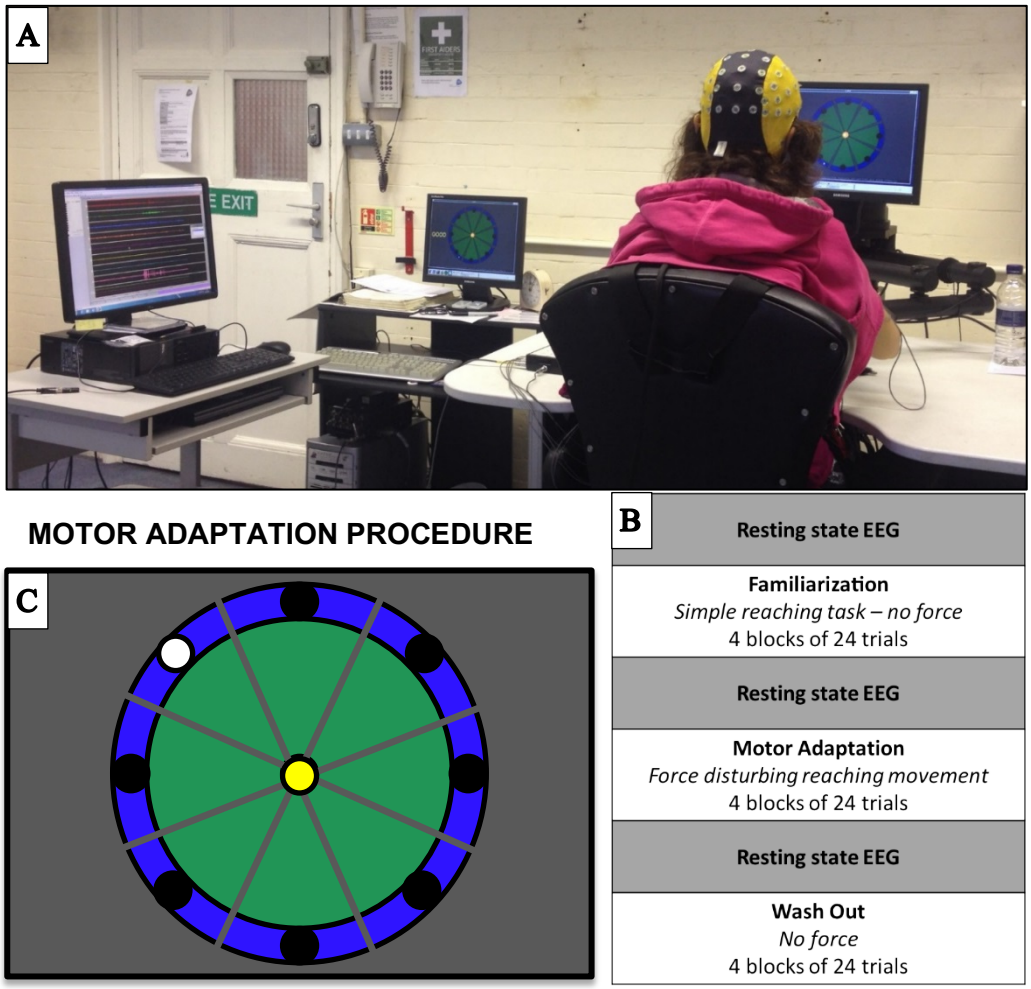


Figure 2.1. Experimental setup.

Photo of the actual setup (A), a schema of the motor adaptation task procedure (B), and a task screen visible to the participant (C).

2.4.2. Apparatus

The kinematic data were recorded by the encoders embedded within the joystick of the MIT-Manus2 (InMotion Technologies, Cambridge, MA, USA) robotic manipulandum. The end-effector position in the horizontal plane was sampled at 200 Hz and stored on the PC for offline analyses. MIT-Manus is the most widely used system for robot-assisted rehabilitation post stroke and has produced the largest body of clinical evidence so far, which justified choosing it for large clinical trials assessing efficacy of robot-mediated rehabilitation (Rodgers et al., 2017). The reliability of the measurement performed by the robotic arm was found satisfactory in a repeated protocol on a healthy population before expanding the clinical applications (Finley et al., 2009).

Brain activity was recorded through a 64-channel Waveguard cap and amplified by a TMSi Ref-Ext amplifier (ANT Neuro, Enschede, Netherlands), digitized at 1024 Hz and band-pass filtered from 0.1 to 500 Hz. During the recording, data were referenced to the Fz electrode and impedances were kept below 5 kΩ. The positions of the electrodes were in accordance with a standard 10-5 system (Figure 2.2).

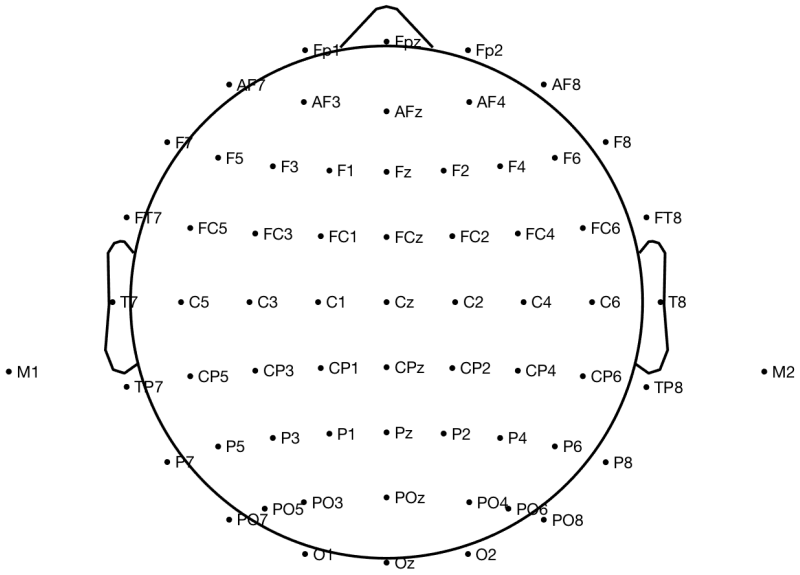


Figure 2.2. Electrode locations used in the study.

Electromyographic (EMG) activity was also recorded, but is beyond the scope of this work. However, the data collected during this work were analysed and partially published, showing patterns of activity expected for the motor adaptation process (Pizzamiglio et al., 2017).

To synchronize the recorded signals, the robot PC sent a train of 15 consecutive TTL pulses at each visual cue (i.e. trigger at the beginning of a trial, time = 0 sec) via a double - split BNC cable to the EMG and the EEG recording systems.

2.4.3. Additional measures used - description and rationale

The following additional measures were used as screening tools and the results were not analysed as an outcome measure. The purpose of the screening was to make sure the differences in motor adaptation results obtained from different groups are not caused by differences in ability to understand the instructions (cognitive screen), visual input (testing for visual neglect), or fatigue.

Brief Fatigue Inventory (BFI, (Mendoza et al., 1999)): Fatigue is a symptom very often seen even in very mild brain injury of different aetiology and is reported as having a substantial impact on daily functioning and quality of life (e.g. (LaChapelle & Finlayson, 1998)). BFI is a simple tool to assess the severity of fatigue in the last 24 hours and the impact that it has on the daily living.

Montreal Cognitive Assessment (MoCa, (Nasreddine et al., 2005)): This is a standardized measure for mild cognitive impairment. The participant solves 11 cognitive tasks assessing his attention, memory, visual skills, naming, verbal fluency and orientation. It is administered in 10 minutes. The reason to include this test is to evaluate the ability of the participant to understand and follow the instructions.

The Oxford Cognitive Screen (OCS, (Demeyere, Riddoch, Slavkova, Bickerton, & Humphreys, 2015) is a rapid cognitive screen that was designed specifically for the stroke population. It reports scores in different cognitive domains, screening also for aphasia and visual neglect.

It is also important to precisely measure motor abilities of the participant to be able to differentiate the effects of learning, motor function and motor learning during the data analysis. The motor function of the participants was tested in three tasks.

Grip force measure: More precise dexterity was measured using a dynamometer – an electronic grip sensor (Biometrics Co Ltd UK). The participant's task was to squeeze the dynamometer as hard as they can for three seconds following one practice trial. The test was administered to both dominant and non-dominant hand (procedure adapted from the NIH Toolbox strength measure (Reuben et al., 2013) for assessing neurological patients).

Pinch force measure: The assessment of the finest motor skills was similar to the grip strength measure procedure, but using a pinchmeter (Biometrics Co Ltd UK). Fugl-Meyer Assessment – Upper extremity (F-M, Fugl-Meyer, Jääskö, Leyman, Olsson, & Steglind, 1975): The Fugl-Meyer assessment is a scale of motor function impairment designed for post-stroke hemiplegic patients. It is the most often used outcome scale in stroke rehabilitation assessment (Deakin, Hill, & Pomeroy, 2003). The maximum motor function score is 100 points, with 66 points dedicated to hand function assessment - achieved when the participants hand function is not affected. The participant's task is to perform specific movements of the arm and hand. The movements and reflexes are rated on a 3 point scale. Upper extremity assessment takes 6-30 minutes depending on the

hand function. In this work, I used guidelines formulated in Deakin, Hill, & Pomeroy (2003).

2.4.4. Participant recruitment

2.4.4.1. Healthy adults

Participants were recruited from the community via leaflets, emails and personal communication. Inclusion criteria included: adults over 18 years old, right handed, with no neurological history and good communicative command of English. They were excluded from the study if they admitted to have a history of neurological disorders that could influence the EEG data recording, or left-handedness: for the maximum homogeneity I only tested right hand movement, left-handed participants were excluded, since a) the non-dominant hand performs in a different way, b) brain activity pattern is different for dominant versus non-dominant hemisphere.

In total, 40 healthy participants agreed to participate in the study. Of those, only 29 participant's data were included in the final analysis. Such a great rate of data rejection is attributed to the nature of the experimental paradigm, with significant length (data acquisition with cap preparation took up to 4 hours) and substantial amount of synchronised equipment causing by nature more technical difficulties. Two participants did not come back to the actual EEG recording session. During the recording of four participants, technical difficulties occurred that caused discontinuation of the protocol - these involved breaking of the optic fibre cable from the amplifier to the EEG recording system, uncorrectable noise in the data or experimenter mistakes (mistaken task conditions). Three participants admitted post factum to neurological conditions that could influence the data quality (ADHD, active depression, antiepileptic medication for

migraine diagnosis). Finally, data of two participants were excluded due to profound uncorrectable movement artifacts (one general movement, one jaw clenching). Median age was 30 years old, age range 20 to 63. For the part of analysis comparing younger to older healthy participants, the participants group was split by the median. That way the younger group had a median age of 23, age range 20-29, and the older median 49, age range 32-63.

2.4.4.2. Stroke patients

Stroke patients were recruited in the follow-up stroke clinic at Queens Hospital, Romford, BHR University Hospital Trust. Over 250 patients were screened in the clinic, of which 10% met the stringent inclusion criteria, of which 9 agreed to participate. The inclusion criteria involved age - only adults over 18 years old were eligible, right hand dominance - at least before the stroke. Eligible participants also had to have a first ever vascular episode that initially affected their right hand function. It was also important for the patients to be well recovered (Fugl-Meyer score over 56 out of a possible total of 66) to be able to complete the demanding procedure of motor adaptation protocol. Additionally, the participants needed not to report any neurological history before the insult and no seizure disorder, even controlled with medication and have a good command of English. Of the eligible participants, 11 agreed to participate, of which one withdrew from the study and one was excluded due to a mistake in reporting handedness. The recruitment resulted in testing 9 stroke participants, median age 56, age range 34-78, 1 female. From the healthy group, a subset of 9 age matched healthy participants was subsampled to serve as a healthy control group (median age 56, age

range 42-63, 4 females). The groups did not significantly differ by age ($t(16) = -0.290$, $p = 0.776$).

2.4.5. Ethics

All participants provided informed consent and were recruited and tested according to the Declaration of Helsinki and appropriate ethics approval were sought separately for healthy controls (UREC 1516_25) and for stroke patients (IRAS 195798) - vide Appendix 1 and 3 for appropriate approvals.

2.4.6. Procedure

Due to the total time required to complete the whole procedure (over 4 hours), it was usually performed in two sessions, unless the participants clearly stated they preferred to do it in one session. Usually the screening and psychometric testing was completed in a first session. In most cases of stroke participants, the screening was performed at the comfort of their homes. Tests used during the first session included a cognitive screen (MoCa for healthy participants or OCS for stroke), a hand function measure (F-M) and a verbal learning tests (CVLT). Participants also filled in a in-house medical questionnaire and fatigue inventory. Except for the cognitive screen, all the tests were exactly the same for healthy and stroke participants. The cognitive screen for stroke patients was a measure specifically designed for this group. Figure 3 presents the detailed recruitment and assessment procedure for stroke patients. The main difference to control testing procedure is the recruitment procedure and a cognitive function test (Oxford Cognitive Screen, OCS) designed specifically to assess cognitive functioning of stroke patients, that allows screening for visual neglect and aphasia. None of the stroke participants presented with visual neglect or aphasia which lead to no exclusions on that

ground. The average F-M result for stroke participants was 64 points, with range 58-66. The control group show as expected a ceiling effect in that measure.

In the second session in the lab, after the EEG cap preparation, the participant used a dynamometer and pinchmeter on both hands to obtain the maximum grip and pinch strength. After that. the participant sat in a chair directly in front of a robot device (MIT-Manus, IMT2, InMotion Technologies, Cambridge, MA, USA) and was asked to grasp the end-effector joystick with the right hand. The arm was positioned in a semi-pronated fashion at 70° of shoulder extension and 120° of elbow flexion and supported by a custom-made thermoplastic trough fixed to the joystick. The arms were at the same level as the end-effector joystick. Safety belt straps were fastened across the participant's chest in order to restrict trunk movements.

2.5. Data analysis

Offline data analyses were carried out with MatLab 2018b (The MathWorks, Inc.), with the support of EEGLab and FieldTrip open-source toolboxes for the analysis of EEG data (Delorme & Makeig, 2004; Oostenveld, Fries, Maris, & Schoffelen, 2011).

2.5.1. EEG pre-processing

A pre-processing pipeline for EEG data has been developed with EEGLab toolbox (Delorme & Makeig, 2004). Data were band-pass filtered between 0.5 Hz and 100 Hz, downsampled to 1000 kHz to match the kinematics and notch filtered at 50 Hz and 25 Hz to remove the power line noise and harmonics. Data were segmented into epochs of 3 seconds each from -1000 ms to 2000 ms with respect to each trigger (i.e. visual cue). The choice of the length of the epoch was motivated by capturing the neural

activity during the duration of the whole reaching movement that usually happens between around 300 – 1200ms after the visual cue. This approach has been previously used in e.g. time-frequency analysis of reaching movement in stroke (Rossiter et al., 2014). Visual inspection was performed on segmented data and served to identify 1) EEG channels affected by sustained noise throughout the whole experiment duration (i.e. bad channels), and 2) trials heavily corrupted by non-stereotypical artefacts (i.e. bad trials). A period between -1000 ms and -100 ms before the visual cue in each trial was defined as baseline, representing the reference for the task-related signal (i.e. data after the visual due). For each channel in each trial, the baseline was removed from the task-related data, bad channels were removed and data re-referenced to a common average. Data were decomposed using Independent Component Analysis (ICA) with the extended Infomax algorithm as provided by EEGLab (Delorme, Sejnowski, & Makeig, 2007). Spectral, spatial and temporal features of each Independent Component (IC) were inspected and those symbolic of stereotypical artefacts (e.g. electrical noise, blink, neck muscles, etc.) were removed from the data. The remaining components were back-projected to the scalp channels and removed channels were interpolated (method = 'spherical' as implemented in EEGLab) (Ferree, Eriksen, & Tucker, 2000; Perrin, Pernier, Bertrand, & Echallier, 1989). Data were re-referenced to the common average and one last visual inspection was performed to check the quality of the cleaned data and remove remaining noisy trials. The preprocessing pipeline did not diverge from the standards used in EEG signal processing and was already published in papers from the same lab (e.g. Pizzamiglio et al., 2018).

2.5.2 Event-Related Potentials

ERPs were calculated for each subject, condition and channel as simple arithmetic averages across trials.

ERPs were evaluated for the following conditions: late familiarization (Fam_l, average of second half of trials in familiarization condition), early motor adaptation (MA_e, average of first half of trials in motor adaptation condition), and late motor adaptation (MA_l, average of second half of trials in motor adaptation condition). Wash out analyses in healthy population revealed no differences between wash out and familiarization condition (Pizzamiglio et al., 2017), so for clarity the analysis will focus on the differences between familiarization and motor adaptation conditions. The ERP approach is commonly used in error processing literature (e.g. Krigolson & Holroyd, 2006).

2.5.3 Event-Related Spectral Perturbation

Time-frequency domain data were calculated using a convolution with Morlet wavelets (Torrence & Compo, 1998) per each subject, trial and condition in the frequency range between 3 and 50 Hz with 2 cycles at the lowest frequency and 16 at highest and Hanning window of 743ms. ERSP change was obtained by subtracting the average baseline power (-1000 to 0 ms) from the power at each time-frequency point at each channel post the visual cue. The choice of Morlet wavelets and parameters was standard, confer e.g. Cohen (2019).

2.5.4 Phase locking value

Phase locking value (PLV) as a measure of functional connectivity between electrodes, was calculated per each pair of electrodes per each time point in all frequency bins (delta, theta, alpha, beta, gamma) by first filtering the data to the specific band (FIR filter), then taking Hilbert transform of the signal and assessing the variability of the difference between the instantaneous phase of the pair of the electrodes at each time point, following the procedure outlined in (Lachaux et al., 1999). The values were calculated for each condition, in analogy to the conditions analysed in the time domain and standardised for each timepoint (mean subtracted and divided by the standard deviation of each channel pair at frequency band and condition). PLV is a popular functional connectivity measure in EEG and has been previously used in motor-related context (e.g. Rosjat et al., 2018).

2.5.5 Reaching kinematics

Kinematic data from the robot were interpolated to the sampling rate of 1 kHz. The starting of a reaching movement was defined as movement onset and calculated as the time point at which speed exceeded the threshold of 0.03 m/s as previously used in literature (Hunter, Sacco, Nitsche, & Turner, 2009; Pizzamiglio et al., 2017); the end of a reaching movement was defined as movement offset and calculated as the time point after movement onset at which movement velocity lowered below the threshold of 0.03 m/s. Maximum velocity was noted and the perpendicular distance of the effector to the line joining the start and end point of movement at the time of maximum velocity served as one of the measures of the size of error. Another measure, trial-by-trial trajectory

error was assessed through summed error (cm), defined as the absolute cumulative perpendicular distance between the actual trajectory and a straight line connecting the central starting point with the peripheral target between the times of movement onset and offset (Figure 2.3). Finally, to capture individual differences in motor adaptation, a measure of performance index was introduced, as the difference between the averaged summed error in the last and first five trials expressed as a percentage of the first five trials summed error.

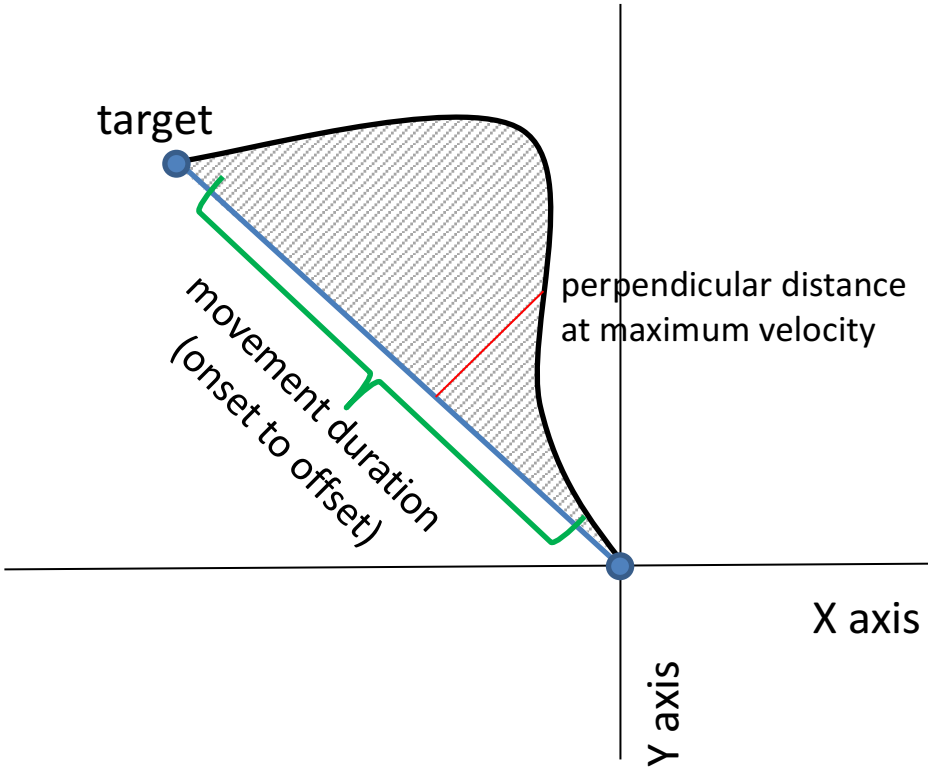


Figure 2.3. A schematic representation of kinematic measures.

Blue line represents a perfect straight line between the starting point and the target. Black line represents position of the cursor at each time point during one trial. The part of perfect line limited by green curly bracket symbolises the part of the trial between movement onset and offset, when the velocity was higher than 0.03 m/s. Red line represents the maximum velocity error measure – the perpendicular distance at a point when the velocity was highest in the trial. Summed error was calculated as a sum of perpendicular distances at each time point between movement onset and offset.

Dynamometer and pinchmeter recordings were summarised into a grip and pinch asymmetry values, as a ratio between the right peak force and left peak force for both types of measurement.

2.5.6 Statistical analysis

2.5.6.1. Regression model

A multiple linear regression approach was used to model the relationship between the variables. To initially reduce the number of entered predictors, the values were averaged from both motor adaptation conditions together. To obtain uniform level of values, the values were standardised to the z-score (mean from each value was subtracted and divided by standard deviation). Stepwise multiple linear regression models (with forward and backward algorithm; inclusion/exclusion probability levels: $\alpha Enter < 0.05 / \alpha Exclude > 0.1$) were used to select predictors from the following list: age, ERP in central ROI in the perimovement time of interest (270-330ms) in motor adaptation, beta time-frequency in the same ROI and time of interest in motor adaptation, alpha connectivity between C3 and FCz in baseline time of interest (-400 - 300ms before movement onset) in MA, alpha connectivity between C3 and C4 in the same time of interest and condition, pinch asymmetry and stroke, with summed error averaged for motor adaptation conditions and performance index as dependent variables in separate models. A similar stepwise approach has been previously used in literature to identify best spectral predictors of motor performance (Espenhahn et al., 2019).
More detailed correlations were also performed post hoc. Since some of the variables were not normally distributed as tested with Shapiro-Wilk test, a nonparametric

Spearman's rho correlations were performed. Multiple comparisons were corrected with FDR adjustment.

2.5.6.2. Group differences

ERP components in the time window of interest for the whole set of electrodes were analysed using permutation-based statistics with false discovery rate (FDR) correction for multiple comparisons to compare potentials between groups (young vs older, or stroke vs controls) in each of the conditions as implemented in the EEGlab toolbox (Delorme and Makeig, 2004). Time window of interest for the reaching movement was defined as the time around 300ms (average of 270-330 ms) post visual cue, which is also close to the movement onset (Naranjo et al., 2007). In the time window of interest, a permutation based ANOVA model as implemented in EEGlab was utilised to analyse the differences between the groups and conditions for all electrodes initially.

For the timecourse analysis, the FCz electrode was chosen as the electrode of interest in line with classical ERN literature (Krigolson and Holroyd, 2007; MacLean et al., 2015) and the differences between the conditions were also analysed with EEGlab built-in permutation-based statistics with FDR correction.

The signal of electrodes surrounding FCz (FC1, FC2, Cz, C1, C2, including FCz) was averaged for the purpose of analysis of the region of interest (ROI). Mean data for the time window of interest for ROI was analysed in a 2 (group) x 3 (condition) repeated measures ANOVA model, with values reported with Greenhouse-Geiser correction when the assumption of sphericity was not met. Analysis of simple main effects was conducted with Bonferroni correction for multiple comparisons. Similar statistical

model was implemented to analyse data averaged for the time window of interest for the electrode of interest, FCz.

The data timelocked to movement onset were analysed in a 2 (group) x 3 (condition) x 2 (timing: pre- vs post-movement 100 ms) repeated measures ANOVA in the same ROI and electrodes of interest as with the visual-cue timelocked data. ERSP in the time window of interest for the whole set of electrodes was analysed using permutation-based statistics with false discovery rate (FDR) correction for multiple comparisons to compare values between groups (young vs older, or stroke vs controls) in each of the conditions as implemented in the EEGlab toolbox (Delorme and Makeig, 2004). Time window of interest for the reaching movement was defined as the time around 300ms (average of 270-330 ms) post visual cue, which encompasses the typical movement onset.

For a full spectrum evolution in time analysis, the C3 electrode was chosen as the electrode of interest in line with classical ERSP literature (Pfurtscheller & da Silva, 1999; Torrence & Compo, 1998) and the differences between the conditions were also analysed with EEGlab built-in permutation-based statistics with FDR correction.

Additionally, to maintain consequence with the time-domain analysis, the signal of electrodes surrounding FCz (FC1, FC2, Cz, C1, C2, including FCz) was averaged for the purpose of analysis of the region of interest (ROI) in the beta band in the time of interest. Mean data for the time window of interest for ROI was analysed in a 2 (group) x 3 (condition) repeated measures ANOVA model, with values reported with Greenhouse-Geiser correction when the assumption of sphericity was not met. Analysis

of simple main effects was conducted with Bonferroni correction for multiple comparisons.

Similar statistical model was implemented to analyse data averaged for the time window of interest for the electrode of interest, C3 in 300 ms time bins to analyse the statistical properties of development of ERSP over time in the trials, with 2 (group) x 3 (condition) x 4 (time window) factors. As a final zoom into the data, the evolution of beta power of the C3 electrode was plotted at each timepoint for each group.

As with previous measures, also in connectivity measure - PLV, I focused on identifying differences between the groups and for initial analysis I defined the time of interest at 270-330 ms post visual cue and the main electrodes of interest as C3 - over the primary motor cortex contralateral to the moving hand and frontocentral FCz - over the SMA, consistent with electrode choice in the movement related PLV literature (Rosjat et al., 2018). I first analysed the whole-brain functional connectivity pattern with C3 as a seed region in the time of interest in each frequency band, testing PLV averaged for the time window of interest with a t-test corrected with FDR (Benjamini & Hochberg, 1995) in theta, alpha and beta band as the ones identified in literature as important for error processing and motor control (Cohen, 2016; Pfurtscheller et al., 2003; Popovych et al., 2016). Based on the functional connectivity pattern that emerged at the initial time of interest that additionally validated focusing on the two specific electrodes of interest, I proceeded to analysing the timecourse of connectivity for each electrode pair of interest (C3-C4, C3-FCz) in theta, alpha and beta band, testing statistical significance of differences between groups with t-tests at each time points adjusted with FDR correction. To further understand the nature of increase of the

connectivity around the movement onset, I performed the same timecourse analysis on the data timelocked to the movement onset. As a final zoom I tested the movement onset timelocked data for each pair of interest with a repeated measures ANOVA model: 3 (condition, within: late familiarization, early motor adaptation and late motor adaptation) x 3 (timing, within: baseline, -400 -300ms, premovement -100 0ms, post movement onset 0 100ms) x 2 (group, between). PLV for each timepoint within each timing window was averaged before entering it into the ANOVA model. Post hoc - where informative - I also performed simpler ANOVAs per each timing level to understand the moderation of the timing window on the changes in PLV dependent on the condition. I finally analysed simple main effects as t values, corrected with Bonferroni correction. I report here all significant effects of the ANOVA models, with values reported with Greenhouse-Geiser correction when the assumption of sphericity was not met. Occasionally I cite specific statistics for insignificant factors, where it informed the conclusions (e.g. no significant main effect of group or no effect of condition in one time window as opposed to a different one).

Each kinematic measure was analysed in a 3 (within, condition: late familiarization, early motor adaptation, late motor adaptation) by 2 (group: younger vs older participants or stroke vs age matched controls participants) repeated measures ANOVA model. Where appropriate, Greenhouse-Geisser correction was used. Multiple comparisons were controlled using Bonferroni correction. In case of the performance index measure, independent samples t-test was used to check for differences between described groups.

Some of the variables were not normally distributed as tested by Shapiro-Wilk test, the majority however, was. The non-normality of the distribution was driven not by kurtosis but by skewness in all cases, and it was a skewness considered acceptable for parametric testing (George & Mallery, (2010) suggest values between -2 and 2 as acceptable). The permutation testing procedure as implemented in the EEGlab toolbox deals efficiently with the problem of non – normality. In case of repeated measures ANOVA employed here as a test for most detailed hypotheses, all main effects were also tested with non-parametric analogies to ANOVA, namely Mann-Whitney U for testing between groups and Wilcoxon signed rank test for testing between conditions and obtained the same results. For the clarity of the discourse, only the parametric results are cited throughout the thesis, especially since it has been argued that F and t statistics retain robustness with skewed distribution as long as the tested groups are kept equal in number (Field, 2005).

3. Kinematic characteristics of the motor adaptation process

3.1. Introduction

Motor adaptation is a process of learning a previously known skill in the presence of an environmental perturbation. It is characterized by a gradual improvement of performance, but the skill fades quickly after the perturbation is no longer in place. As a model of re-learning, it has been studied in order to understand mechanisms of neurorehabilitation (Dipietro et al., 2012) and is typically studied with error-based experimental paradigms involving visuomotor rotation or force-field tasks (Krakauer & Mazzoni, 2011). The effects of adaptation have been observed in the kinematics of motor output, in the pattern of muscle activity (Darainy & Ostry, 2008; Gribble, Mullin, Cothros, & Mattar, 2003; Thoroughman & Shadmehr, 1999) and in the activity of the central nervous system (Krebs et al., 1998; Shadmehr & Holcomb, 1997), which will be discussed in further chapters.

At the level of kinematic analysis, motor adaptation emerges across a number of trials of movement after introducing a perturbation to the movement. At first, a significant motor error is produced, accompanied with more effort and changes in velocity of the movement to accommodate for the perturbation. With time, as the process of adaptation takes place, the error is reduced and the temporal characteristics of the movement - velocity, movement onset and offset - start to resemble those of unperturbed movements (Shadmehr & Mussa-Ivaldi, 1994). The motor system learns how to optimally accommodate for the perturbation, optimising also the force input into the movement, as reflected in the muscle activity, with an initial increase of muscle activity that is followed by a reduction thereafter (Darainy & Ostry, 2008; Pizzamiglio,

Desowska, Shojaii, Taga, & Turner, 2017; Thoroughman & Shadmehr, 1999). This pattern is thought to be a compensatory strategy to reduce movement variability (Osu, Morishige, Miyamoto, & Kawato, 2009; Seidler-Dobrin, He, & Stelmach, 1998) and increase the task performance accuracy (Gribble et al., 2003) at a lower energetic cost (Huang & Ahmed, 2014). A kinematic measure of summed error decrease is typically associated with reduction in muscle co-contraction (Huang & Ahmed, 2014; Milner & Franklin, 2005).

The mechanism explaining the motor adaptation process proposed in the literature is predictive model formation in the central nervous system, expressed in trial-to-trial modification of the forward model responsible for motor to sensory mapping and updating this feedback to produce motor plans for the next trial (Krakauer & Mazzoni, 2011).

3.1.1 Expected pattern of kinematic results

During the familiarization procedure, participants learn quickly how to perform the reaching movement efficiently. In the initial phase of the motor adaptation, the force field pushes the participants off the optimal trajectory, as expected by the direction of the force added. With time, the participants usually adapt to the force field and optimize the trajectory of the movement (Huberdeau, Haith, & Krakauer, 2015). There are individual differences in the rate of motor adaptation, and some participants show signs of slow-learning. When the force field is taken away again (Wash Out condition), the participants, expecting the force field, show a contrasting adaptation effect: the trajectory of the reaching movement is pushed to the opposing side than the force added during the motor adaptation phase, showing what human force has been used to

compensate for the force added by the robot. This effect, however, fades very quickly, within a few trials the trajectory comes back to straight.

3.1.2 Motor adaptation though the lifespan - the factor of age

Implicit skill learning peaks at the age of 12, declining steadily afterwards (Janacsek, Fiser, & Nemeth, 2012). Both motor adaptation and skill learning are less accurate in older adults (Hardwick & Celnik, 2014). Adapting to external perturbations has been shown to be slower in ageing, however older adults were still able to reach the optimal adaptation outcome in prism adaptation paradigm (Fernández-Ruiz, Hall, Vergara, & Díiaz, 2000). Even if the older adults exhibit normal sequence learning, they present with a reduced velocity modulation (Seidler, 2006). However, it seems that it is not the cerebellar mechanism of updating internal model that is responsible for this decline, but decline in cognitive resources (Seidler, 2006; Vandevoorde & Orban de Xivry, 2019).

3.1.3 Motor adaptation after brain injury - the case of stroke

Recovering from a cerebrovascular episode, in which motor functions are initially affected, is argued to be a specific case of motor learning (Dipietro et al., 2012), thus applying the mechanisms of motor skill learning to motor recovery from stroke could promote recovery (Matthews, Johansen-Berg, & Reddy, 2004).

What happens to the motor learning process itself after stroke still remains uncertain. Stroke patients are still able to learn new motor skills (Meehan, Randhawa, Wessel, & Boyd, 2011). Winstein et al. (1999) argued that it is rather motor execution and control that are affected in hemiplegia rather than the learning ability itself. Scheidt and Stoeckmann (2007) analysed the strategy of motor learning in stroke patients. Their

findings suggest that although the strategy is the same both in stroke and in healthy adults, stroke patients rely on feedback from the previous task to a lesser extent than healthy participants.

The purpose of this study was to analyse kinematic measures of motor adaptation across the healthy lifespan to establish a healthy pattern of adaptation as a baseline to further analyse motor adaptation in stroke survivors. The focus of this chapter are the measures observed in behavioural output of the motor adaptation process. I expected to observe an increase in kinematic error as a result of introducing the perturbation that would reduce trial by trail. This process is a reflection of internal model updating that leads to optimal performance in perturbing environment. The timing and velocity of movement were analysed in young adults, middle aged and older adults and finally stroke participants.

3.2. Method

3.2.1 Participants

Detailed description of participants and recruitment process can be found in General methods chapter. In brief, 29 healthy participants with a broad range of age and nine stroke patients volunteered to participate in the study. Of the healthy participants, nine were subsampled as age matched controls for the stroke patients. None of the participants had previous history of neurological, neuromuscular or orthopaedic disease (except of the stroke in case of stroke patients). All participants were right hand dominant. Stroke patients had a stroke that initially affected their right hand function, but were well recovered by the time they participated in the study (Fugl-Meyer score

>= 55 points).The study was approved by the University of East London Ethics Committee and NHS ethics committee (UREC 1516_25; IRAS 195798) and conducted in accordance with the Declaration of Helsinki.

The kinematic variables were analysed first to explore the pattern of motor adaptation in healthy young adults and their development over age. I analysed the results from participants over the whole lifespan, subsampling participants in their early twenties as those who would adapt optimally in or adult group, since implicit skill learning peaks at 12 years of age followed by a steady decline over lifetime (Janacsek et al., 2012). The results for healthy participants will be presented in division for the optimal and healthy lifespan group. Once the healthy pattern of kinematic measures is established, I move on to analyse the same variables using the same paradigm in well recovered stroke patients to see how a stroke affecting the dominant hand function can alter the pattern of motor adaptation.

3.2.2 Apparatus

The kinematic data were recorded by the encoders embedded within the joystick of the MIT-Manus2 (InMotion Technologies, Cambridge, MA, USA) robotic manipulandum.

Brain activity was recorded through a 64-channel Waveguard cap and amplified by a TMSi Ref-Ext amplifier (ANT Neuro, Enschede, Netherlands), and will be described in detail in the relevant chapter.

3.2.3 Procedure

After the EEG cap preparation, the participant sat in a chair directly in front of a robot device (MIT-Manus, IMT2, InMotion Technologies, Cambridge, MA, USA) and was asked to grasp the end-effector joystick with the right hand.

The task was to perform a straight reaching movement from a central starting point to a peripheral target within an instructed period of 1.0 – 1.2 seconds. A vertical screen situated at eye-level gave online feedback regarding the position of the displaced robot handle. After each movement, the participant relaxed the arm as the robot repositioned it to the central point. A single trial started with a visual cue prompting the participant to perform the reaching movement and ended with the passive return to the central position.

The experimental protocol was based on 3 conditions, each composed of 96 reaching trials. The familiarization condition (Fam) was performed in a null force-field. During the motor adaptation condition (MA), the robot applied a velocity-dependent force-field in the clockwise direction of 25 Ns/m absolute intensity, perpendicular to the trajectory of the end-effector joystick.

3.2.4 Data analysis

3.2.4.1. Reaching kinematics preprocessing

Offline data analyses were carried out with MatLab 2015b (The MathWorks, Inc.). Kinematic data from the robot were interpolated to sampling rate of 1 kHz. The starting of a reaching movement was defined as movement onset and calculated as the time point at which speed exceeded the threshold of 0.03 m/s as previously used in literature (Hunter, Sacco, Nitsche, & Turner, 2009; Pizzamiglio et al., 2017); the end of

a reaching movement was defined as movement offset and calculated as the time point after movement onset at which movement velocity lowered below the threshold of 0.03 m/s. Maximum velocity was noted and the perpendicular distance of the effector to the line joining the start and end point of movement at the time of maximum velocity served as one of the measures of the size of error. Another measure, trial-by-trial trajectory error was assessed through summed error (cm), defined as the absolute cumulative perpendicular distance between the actual trajectory and a straight line connecting the central starting point with the peripheral target between the times of movement onset and offset. Finally, to capture individual differences in motor adaptation, a measure of performance index was introduced, as the difference between the averaged summed error in the last and first five trials expressed as a percentage of the first five trials summed error.

3.2.4.2 Statistical analysis

Each kinematic measure was analysed in a 3 (within, condition: late familiarization, early motor adaptation, late motor adaptation) by 2 (group: younger vs older participants or stroke vs age matched controls participants) repeated measures ANOVA model. Where appropriate, Greenhouse-Geisser correction was used. Multiple comparisons were controlled using Bonferroni correction. In case of the performance index measure, independent samples t-test was used to check for differences between described groups.

3.3. Results

3.3.1. Kinematic measures of healthy participants over lifespan

3.3.1.1 Movement Onset

There was a main effect of condition on movement onset ($F(2,54) = 8.793$, $p < 0.001$, $^2 = 0.246$), no main effect of group young vs older adults ($F(1,27) < 0.000$, $p = 0.997$, $^2 < 0.000$) and no interaction effect ($F(2,54) = 0.099$, $p = 0.906$, $^2 = 0.004$). Analysis of simple effects revealed that movement onset was significantly later in the late familiarization condition than both in the early motor adaptation ($p = 0.003$, Bonferroni adjusted) and late motor adaptation ($p = 0.023$, Bonferroni adjusted) conditions.

3.3.1.2 Movement Offset

There was a main effect of condition on movement offset ($F(1.341,36.196) = 11.059$, $p = 0.001$, $^2 = 0.291$), no main effect of group young vs older adults ($F(1,27) = 2.678$, $p = 0.113$, $^2 = 0.090$) and no interaction effect ($F(1.341,36.196) = 1.368$, $p = 0.260$, $^2 = 0.048$). Analysis of simple effects revealed that movement offset was significantly later in the early motor adaptation condition than both in the late familiarization ($p = 0.003$, Bonferroni adjusted) and late motor adaptation ($p = 0.001$, Bonferroni adjusted) conditions and that pattern was observed only in the younger participant group ($p = 0.016$ and $p=0.001$ Bonferroni corrected, respectively). In the older participant group there was no significant simple effect of condition.

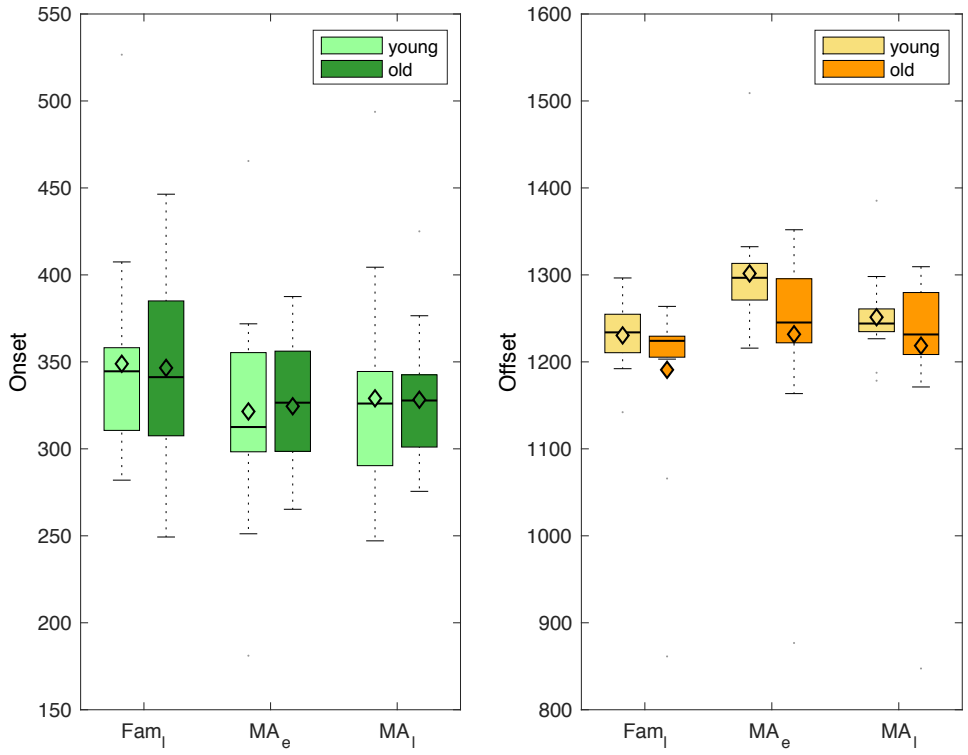


Figure 3.1. Movement onset and offset in healthy participants.

A diamond represents mean, middle line median, bottom and top edges of the box indicate the 25th and 75th percentiles, and the whiskers mark most extreme data points not considered outliers.

3.3.1.3 Maximum velocity

There was a main effect of condition on maximum velocity ($F(2,54) = 6.850$, $p = 0.008$, $^2 = 0.202$), no main effect of group young vs older adults ($F(1,27) = 3.590$, $p = 0.069$, $^2 = 0.117$) and no interaction effect ($F(2,54) = 1.455$, $p = 0.242$, $^2 = 0.051$), however in this case both main effect of group and the interaction showed a tendency for significance. Analysis of simple effects revealed that maximum velocity was significantly lower in the late familiarization condition than both in the early motor adaptation ($p = 0.042$, Bonferroni adjusted) and late motor adaptation ($p = 0.024$, Bonferroni adjusted) conditions.

3.3.1.4 Perpendicular distance at maximum velocity

In case of perpendicular distance at the maximum velocity point, there was a main effect of condition ($F(1.338,36.117) = 23.107$, $p < 0.001$, $^2 = 0.461$), no main effect of group ($F(1,27) = 0.332$, $p = 0.569$, $^2 = 0.012$) and no interaction effect ($F(1.338,36.117) = 1.602$, $p = 0.217$, $^2 = 0.056$). Analysis of simple effects revealed that the distance at maximum velocity differed significantly between all conditions, significantly lower in the late familiarization condition than both in the early motor adaptation ($p < 0.001$, Bonferroni adjusted) and late motor adaptation ($p = 0.039$, Bonferroni adjusted), but also lower in late motor adaptation than in early motor adaptation ($p < 0.001$, Bonferroni adjusted), suggesting a reduction of the error in later stages of adaptation. This effect was even stronger when looking at simple effect of condition at each group's levels separately, where there was no significant difference

between late familiarization and late motor adaptation neither in the young ($p = 0.111$, Bonferroni adjusted) nor in the older group ($p = 0.528$, Bonferroni adjusted).

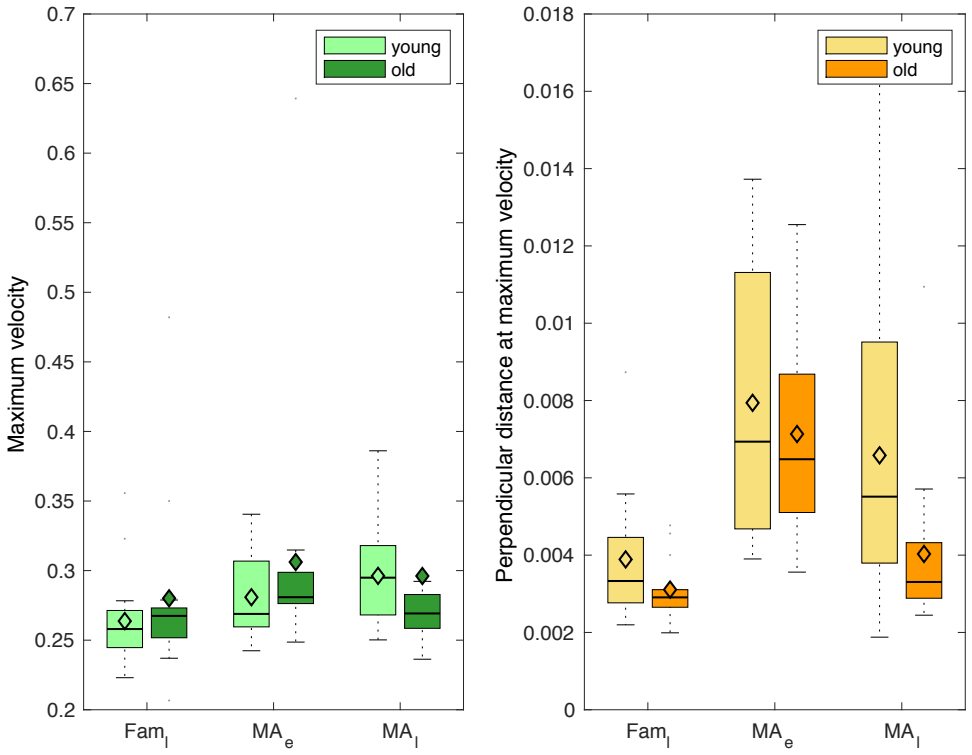


Figure 3.2. Maximum velocity and perpendicular distance at maximum velocity. Diamond represents mean, middle line median, bottom and top edges of the box indicate the 25th and 75th percentiles, and the whiskers mark most extreme data points not considered outliers.

3.3.1.5 Summed Error

In case of summed error, which is a different measure to quantify movement error committed by the participants, there was a main effect of condition on ($F(1.112,30.015) = 111.013$, $p < 0.001$, $^2 = 0.804$), no main effect of group young vs older adults ($F(1,27) = 0.895$, $p = 0.352$, $^2 = 0.032$) and no interaction effect ($F(1.112,30.015) = 0.750$, $p = 0.407$, $^2 = 0.027$). Analysis of simple effects revealed that summed error differed significantly between all conditions, significantly lower in the late familiarization condition than both in the early motor adaptation ($p < 0.001$, Bonferroni adjusted) and late motor adaptation ($p < 0.001$, Bonferroni adjusted), but also lower in late motor adaptation than in early motor adaptation ($p = 0.001$, Bonferroni adjusted), suggesting a reduction of the error in later stages of adaptation, as was the case for the other error measure. That pattern was the same when looking at the simple effects on different levels of the group factor ($p < 0.001$, $p < 0.001$, $p = 0.022$ respectively, in younger adults and $p < 0.001$, $p < 0.001$, $p = 0.026$ in older adults group, all Bonferroni corrected).

3.3.1.6 Performance index

Performance index, which is a summed-error-derived measure of individual learning rate did not differ between the younger and older group ($t(27) = -0.444$, $p = 0.661$).

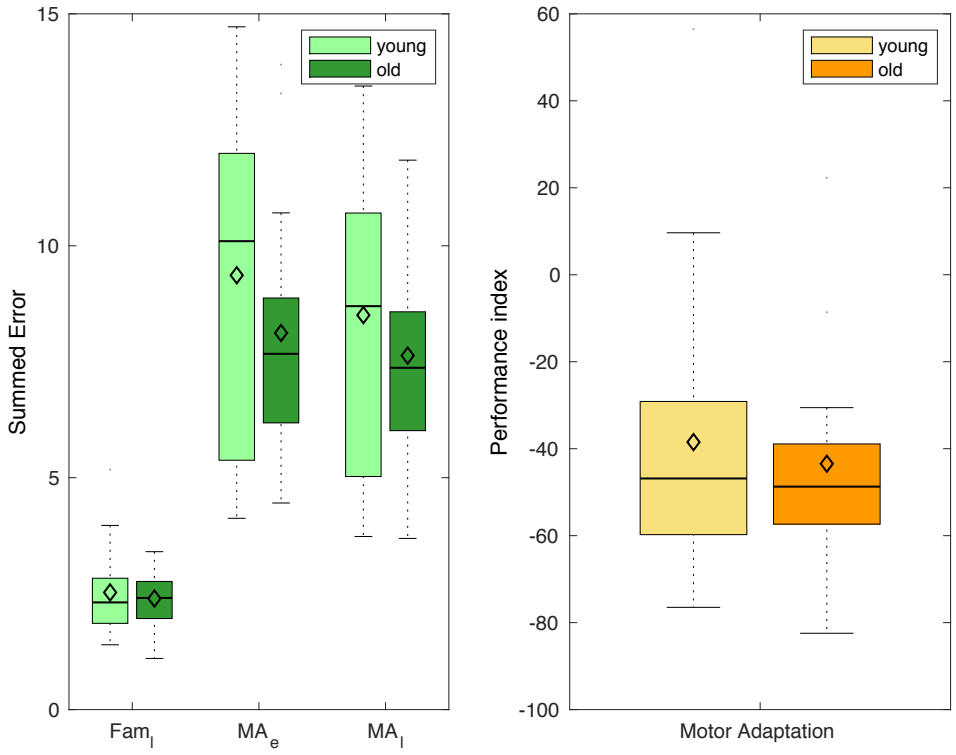


Figure 3.3. Summed error and performance index.

Diamond represents mean, middle line median, bottom and top edges of the box indicate the 25th and 75th percentiles, and the whiskers mark most extreme data points not considered outliers.

3.3.2 Kinematic measures in stroke patients

3.3.2.1 Movement Onset

There was a main effect of condition on movement onset ($F(1.225,19.599) = 6.015$, $p = 0.019$, $^2 = 0.273$), no main effect of stroke versus controls ($F(1,16) = 0.913$, $p = 0.353$, $^2 = 0.054$) and no interaction effect ($F(1.225,19.599) = 0.360$, $p = 0.599$, $^2 = 0.022$). Analysis of simple effects revealed that movement onset was significantly later in the late familiarization condition than in the early motor adaptation ($p = 0.048$, Bonferroni adjusted).

3.3.2.2 Movement Offset

There was a main effect of condition on movement offset ($F(1.118,17.882) = 4.741$, $p = 0.016$, $^2 = 0.229$), no main effect of stroke versus controls ($F(1,16) = 0.005$, $p = 0.945$, $^2 < 0.001$) and no interaction effect ($F(1.118,17.882) = 1.408$, $p = 0.255$, $^2 = 0.081$). Analysis of simple effects showed no differences between conditions.

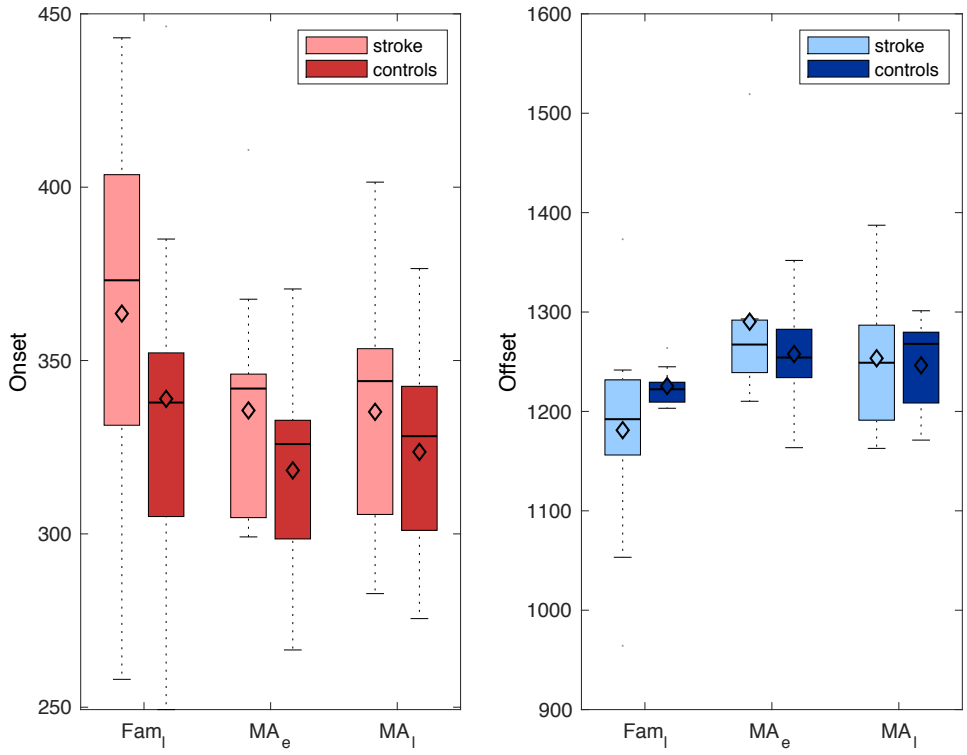


Figure 3.4. Movement onset and offset in stroke versus control group.

Diamond represents mean, middle line median, bottom and top edges of the box indicate the 25th and 75th percentiles, and the whiskers mark most extreme data points not considered outliers.

3.3.2.3 Maximum velocity

There was a main effect of condition on maximum velocity ($F(1.245,19.917) = 7.047$, $p = 0.011$, $^2 = 0.306$), a main effect of stroke versus controls ($F(1,16) = 11.078$, $p = 0.004$, $^2 = 0.409$) and no interaction effect ($F(1.245,19.917) = 0.914$, $p = 0.372$, $^2 = 0.054$). Analysis of simple effects revealed that maximum velocity was significantly lower in the late familiarization condition than in the early motor adaptation ($p = 0.009$, Bonferroni adjusted).

3.3.2.4 Perpendicular distance at maximum velocity

There was a main effect of condition on perpendicular distance at maximum velocity ($F(2,32) = 20.316$, $p < 0.001$, $^2 = 0.559$), no main effect of stroke versus controls ($F(1,16) = 3.609$, $p = 0.076$, $^2 = 0.184$) and no interaction effect ($F(2,32) = 1.488$, $p = 0.241$, $^2 = 0.085$). Analysis of simple effects revealed that the distance at maximum velocity differed significantly between all conditions, and was significantly lower in the late familiarization condition than both in the early motor adaptation ($p < 0.001$, Bonferroni adjusted) and late motor adaptation ($p = 0.044$, Bonferroni adjusted), but also lower in late motor adaptation than in early motor adaptation ($p = 0.002$, Bonferroni adjusted). At the group level, only the difference between late familiarization and early motor adaptation held significance for stroke ($p = 0.029$, Bonferroni corrected) and in healthy controls group late familiarization and early motor adaptation ($p = 0.004$, Bonferroni corrected) and early and late motor adaptation ($p = 0.015$, Bonferroni corrected).

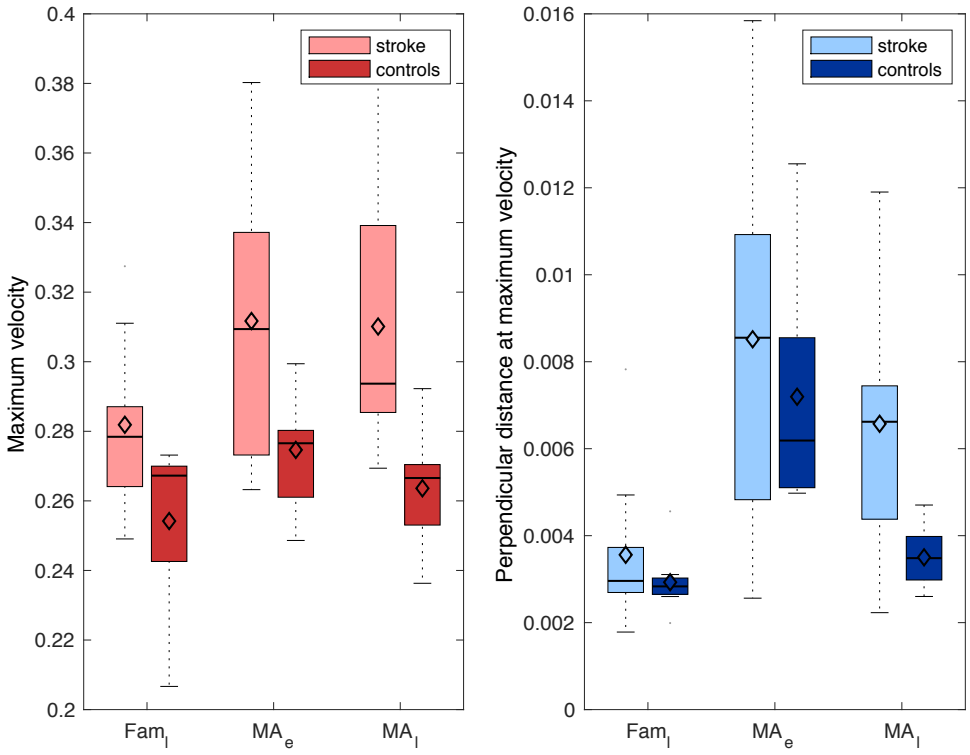


Figure 3.5. Maximum velocity and perpendicular distance at maximum velocity in stroke versus control group.

Diamond represents mean, middle line median, bottom and top edges of the box indicate the 25th and 75th percentiles, and the whiskers mark most extreme data points not considered outliers.

3.3.2.5 Summed Error

In case of summed error, there was a main effect of condition ($F(1.014,16.220) = 28.002$, $p < 0.001$, $^2 = 0.636$), no main effect of stroke versus controls ($F(1,16) = 2.305$, $p = 0.148$, $^2 = 0.126$) and no interaction effect ($F(1.014,16.220) = 0.802$, $p = 0.385$, $^2 = 0.048$). Analysis of simple effects revealed that the summed error was significantly lower in the late familiarization condition than both in the early motor adaptation ($p < 0.001$, Bonferroni adjusted) and late motor adaptation ($p < 0.001$, Bonferroni adjusted). At each group's level, this pattern of differences held significance with $p = 0.040$, $p= 0.031$ respectively in stroke, and $p <0.001$, $p <0.001$ in healthy controls, all values Bonferroni adjusted.

3.3.2.6 Performance index

Performance index did not differ between the stroke and healthy age matched control group ($t (16) = -2.038$, $p = 0.058$).

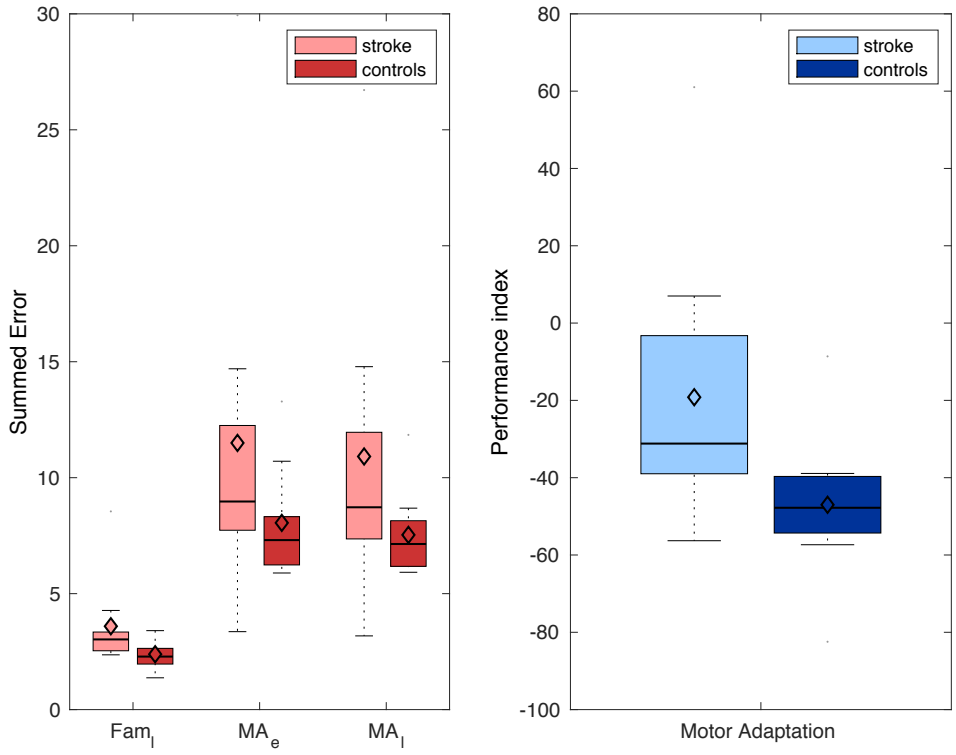


Figure 3.6. Summed error and performance index in stroke versus control group. Diamond represents mean, middle line median, bottom and top edges of the box indicate the 25th and 75th percentiles, and the whiskers mark most extreme data points not considered outliers.

3.4. Discussion

The purpose of this chapter was to show the kinematic measures in this experiment followed the well researched pattern and that was indeed the case. All kinematic measures showed values as expected based on previous findings in healthy young participants (Pizzamiglio et al., 2017) and followed a similar trend, with significant differences between the conditions illustrating increase of kinematic error and change in velocity in the motor adaptation conditions.

Performance index did not differ between groups, suggesting that neither age nor stroke is a factor crucial for reaching desired outcome performance in motor adaptation process, which is in line with previous findings (Fernández-Ruiz et al., 2000). Perpendicular distance at maximum velocity additionally showed a significant decrease in late motor adaptation as compared to early motor adaptation, suggesting optimisation of motor output trajectory as adaptation stabilised. This effect was not seen when simple effect was probed only in the stroke group, perhaps due to the number of tested participants. In healthy participants, this effect was seen also in a more global measure of summed error, however it was not the case in the stroke participants nor the age-matched subsample.

There were no differences between the groups and no interactions of group x condition in most of the measures, with the exception of maximum velocity that was significantly higher in all conditions in stroke patients. This is in line with a concept of impaired velocity modulation influencing the motor adaptation process (Fernández-Ruiz et al., 2000; Seidler, 2006). The task in the present study was a fast-paced one, when the target had to be reached between 1 and 1.2 seconds after visual cue to produce a positive feedback, which may be a factor motivating the participants to excessively focus on

their speed. If stroke participants struggled to reach the target, they might have been trying to compensate with velocity, which - judging by the fact that intergroup differences in error measures did not reach significance - might have been a good compensating strategy.

The crucial finding of this chapter is the lack of differences in error measures between stroke and healthy participants, suggesting that stroke patients, even after an injury affecting their dominant hand movement, can still adapt the movement of their affected hand to perturbation to reach an optimal outcome.

An important caveat to this conclusion is the fact that all of recruited stroke participants were, for practical reasons, well recovered. This ability to recover could serve as a proof that their motor adaptation system - a system that accommodates for perturbances in their movement - was unaffected by the injury.

The kinematic results in this experiment are not novel – the motor performance in motor adaptation has been already well researched and it was not expected to be different here. This chapter however is an important element of the thesis, providing a motor basis of the neural correlates of motor adaptation discussed further.

4. Event related potentials

4.1 Introduction

Electroencephalography (EEG) enables access to the dynamics of brain activity during the process of adaptation due to the high temporal resolution of the technique. The most direct access to brain dynamics is via analysis of the time domain data - event related potentials (ERP). ERPs can be interpreted as a recording of dipole fields generated by cortical pyramidal cell populations activated in synchrony by a specific event (Murakami & Okada, 2006).

Prism adaptation experiments have allowed identification of two crucial event-related potential components in the adaptation process, the positive potential around 300 ms after a cue (P300) related to learning and an error related negativity (ERN) related to error processing (MacLean, Hassall, Ishigami, Krigolson, & Eskes, 2015). Other domains of learning such as time estimation learning studies also revealed the relation between those two ERP components and learning performance (Luft, Takase, & Bhattacharya, 2014).

The ERN was first studied during discrete response error processing (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000), but has also been observed in continuous motor control tasks (Krigolson & Holroyd, 2006). The ERN has been found to start before the motor reaction and was thought to be responsible for building a predictive model of feedback in error tasks (Krigolson & Holroyd, 2006). The source of the ERN is thought to originate from the anterior cingulate cortex (ACC) (Krigolson & Holroyd, 2006).

ERN correlates of motor adaptation of arm reaching tasks need to be disentangled from the ERP components measured during reaching alone. A self-generated voluntary movement elicits a characteristic sequence of ERP components including a slow negative Bereitschaftspotential (BP) at first, a steeper Negative Slope (NS) preceding the movement and the Motor Potential (MP) – a negativity appearing around the movement onset (Wiese et al., 2005). Further subcomponents have been identified during finger movements and include a peak of negative slope of BP, an initial slope of MP, a parietal peak of MP and the frontal peak of MP (fpMP)(Tarkka & Hallett, 1991a) which is located over the frontocentral supplementary motor area (SMA). The fpMP has been interpreted as crucial for feedback processing in simple movement trials without error processing (Tarkka & Hallett, 1991b). In arm reaching ERP studies, the crucial time window for movement preparation has been identified around 300 ms after the visual cue over the midline electrodes (Naranjo et al., 2007). Frontocentral and parietal ERPs have been found crucial for identification of robot-mediated arm movement in an online correction of movement study (Dipietro, Poizner, & Krebs, 2014).

To our knowledge, there has been no research on ERP correlates of motor adaptation post stroke. Also ERPs as a technique in general have not been extensively studied in the field of motor recovery post stroke - a recent systematic review on recovery biomarkers reported only three ERP studies, all focusing on sensory evoked potentials, which - however contributing to the motor ability post stroke - are not related to intentional movement (Triccas et al., 2019). In a study analyzing ERPs related to voluntary hand movement post stroke without the element of motor adaptation (Wiese et al., 2005), stroke patients did not differ from the controls in the characteristics of BP,

whereas the NS was reduced in the lesioned hemisphere and MP increased over the contralesional hemisphere, which suggested that it is motor execution and not motor preparation that is affected post stroke.

The purpose of the current study was to follow the three step framework of the hypotheses mentioned in chapter 1, to a) establish a healthy pattern of ERP corelates of robot assisted reaching in the motor system in the first step – expressed as a negative deflection around the movement onset, b) to extract in the second step the features related specifically to motor adaptation in the error processing system, specifically the ERN component and c) in the third step to measure how it is influenced by stroke affecting the motor system adopting an explorative approach with no specific literature-based hypotheses. The goal of the current experiment was to isolate and analyse the ERN component accompanying reaching movement during robot-mediated force-field motor adaptation. It was hypothesized that the brain activity related to adaptation engages a robust error processing system expressed in a distinct pattern of brain activity during the motor adaptation condition in healthy participants. Given that there was no significant differences in the kinematic measures between stroke participants and healthy controls as reported in the previous chapter, and scarcity of literature on the subject, I left ERP analysis after stroke as exploratory and did not hypothesize specific changes in the error processing system in that population.

4.2. Method

4.2.1. Participants

Detailed description of participants and recruitment process can be found in Chapter 2. In brief, 29 healthy participants with a broad range of age and nine stroke

patients volunteered to participate in the study. Of the healthy participants, 9 were subsampled as age matched controls for the stroke patients. None of the participants had previous history of neurological, neuromuscular or orthopaedic disease (except of the stroke in case of stroke patients). All participants were right hand dominant. Stroke patients had a stroke that initially affected their right hand function but were well recovered by the time they participated in the study (Fugl-Meyer score >= 55 points). The study was approved by the University of East London Ethics Committee and NHS ethics committee (UREC 1516_25; IRAS 195798) and conducted in accordance with the Declaration of Helsinki.

The ERP features were analyzed first to explore the pattern of motor adaptation in healthy young adults and their development over age. We analyzed participants over the whole lifespan, subsampling participants in their early twenties as those who would adapt optimally in the adult group. The results for healthy participants will be presented in division for the optimal and healthy lifespan groups. Once the healthy pattern of kinematic measures was established, we moved on to analyse the same variables using the same paradigm in well recovered stroke patients to see how a stroke affecting the dominant hand function can alter the pattern of neural correlates of motor adaptation.

4.2.2. Apparatus

Brain activity was recorded through a 64-channel Waveguard cap and amplified by a TMSi Ref-Ext amplifier (ANT Neuro, Enschede, Netherlands), digitized at 1024 Hz and band-pass filtered from 0.1 to 500 Hz. During the recording, data were referenced to the Fz electrode and electrode impedances were kept below 5 kΩ.

The kinematic data were recorded by the encoders embedded within the joystick of the MIT-Manus2 (InMotion Technologies, Cambridge, MA, USA) robotic manipulandum.

4.2.3 Procedure

After the EEG cap preparation, the participant sat in a chair directly in front of a robot device (MIT-Manus, IMT2, InMotion Technologies, Cambridge, MA, USA) and was asked to grasp the end-effector joystick with the right hand.

The task was to perform a straight reaching movement from a central starting point to a peripheral target within an instructed period of 1.0 – 1.2 seconds. A vertical screen situated at eye-level gave online feedback regarding the position of the displaced robot handle. After each movement, the participant relaxed the arm as the robot repositioned it to the central point. A single trial started with a visual cue prompting the participant to perform the reaching movement and ended with the passive return to the central position.

The experimental protocol was based on 3 conditions, each composed of 96 reaching trials. The familiarization condition (Fam) was performed in a null force-field. During the motor adaptation condition (MA), the robot applied a velocity-dependent force-field in the clockwise direction of 25 Ns/m absolute intensity, perpendicular to the trajectory of the end-effector joystick.

4.2.4 Data analysis

Offline data analyses were carried out with MatLab 2015b (The MathWorks, Inc.), with the support of EEGLab and FieldTrip open-source toolboxes for the analysis of EEG data (Delorme & Makeig, 2004; Oostenveld, Fries, Maris, & Schoffelen, 2011).

4.2.4.1 EEG pre-processing

A pre-processing pipeline for EEG data has been developed with EEGLab toolbox (Delorme & Makeig, 2004) and has been described in more detail in chapter 2. In brief, data were band-pass filtered between 0.5 Hz and 100 Hz, notch filtered at 50 Hz and 25 Hz to remove the power line noise and harmonics, epoched between -1000 to 2000ms around visual cue with baseline between -1000 and 0 ms. After bad channel and epoch removal, the data were subjected to ICA, removed channels interpolated and re-referenced to common average.

To perform a more detailed analysis of the temporal relation between the observed EEG potentials and performed movement and perceived errors, the same data were also timelocked to the kinematic movement onset. Shorter epochs were extracted between -500 and 800 ms around movement onset and the period between -500 and -300 ms in each served as baseline (which was overlapped with the pre-visual cue period), that was subsequently removed from the signal in each epoch. This allowed to compare in more detail the times before and after sensory feedback of error commission.

4.2.4.2 Event-Related Potentials

ERPs were calculated for each subject, condition and channel as simple arithmetic averages across trials.

ERPs were evaluated for the following conditions: late familiarization (average of second half of trials in familiarization condition), early motor adaptation (average of

first half of trials in motor adaptation condition), and late motor adaptation (average of second half of trials in motor adaptation condition). wash out analyses in healthy population revealed no differences between wash out and familiarization condition (Desowska et al., 2018, Pizzamiglio, Desowska, Shojaii, Taga, & Turner, 2017), so for clarity the analysis will focus on the differences between familiarization and motor adaptation conditions.

4.2.4.3 Statistical analysis

ERP components in the time window of interest for the whole set of electrodes were analyzed using permutation-based statistics with false discovery rate (FDR) correction for multiple comparisons to compare potentials between groups (young vs older, or stroke vs controls) in each of the conditions as implemented in the EEGlab toolbox (Delorme and Makeig, 2004). Time window of interest for the reaching movement was defined as the time around 300ms (average of 270-330 ms) post visual cue, which is also close to the movement onset (Naranjo et al., 2007). In the time window of interest, a permutation-based ANOVA model as implemented in EEGlab was utilized to analyse the differences between the groups and conditions for all electrodes initially.

For the time course analysis, the FCz electrode was chosen as the electrode of interest in line with classical ERN literature (Krigolson and Holroyd, 2007; MacLean et al., 2015) and the differences between the conditions were also analyzed with EEGlab built-in permutation-based statistics with FDR correction.

The signal of electrodes surrounding FCz (FC1, FC2, Cz, C1, C2, including FCz) was averaged for the purpose of analysis of the region of interest (ROI). Mean data

for the time window of interest for ROI was analyzed in a 2 (group) x 3 (condition) repeated measures ANOVA model, with values reported with Greenhouse-Geiser correction when the assumption of sphericity was not met. Analysis of simple main effects was conducted with Bonferroni correction for multiple comparisons. Similar statistical model was implemented to analyse data averaged for the time window of interest for the electrode of interest, FCz.

The data time locked to movement onset were analyzed in a 2 (group) x 3 (condition) x 2 (timing: pre- vs post-movement 100 ms) repeated measures ANOVA in the same ROI and electrodes of interest as with the visual-cue time locked data.

4.3 Results

4.3.1 ERP measures of healthy participants over lifespan

4.3.1.1 Voluntary reaching characteristics

In the initial analysis of the time window of interest (270-330 ms post visual cue, figure 4.1), there were no differences between the younger and older group. In both early and late motor adaptation conditions, there was a more pronounced frontocentral negative deflection, maximal at the FCz electrode (potential -5.84 in older and -4.78 μV in younger group in early motor adaptation condition) as compared to the conditions without the force field.

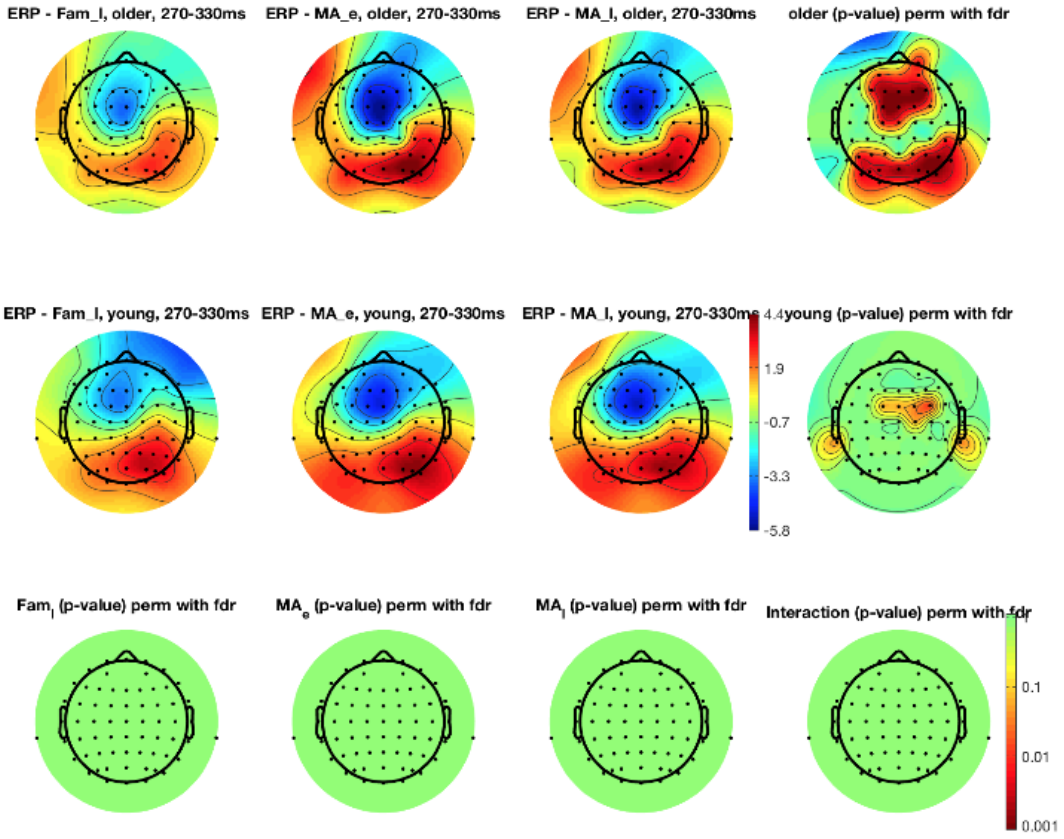


Figure 4.1. Time of interest analysis of all-scalp ERPs - healthy participants.

ERP topographical maps at the time of interest (270-330 ms post visual cue to move) and maps of statistical significance of differences between conditions and groups (permutation based statistics, FDR correction).

Further analysis of the time course in the FCz electrode demonstrated a negative voltage deflection that became significantly different between the conditions around the movement onset (figure 4.2).

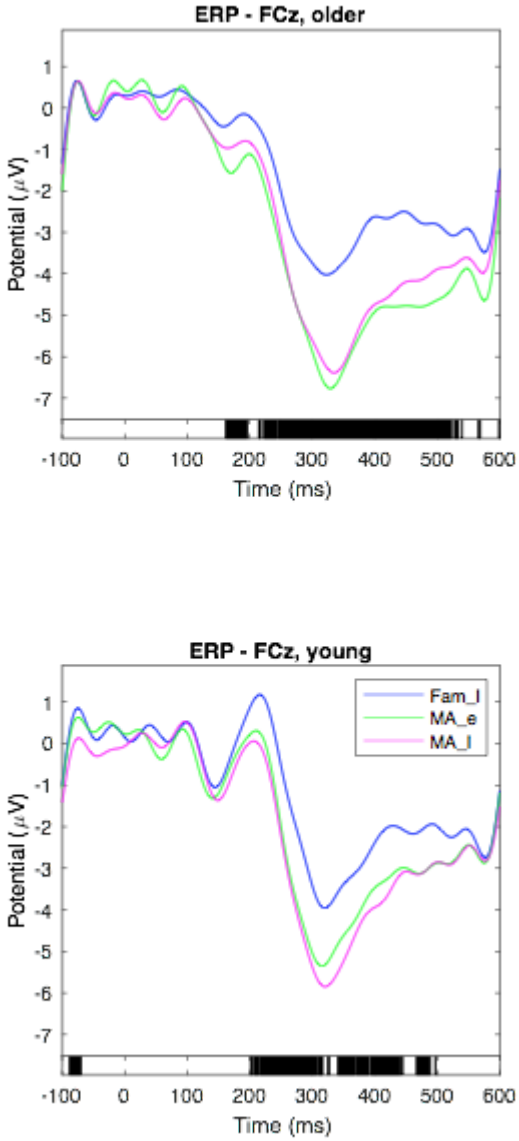


Figure 4.2. FCz timecourse differences between conditions - healthy participants. Black fields on the x axis show significant differences between conditions at the level $p<0.05$ (permutation-based statistics, FDR correction).

In the repeated measures ANOVA analyzing the mean amplitudes in 270-330ms time window of interest in the ROI signal (averaged FC1, FCz, FC2, C1, Cz, C2 electrodes) only the main effect of condition was significant ($F(1.585, 42.801) = 16.707$, $p < 0.001$, $\eta^2 = 0.382$), and main effect of age group ($F(1,27) = 1.104$, $p = 0.303$, $\eta^2 = 0.039$) and interaction were insignificant ($F(1.585, 42.801) = 0.866$, $p = 0.405$, $\eta^2 = 0.031$).

Similar analysis was conducted for the FCz electrode, and yielded similar results with only the main effect of condition significant ($F(1.582,42.720) = 19.701$, $p < 0.001$, $\eta^2 = 0.422$), main effect of age ($F(1,27) = 0.406$, $p = 0.530$, $\eta^2 = 0.015$) and interaction effect of condition*age ($F(1.582,42.720) = 0.490$, $p = 0.615$, $\eta^2 = 0.018$) were insignificant.

4.3.1.2 Timing relative to movement onset

In the ROI an additional analysis was performed to include also the factor of timing relative to movement onset, comparing pre - and post-movement 100 ms period between conditions and groups in a repeated measures ANOVA model. There was a main effect of condition ($F(2.54) = 14.074$, $p < 0.001$, $\eta^2 = 0.343$), a main effect of timing ($F(1,27) = 27.036$, $p < 0.001$, $\eta^2 = 0.500$), an interaction effect between condition and timing ($F(2,54) = 4.190$, $p = 0.020$, $\eta^2 = 0.134$), but no main effect of age group ($F(1,27) = 3.364$, $p = 0.078$, $\eta^2 = 0.111$) and no significant interactions of the group factor (all $p > 0.05$) (figure 4.3).

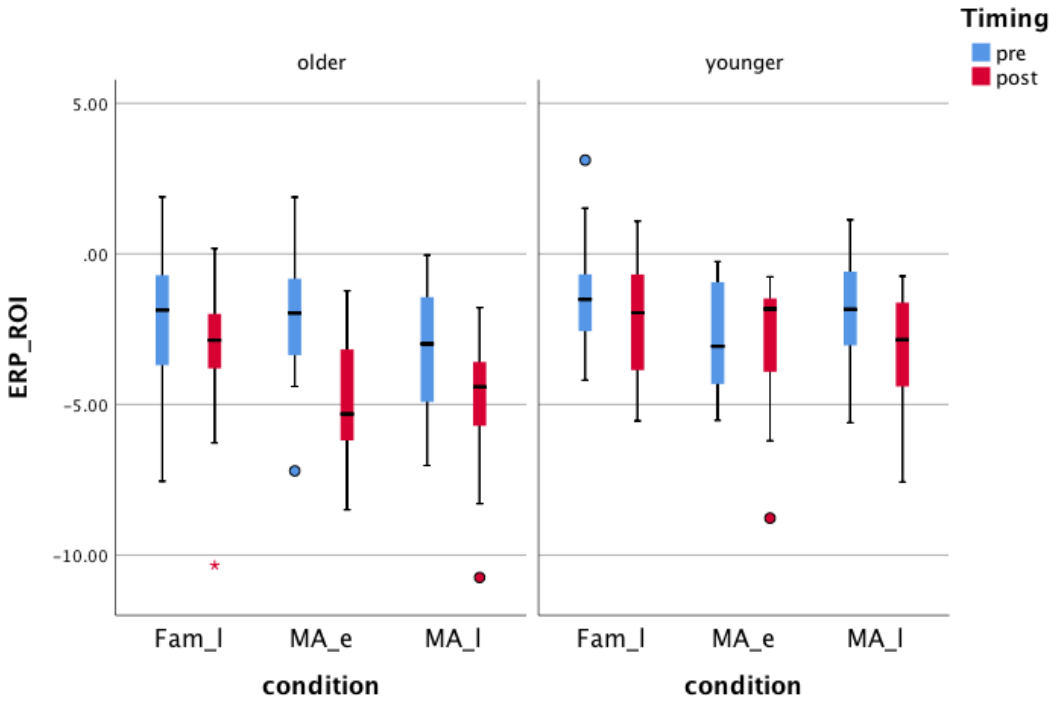


Figure 4.3. ERP amplitude of ROI electrodes.

Average amplitude (μV) 100ms before movement onset against 100 ms post movement onset. Circles and star represent outliers.

4.3.2. ERP measures in stroke patients

4.3.2.1 Voluntary reaching after stroke

In the analysis utilizing a broader look at the data with permutation testing, the deflection characteristic for motor adaptation conditions was not as pronounced in the stroke group, with significant differences between groups in the central electrodes in both motor adaptation conditions, but not in the familiarization condition (figure 4.4). The differences between groups were shifted posteriorly (Cz) in relation to the ERN electrode of interest, FCz. Whilst weaker, the differences between conditions prevailed also in the stroke group in the time of interest analysis: the adaptation-related deflection was more pronounced in the motor adaptation than in familiarization conditions.

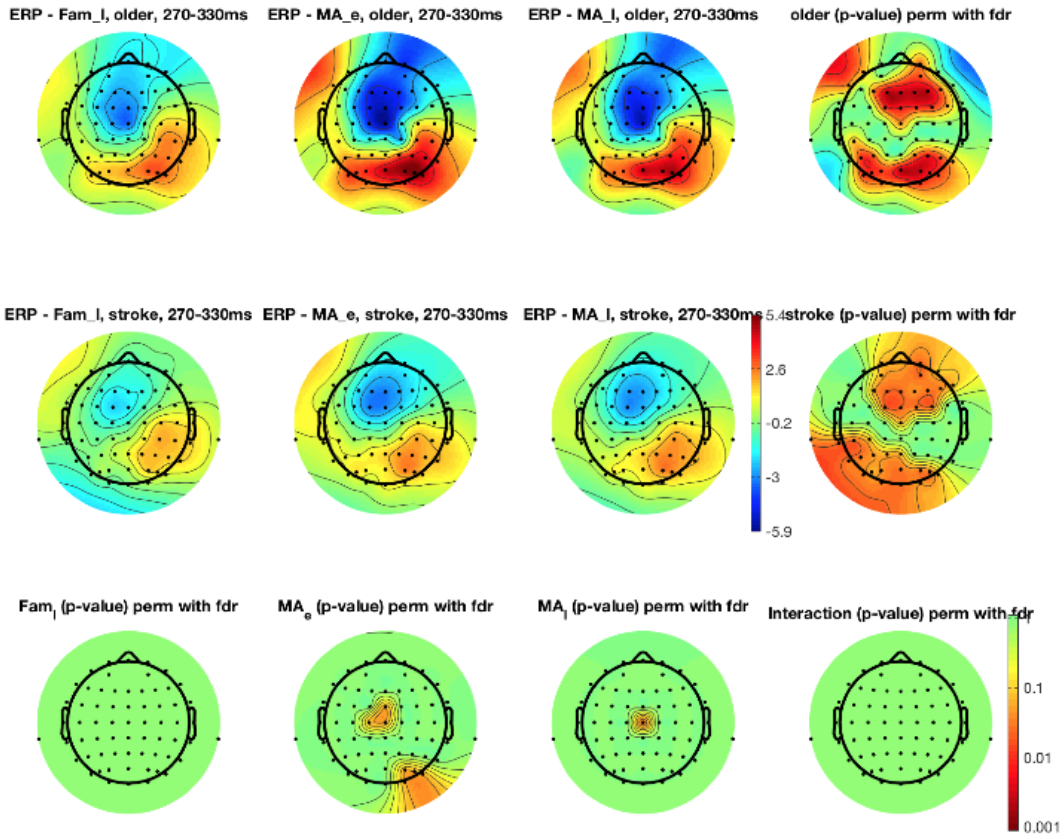


Figure 4.4. Time of interest analysis of all-scalp ERPs – stroke versus controls. ERP topographical maps at the time of interest (270-330 ms post visual cue to move) and maps of statistical significance of differences between conditions and groups (permutation based statistics, FDR correction).

Looking at the timecourse in the FCz electrode, the characteristic pattern of deflection in motor adaptation was not present in the stroke group, with FCz amplitude not showing significant differences between the conditions (figure 4.5).

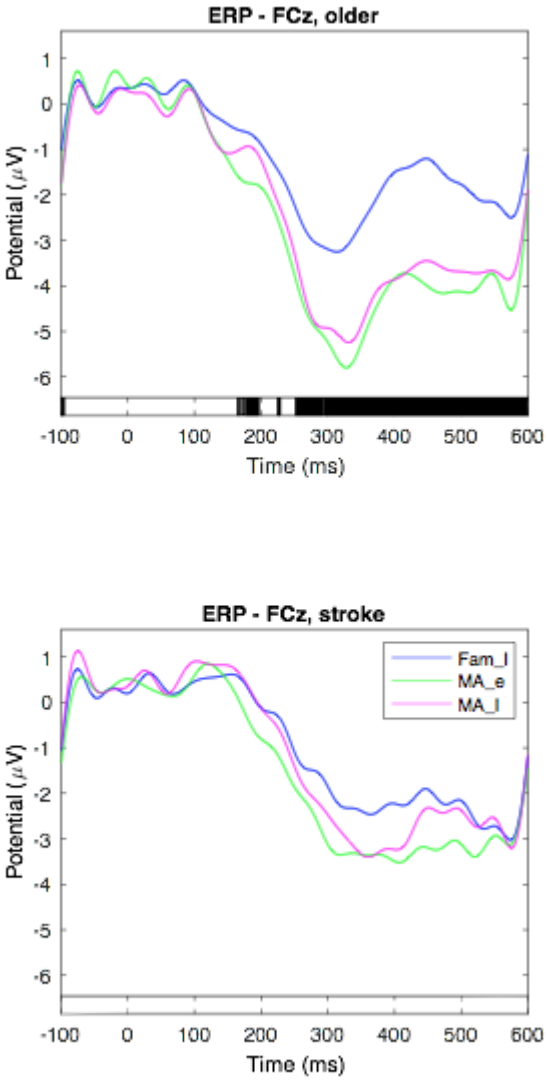


Figure 4.5. FCz timecourse differences between conditions - stroke participants versus controls.

Black fields on the x axis show significant differences between conditions at the level $p<0.05$ (permutation-based statistics, FDR correction).

The more specific analysis in the time of interest did reveal however main effect of condition. In the ROI in the time of interest for the electrodes around the FCz, both factors were significant: main effect of condition, $F(1.468, 23.481) = 13.163$, $p < 0.001$, $\eta^2 = 0.451$; main effect of stroke $F(1, 16) = 11.188$, $p = 0.004$, $\eta^2 = 0.411$, with insignificant stroke*condition interaction effect, $F(1.468, 23.481) = 2.046$, $p = 0.161$, $\eta^2 = 0.113$. (figure 4.6).

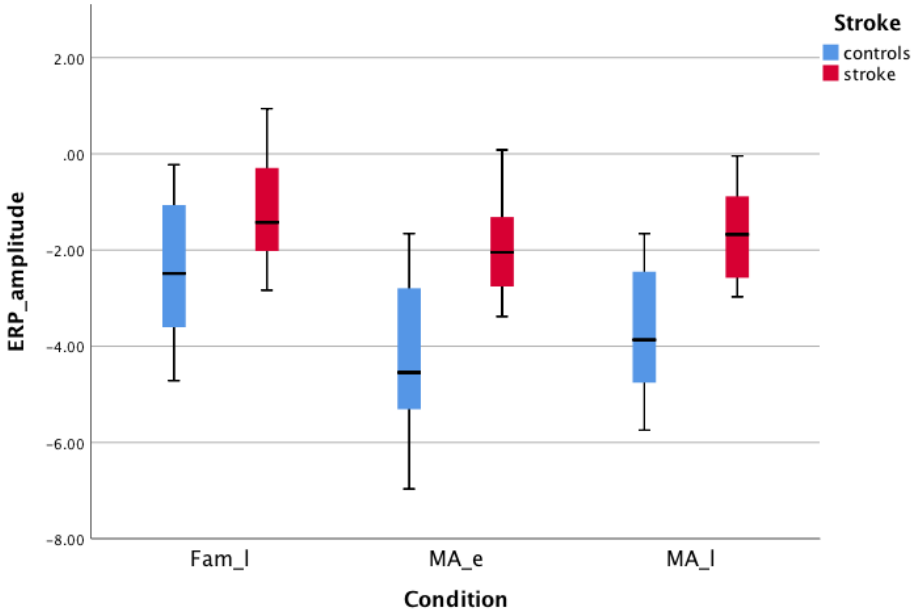


Figure 4.6. ERP amplitude of ROI electrode differences between stroke and healthy control participants.

4.3.2.2 Error processing - in depth analysis of timing in stroke

In the ROI, and additional analysis performed to include also the factor of timing relative to movement onset, compared pre - and post-movement 100 ms period between conditions and groups in a repeated measures ANOVA model. There was a main effect of condition, $F(2,32) = 14.882$, $p < 0.001$, $\eta^2 = 0.482$, main effect of timing, $F(1,16) = 9.349$, $p = 0.008$, $\eta^2 = 0.369$, interaction effect between condition and timing, $F(2,32) = 8.096$, $p = 0.001$, $\eta^2 = 0.336$ and a significant main effect of stroke, $F(1,16) = 4.791$, $p = 0.044$, $\eta^2 = 0.230$. An interaction between stroke and condition, $F(2,32) = 4.001$, $p = 0.028$, $\eta^2 = 0.200$ was also significant. When looking at simple main effects, there were no differences in the premovement period between the conditions in any of the groups and in the postmovement period familiarization differed significantly from both motor adaptation conditions in the control group and only from early motor adaptation in the stroke group, the actual proportion of the means was however much lower, as seen in figure 4.7.

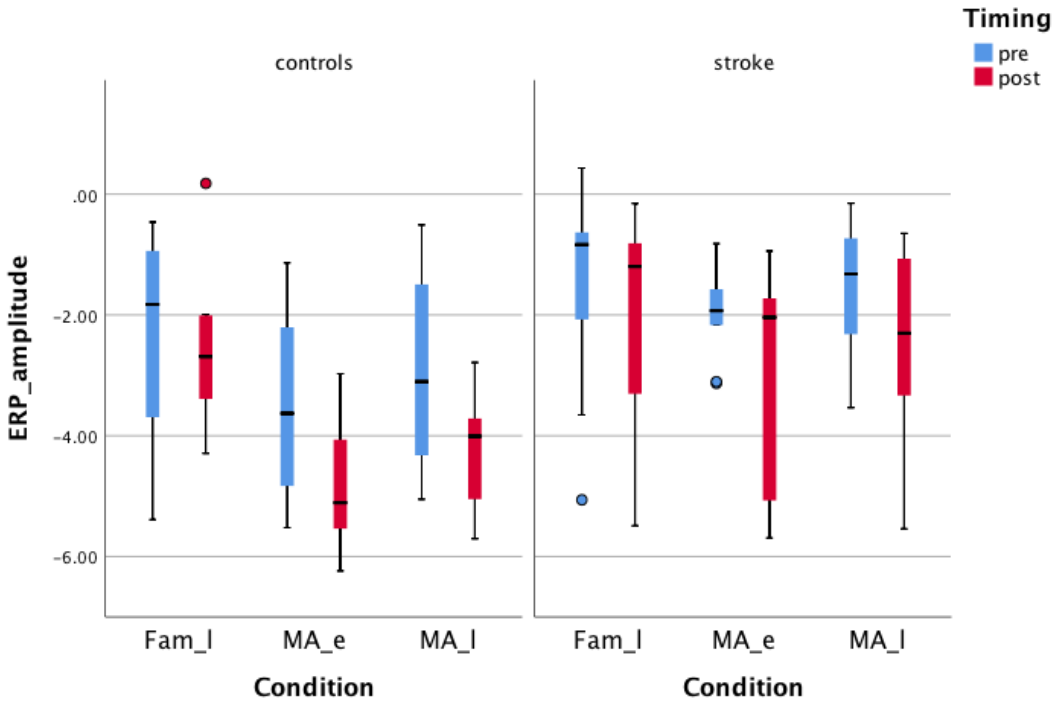


Figure 4.7. ERP amplitude of ROI electrodes.

Average amplitude (μV) 100ms before movement onset against 100 ms post movement onset. Circles and start represent outliers.

4.4. Discussion

The crucial ERP component differentiating motor adaptation from simple reaching in the familiarization condition was a frontocentral negative deflection peaking around 300 ms post visual cue. This component resembles the temporal and topographic characteristics of the ERN, a brain ERP component related to error processing. The same pattern was visible when the data were timelocked to either the visual cue or to the movement onset - a strong negative deflection, pronounced in the central electrodes and peaking around movement onset. Further analysis of the data timelocked to the movement onset revealed that the deflection was significantly deeper in the 100 ms post movement than before, suggesting activation after the appearance of the sensory feedback from movement and error commission. In that light, since the deflection was not mostly pronounced just before movement onset, it is probably not connected to predictive model formation.

This component was not different in the younger and older healthy group, which is in line with the fact that there were no differences between these groups in the kinematic measures.

Significant differences appeared however between the recovered stroke and the healthy age matched control group. The characteristic adaptation pattern in ERP did not seem to be present in the stroke group, with weaker deflection in general, less pronounced differences between conditions, and significant differences between stroke and healthy group. Interestingly, the topography of the ERP suggests that the difference between the group had a more posterior origin than the classical location of the ERN - in Cz, an electrode connected to movement preparation without motor adaptation (Naranjo et al. 2007). Importantly, there were no differences in kinematic measures between the

stroke and healthy control group - even though the stroke participants adapted their movement, they did not show an adaptation related process signature in ERP data, showing activity characteristic for simple unperturbed reaching movement. Additionally, the differences between stroke patients and controls appeared in the motor adaptation conditions only.

4.4.1 Error processing

The crucial ERP component differentiating the motor adaptation condition from the non-adaptation conditions was identified as a negative deflection most pronounced in the FCz electrode. In the literature, this pattern is characteristic for the ERN component and has been linked to error processing with a source in the ACC (Holroyd & Coles, 2002). The ERN has been extensively studied in error response reaction time paradigms, but has also been found in continuous motor correction tasks (Krigolson & Holroyd, 2006). Recently, it has been identified in learning paradigms, in prism adaptation (MacLean et al., 2015; Vocat et al., 2011) and time estimation learning experiments (Luft et al., 2014). This component has been found to be a robust biomarker of error processing independent of the direction of the type or modality of the stimulus (Falkenstein et al., 2000) and the output limb differences (Holroyd, Dien, & Coles, 1998).

According to literature, an internal forward model is formed to predict the consequences of movement given the current state of the motor system and is thought to be crucial for motor control (Wolpert & Miall, 1996; Shadmehr & Holcomb, 1997; Krebs et al., 1998). In continuous movement tasks, the ERN has been interpreted as a proof that the motor system is processing the error information before the actual error

commission, as opposed to the classical 'response ERN' (when an incorrect button is pressed in a reaction time task) and 'feedback ERN' (when the outcome of action is worse than anticipated), that both appear after the error commission (Krigolson & Holroyd, 2006). In the current study, it seems that the negative deflection appears after movement onset, which could be interpreted as an example of feedback ERN. However, it is important to note that this component is also more pronounced in presence of the force field and differentiates motor adaptation form familiarization. Motor adaptation has been defined as learning driven by prediction errors (Shadmehr, Smith, & Krakauer, 2010), and as such it was expected to be accompanied by predictive model formation and a biomarker thereof.

In experiments on longer-term motor adaptation, a shift in activation occurs from the prefrontal areas and frontal eye fields in early phases of adaptation to more activation in the cerebellum and sensorimotor and parietal cortex (Della-Maggiore & McIntosh, 2005; Shadmehr & Holcomb, 1997). This suggests different roles of the frontal, attentional, parietal and sensorimotor systems in the adaptation process. Furthermore, evidence from previous reaching movement studies suggests that it is the posterior parietal cortex (PPC) and the cerebellum that are involved in the online forward control of movement and feedback processing (Desmurget & Grafton, 2000). It has been suggested however that the PPC is part of a hierarchical error processing system, activated after ACC activation (Krigolson & Holroyd, 2006), with the ACC playing a dominant role in processing high-level goals and acting as a motor control filter fed by reward prediction error signals from the midbrain dopaminergic system (Vassena, Holroyd, & Alexander, 2017). In summary, the results of the current study are

consistent with an important role of ACC in the early motor adaptation process, however do not lead to the conclusion that the observed component is a marker of predictive model formation.

4.4.2 Simple sensory feedback processing

A frontocentral component similar to the ERN has been identified and interpreted as a sensory feedback processing response in experiments on hand movement not involving error processing. This frontocentral component appears after the movement onset (fpMP; Tarkka and Hallett, 1991a) and in no-switch trials (Dipietro et al., 2014)). In a robot-mediated reaching study, at 200 ms after the visual cue to move – and before the movement onset – it was the parietal-occipital activity that peaked first in negativity before the frontocentral region and this was interpreted as consistent with the concept of the PPC role in online visuomotor control (Dipietro et al., 2014). It was followed by a peak of negativity over the frontocentral areas and again this was interpreted as activity related to somatosensory feedback from the movement. The ERN component related to predictive model formation has not been observed in preparatory phases of reaching movement without error trials (Naranjo et al., 2007). Therefore, it appears that in tasks without error processing, the central system is not required to build a representation of predicted error to account for environmental perturbation, however the location of the signal suggests that the feedback processing and error processing might have a similar source to some extent.

Recent findings on ACC function in simulated data suggest that this structure is involved in initiating and maintaining motivation for effortful behaviours (Holroyd & McClure, 2015). Thus, it is possible that the results from the present study indicate

simply the extra physical effort put in the motor adaptation task. However, it seems that the ACC acts on a very high-goal level (Holroyd & McClure, 2015) and not on simple physical effort observable in a lab-based reaching experiment.

4.4.3 The role of ERN in pathology

Studies in stroke suggest that for simple movements, there are prefrontal processes involved in motor preparation which are distinct to the motor execution system in the motor cortex and that these processes can be selectively damaged by stroke (Wiese et al., 2005). The clinical studies seem to suggest that the ERN component could be an indicator of the motor learning process that is independent of motor control processes. The current study is the first to show ERP differences between stroke participants and healthy controls during motor adaptation demonstrating an attenuated motor adaptation component without accompanying differences in kinematics.

4.4.4 Conclusions and clinical implications

In the current study on a robot-mediated motor adaptation of reaching movements, a characteristic ERP component over the frontocentral area has been found that differentiates the motor adaptation reaching trials from the reaching-only trials. This component is interpreted as ERN, a component characteristic for movement error processing.

The role of ACC in error processing enables new insight into the process of motor adaptation, a notion proposed as a useful model for neurorehabilitation (Dipietro et al., 2012; Huang & Krakauer, 2009; Lefebvre et al., 2015). Successful neurorehabilitation depends on how the patients are able to re-learn their lost skills. The frontocentral error processing system appears to be a valuable target for further research

in neurorehabilitation. The novelty of this study lies in interpreting the motor adaptation process in the wider context of error processing literature and finding a unique ERP pattern in stroke patients with lack of clear motor adaptation ERN-like component in light of preserved kinematic performance.

5. Event related spectral perturbation

5.1 Introduction

The EEG signal can also be analysed in the frequency domain, with the brain signal grouped in specific frequency bands: delta (1-4Hz), theta (4-7Hz), alpha(8-13Hz), beta (13-30Hz) and gamma (30-80Hz) of different functional meaning (Engel & Fries, 2010). Beta event related spectral perturbation (ERSP) is the most characteristic neural correlate of movement and a part of a complex of spectral changes in the brain involving the faster waves: a self-paced movement is accompanied by contralateral alpha and beta desynchronisation starting before the movement onset, bilateral alpha and beta desynchronisation during the movement, followed by a contralateral beta synchronisation after the movement offset (Crone, Miglioretti, Gordon, & Lesser, 1998; Pfurtscheller & da Silva, 1999; van Wijk, Beek, & Daffertshofer, 2012), with bursts of gamma synchronisation during the duration of the movement as seen in subdural recordings (Pfurtscheller, Graimann, Huggins, Levine, & Schuh, 2003). Since scalp recording is heavily contaminated by muscle activity in the gamma band, it is not always possible to disentangle the movement-related gamma brain signal from the electomyography using scalp electrodes. The alpha rhythm in the motor cortex is also crucial and interpreted as a specific motor mu rhythm, responsible for information processing functions that modulates motor cortex activity during perception of movement (Pineda, 2005; van Wijk, Beek, & Daffertshofer, 2012).

In this thesis, I mainly focus on beta power, since it was hypothesized that the attenuations in beta power can signal facilitation of changes in the motor set (Engel & Fries, 2010). In cue-paced studies, the time window for analysis that allows

identification of spectral phenomena accompanying movement preparation is quite short, but the changes in beta rhythm that allow for accurate classification of intended movement happen within the first second after the cue (Pfurtscheller et al., 2013; Fazli et al., 2012).

In the elderly, the characteristic movement related desynchronisation is still present, but seems more flat and broadband, accompanied with higher level of spectral entropy (Quandt et al., 2016), suggesting a less specific and more diffuse response.

In stroke, movement related beta desynchronisation over the contralateral sensorimotor cortex was found attenuated in comparison with healthy controls, as measured by magnetoencephalography, and correlated with the level of hand impairment (Rossiter, Boudrias, & Ward, 2014). In EEG studies, the magnitude of mu and beta rhythms were correlated with the level of residual function in the upper limb after stroke (Bartur, Pratt, & Soroker, 2019). Also a recent longitudinal brain-computer-interface intervention study suggested a strong relation between upper limb motor recovery and beta activity, with weaker evidence for a similar association with alpha oscillations (Carino-Escobar et al., 2019).

In this chapter, the experimental data will be analysed in the time-frequency domain focusing on following the general three step framework mentioned in chapter 1, hypothesising specifically to a) in the first step, find movement related alpha and beta desynchronization after movement onset over the contralateral sensorimotor cortex established in the literature, b) in the second step, look for differences between simple reaching and motor adaptation conditions in an exploratory manner since it has not been

addressed in the literature and c) in the third step, explore the differences between healthy and stroke patients also not addressed thus far in the literature.

5.2 Method

5.2.1 Participants

Detailed description of participants and recruitment process can be found in chapter 2. In brief, 29 healthy participants with a broad range of age and nine stroke patients volunteered to participate in the study. Of the healthy participants, 9 were subsampled as age matched controls for the stroke patients. None of the participants had previous history of neurological, neuromuscular or orthopaedic disease (except of the stroke in case of stroke patients). All participants were right hand dominant. Stroke patients had a stroke that initially affected their right hand function, but were well recovered by the time they participated in the study (Fugl-Meyer score >= 55/66 points). The study was approved by the University of East London Ethics Committee and NHS ethics committee (UREC 1516_25; IRAS 195798) and conducted in accordance with the Declaration of Helsinki.

The ERSP features were analysed first to explore the pattern of motor adaptation in healthy young adults and their possible modification with age. I analysed participants over the whole lifespan, subsampling participants in their early twenties as those who would adapt optimally in the adult group.. Once the healthy pattern of ERSP measures was established, I moved on to explore the same variables using the same paradigm in well recovered stroke patients.

5.2.2 Apparatus

Brain activity was recorded through a 64-channel Waveguard cap and amplified by a TMSi Ref-Ext amplifier (ANT Neuro, Enschede, Netherlands), digitized at 1024 Hz and band-pass filtered from 0.1 to 500 Hz. During the recording, data were referenced to the Fz electrode and impedances were kept below 5 kΩ.

The kinematic data were recorded by the encoders embedded within the joystick of the MIT-Manus2 (InMotion Technologies, Cambridge, MA, USA) robotic manipulandum.

5.2.3 Procedure

After the EEG cap preparation, the participant sat in a chair directly in front of a robot device (MIT-Manus, IMT2, InMotion Technologies, Cambridge, MA, USA) and was asked to grasp the end-effector joystick with the right hand.

The task was to perform a straight reaching movement from a central starting point to a peripheral target within an instructed period of 1.0 – 1.2 seconds. A vertical screen situated at eye-level gave online feedback regarding the position of the displaced robot handle. After each movement, the participant relaxed the arm as the robot repositioned it to the central point. A single trial started with a visual cue prompting the participant to perform the reaching movement and ended with the passive return to the central position.

The experimental protocol was based on 3 conditions, each composed of 96 reaching trials. The familiarization condition (Fam) was performed in a null force-field. During the motor adaptation condition (MA), the robot applied a velocity-dependent

force-field in the clockwise direction of 25 Ns/m absolute intensity, perpendicular to the trajectory of the end-effector joystick.

5.2.4 Data analysis

Offline data analyses were carried out with MatLab 2015b (The MathWorks, Inc.), with the support of EEGLab and FieldTrip open-source toolboxes for the analysis of EEG data (Delorme & Makeig, 2004; Oostenveld, Fries, Maris, & Schoffelen, 2011).

5.2.4.1 EEG pre-processing

A pre-processing pipeline for EEG data has been developed with EEGLab toolbox (Delorme & Makeig, 2004) and has been described in more detail in chapter 2. In brief, data were band-pass filtered between 0.5 Hz and 100 Hz, notch filtered at 50 Hz and 25 Hz to remove the power line noise and harmonics, epoched between -1000 to 2000ms around visual cue with baseline between -1000 and 0 ms. After bad channel and epoch removal, the data were subjected to ICA, removed channels interpolated and re-referenced to common average.

5.2.4.2 Event-Related Spectral Perturbation

Time-frequency domain data were calculated using a convolution with Morlet wavelets (Torrence & Compo, 1998) per each subject, trial and condition in the frequency range between 3 and 50 Hz with 2 cycles at the lowest frequency and 16 at the highest and a Hanning window of 743ms. ERSP change was obtained by subtracting the average baseline power (-1000 to 0 ms) from the power at each time-frequency point at each channel post the visual cue. The obtained values were averaged per subject per condition in late familiarization, early motor adaptation and late motor adaptation, in analogy to the conditions analysed in the time domain (i.e. ERPs in Chapter 4).

5.2.4.3 Statistical analysis

ERSP in the time window of interest for the whole set of electrodes was analysed using permutation-based statistics with false discovery rate (FDR) correction for multiple comparisons to compare values between groups (young vs older or stroke vs controls) in each of the conditions as implemented in the EEGlab toolbox (Delorme and Makeig, 2004). The time window of interest for the reaching movement was defined as the time around 300ms (average of 270-330 ms) post visual cue, which encompasses the typical movement onset.

For a full spectrum evolution in time analysis, the C3 electrode was chosen as the electrode of interest in line with classical ERSP literature (Pfurtscheller & da Silva, 1999; Torrence & Compo, 1998) and the differences between the conditions were also analysed with EEGlab built-in permutation-based statistics with FDR correction.

Additionally, to maintain consequence with the time-domain analysis, the signal of electrodes surrounding FCz (FC1, FC2, Cz, C1, C2, including FCz) was averaged for the purpose of analysis of the region of interest (ROI) in the beta band in the time of interest. Mean data for the time window of interest for ROI was analysed in a 2 (group) x 3 (condition) repeated measures ANOVA model, with values reported with Greenhouse-Geiser correction when the assumption of sphericity was not met. Analysis of simple main effects was conducted with Bonferroni correction for multiple comparisons.

A similar statistical model was implemented to analyse data averaged for the time window of interest (TOI) for the electrode of interest, C3 in 300 ms time bins to analyse the statistical properties of development of ERSP over time in the trials, with 2 (group) x 3 (condition) x 4 (time window) factors. As a final zoom into the data, the

evolution of beta power of the C3 electrode was plotted at each timepoint for each group.

5.3. Results

5.3.1 Healthy group

The ERSP image in the time of interest averaged around the movement onset showed expected movement related features, with prominent alpha and beta desynchronisation over the bilateral sensorimotor areas, especially visible over the left primary motor area contralateral to the moving hand. There were no significant differences between the younger vs older group nor conditions as measured by the permutation based statistics (figure 5.1,figure 5.2).

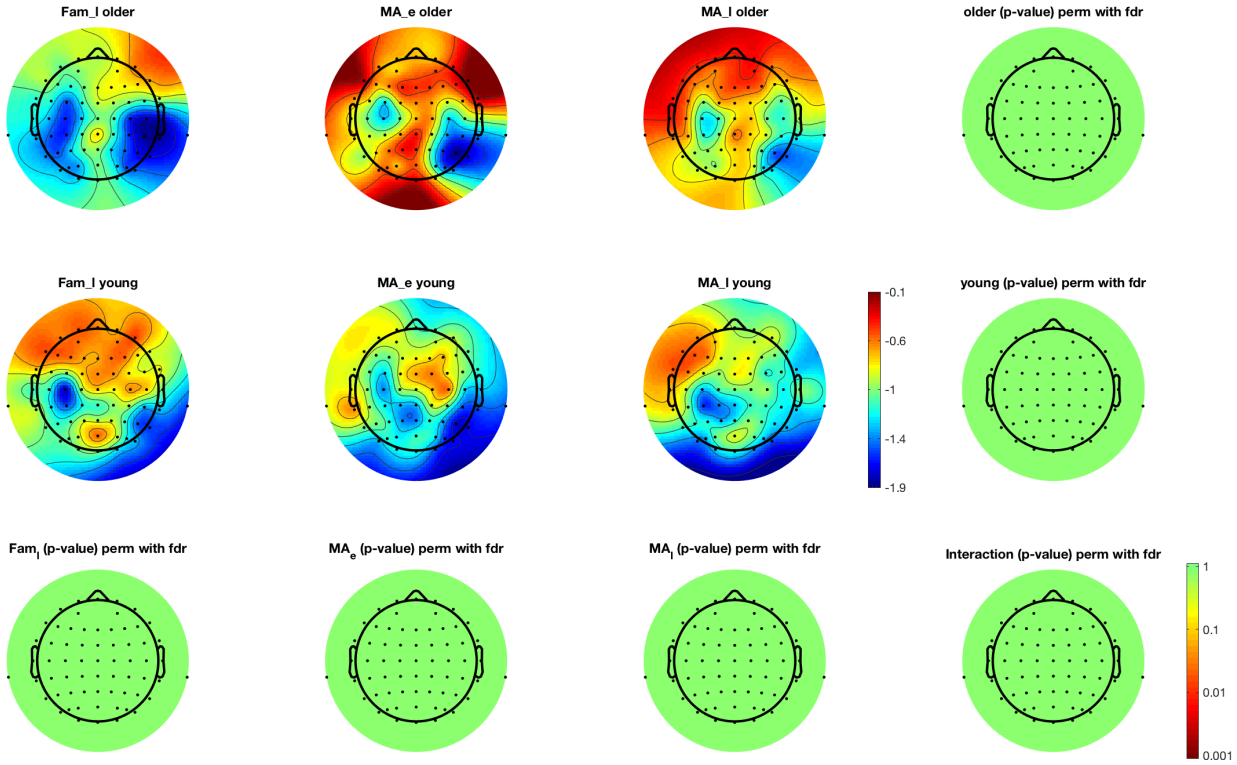


Figure 5.1. Alpha power at the time of interest in the healthy groups.

The topographical plots represent the ERSP averaged for all frequencies in the alpha band (8-13Hz) in all timepoints in the window of interest around movement onset (270-330ms) to show a distribution of alpha power over all scalp electrodes. The bottom and right side plots represent p values as measured by the permutation method with fdr correction (no significant differences in any of the electrodes).

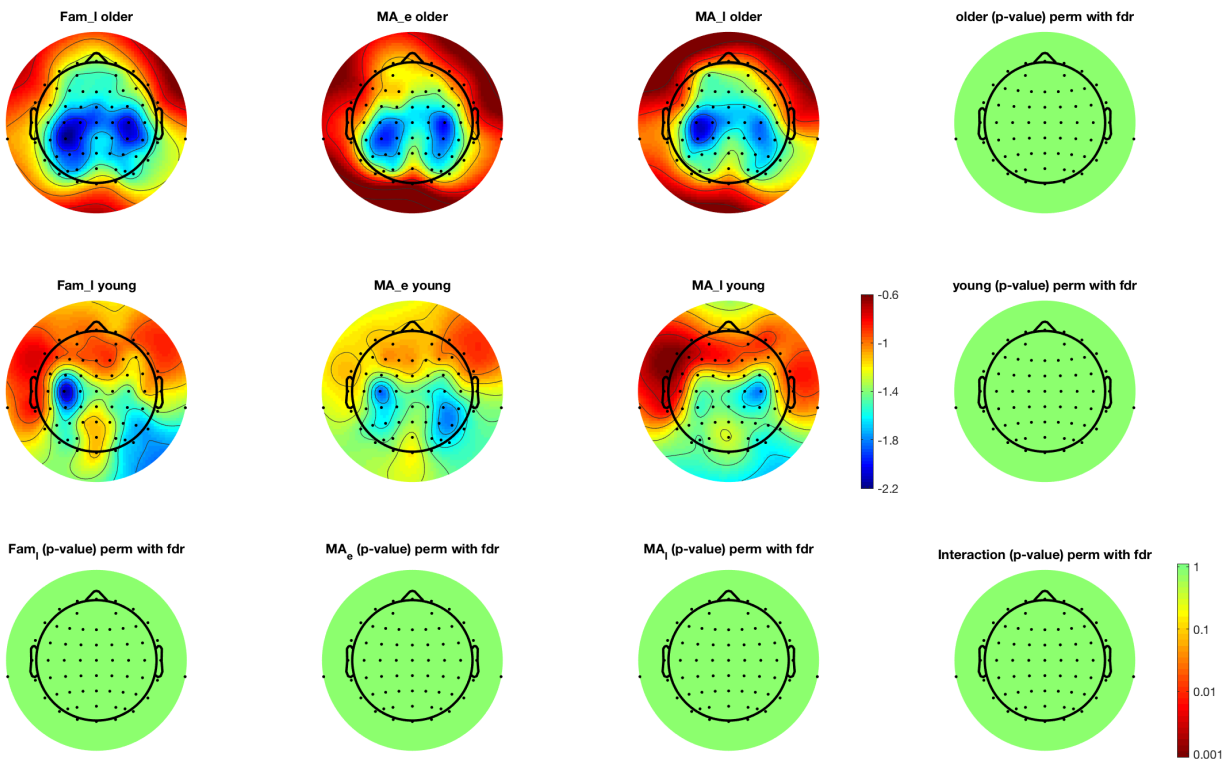


Figure 5.2. Beta power at the time of interest in the healthy groups.

The topographical plots represent the ERSP averaged for all frequencies in the beta band (13- 30 Hz) in all timepoints in the window of interest (270-33-ms) to show a distribution of beta power over all scalp electrodes. The bottom and right side plots represent p values as measured by the permutation method with fdr correction (no significant differences in any of the electrodes).

In the C3 electrode of interest over the primary motor cortex contralateral to the moving arm, a clearly visible pattern of beta and alpha desynchronisation was noted starting around movement onset (~300 ms post visual cue). Again, the pattern was exactly as expected based on the movement desynchronisation literature. The statistical analysis as implemented in EEGlab toolbox yielded no significant differences between groups and conditions (figure 5.3).

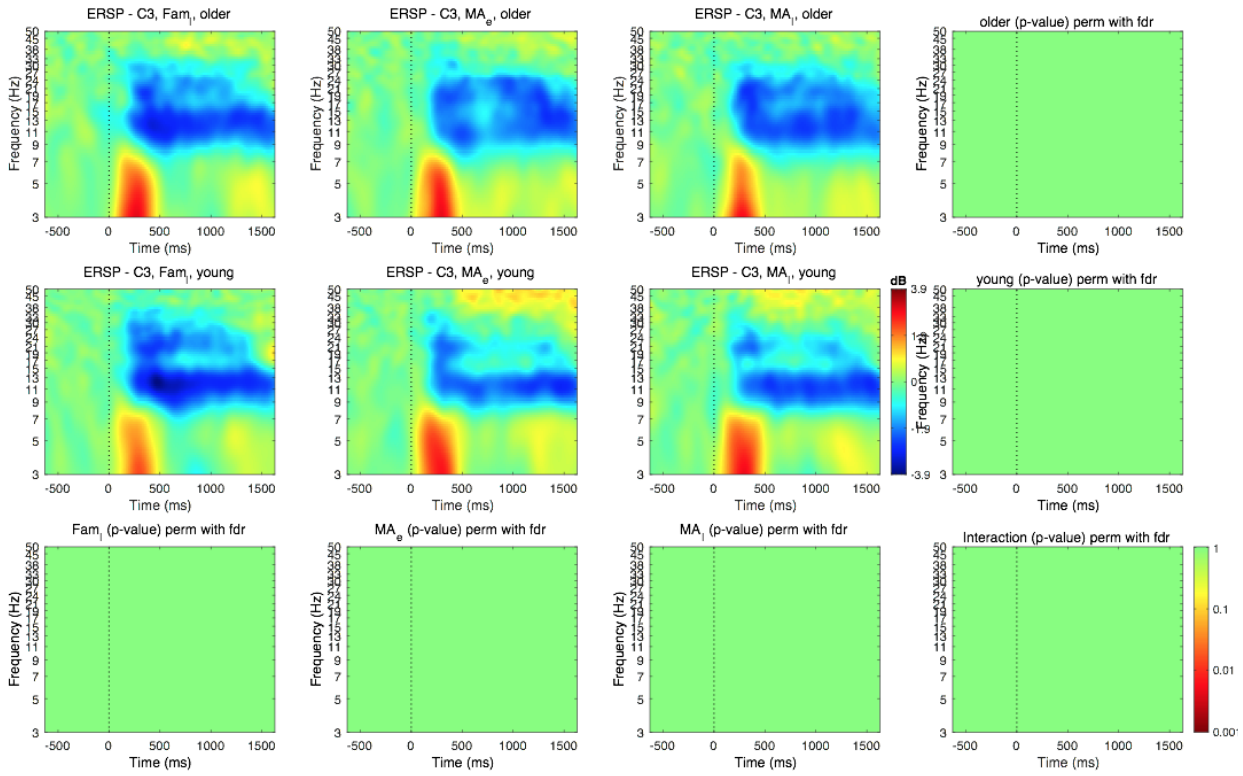


Figure 5.3. Time-frequency plot in C3 electrode of interest.

The plot represents all frequencies obtained from the convolution procedure. Bottom row and right column represent p-values for each time-frequency point (no significant differences between groups and conditions).

A specific ANOVA model for the C3 electrode beta band power binned in different time windows yielded only a main effect of window, ($F(1.282, 34{,}624) = 6.881$, $p = 0.008$, $\eta^2 = 0.203$) with no main effect of group ($F(1,27) = 0.344$, $p = 0.562$, $\eta^2 = 0.013$) nor condition ($F(1.255, 33.898) = 1.832$, $p = 0.184$, $\eta^2 = 0.064$) and no interaction effects. The second time window - the one encompassing the period post movement onset (300-600 ms) showed the lowest ERSP values (figure 5.4). Notably, figure plotting the beta power shows a beta rebound in the younger group in the C3 electrode during the first second after movement onset only in the motor adaptation conditions, but this difference did not reach significance in the statistical testing, as analysed by further condition*window interactions within the participant groups (older: ($F(1.562,21.875) = 1.141$, $p = 0.325$, $\eta^2 = 0.075$; young: ($F(6,78) = 1.907$, $p = 0.090$, $\eta^2 = 0.128$).

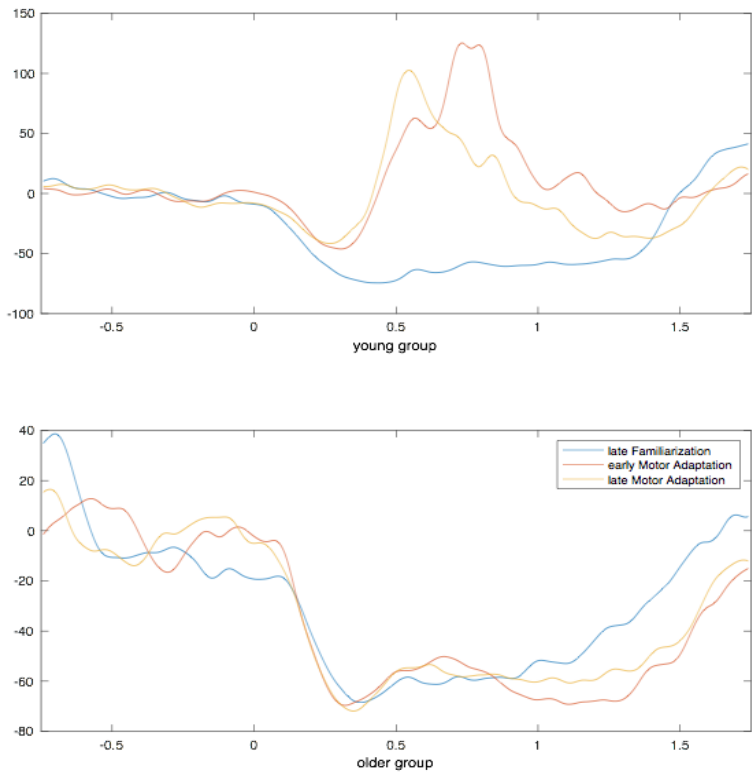


Figure 5.4. Beta band power (13-30 Hz) evolution in time in C3 electrode.

The lines represent different conditions.

Additionally, an analysis for averaged channels over the frontocentral area in the time window of interest around the movement onset for the analogy with ERP design was conducted, but the ANOVA model did not yield any significant factors in the of condition by group.

5.3.2 ERSP in stroke

The ERSP image in the time of interest averaged around the movement onset again showed expected movement related features, with prominent alpha and beta desynchronisation over the bilateral sensorimotor areas. Even though the beta desynchronisation pattern in the stroke groups in the beta band seemed significantly attenuated, the statistical analysis yielded no significant differences between the groups nor conditions as measured by the permutation based statistics (figure 5.5, figure 5.6).

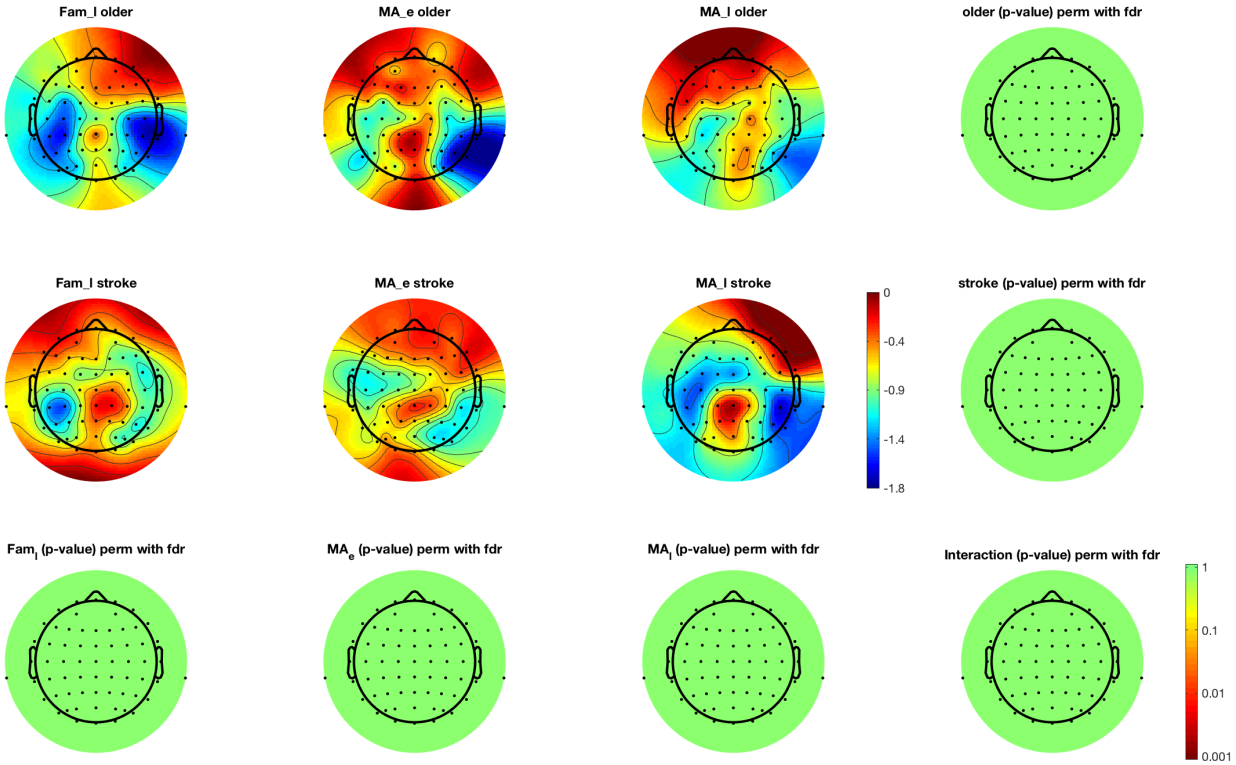


Figure 5.5. Alpha power at the time of interest in the stroke versus control groups. The topographical plots represent the ERSP averaged for all frequencies in the alpha band (8-13Hz) in all timepoints in the window of interest (270-330ms) to show a distribution of alpha power over all scalp electrodes. The bottom and right side plots represent p values as measured by the permutation method with fdr correction (no significant differences in any of the electrodes).

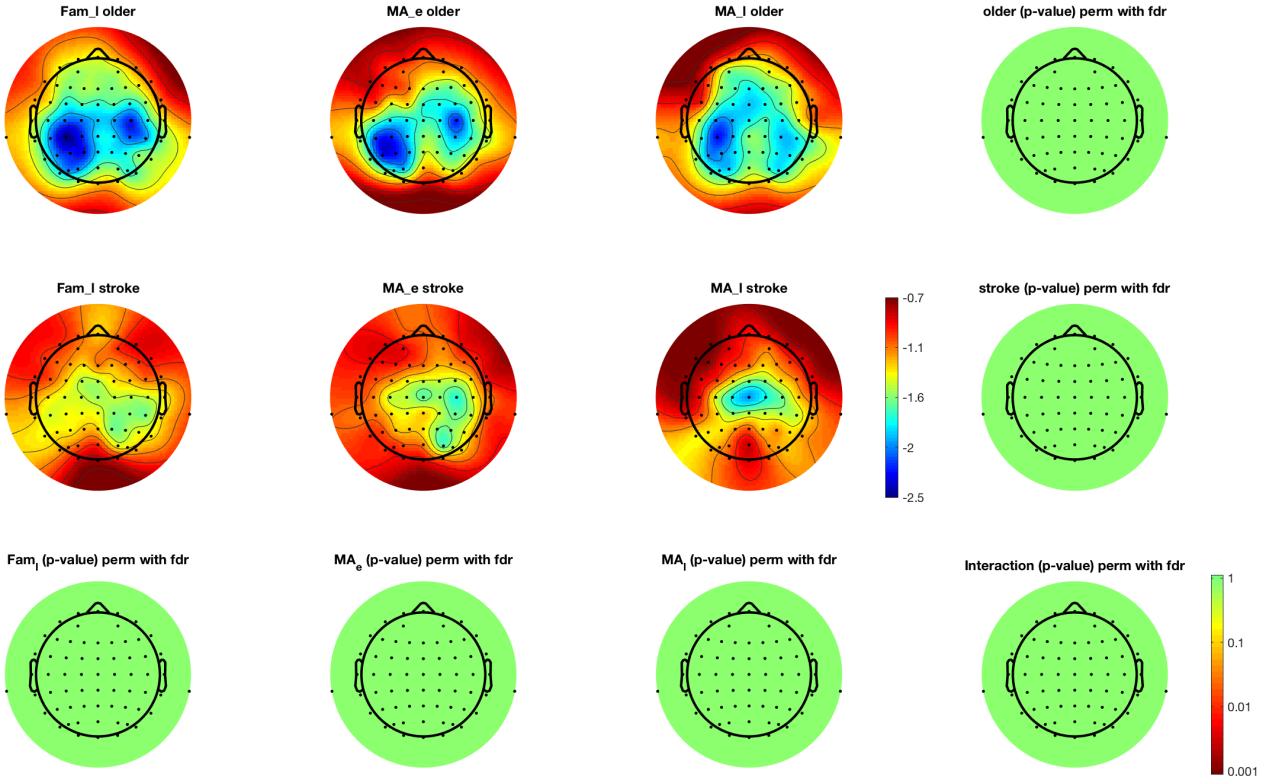


Figure 5.6. Beta power at the time of interest in the stroke versus control groups. The topographical plots represent the ERSP averaged for all frequencies in the beta band (13-30Hz) in all timepoints in the window of interest (270-330ms) to show a distribution of beta power over all scalp electrodes. The bottom and right side plots represent p values as measured by the permutation method with fdr correction (no significant differences in any of the electrodes).

In the C3 electrode of interest over the primary motor cortex contralateral to the moving arm, a clearly visible pattern of beta and alpha desynchronisation was noted starting around movement onset (~300 ms post visual cue). The statistical analysis yielded no significant differences between groups and conditions (figure 5.7).

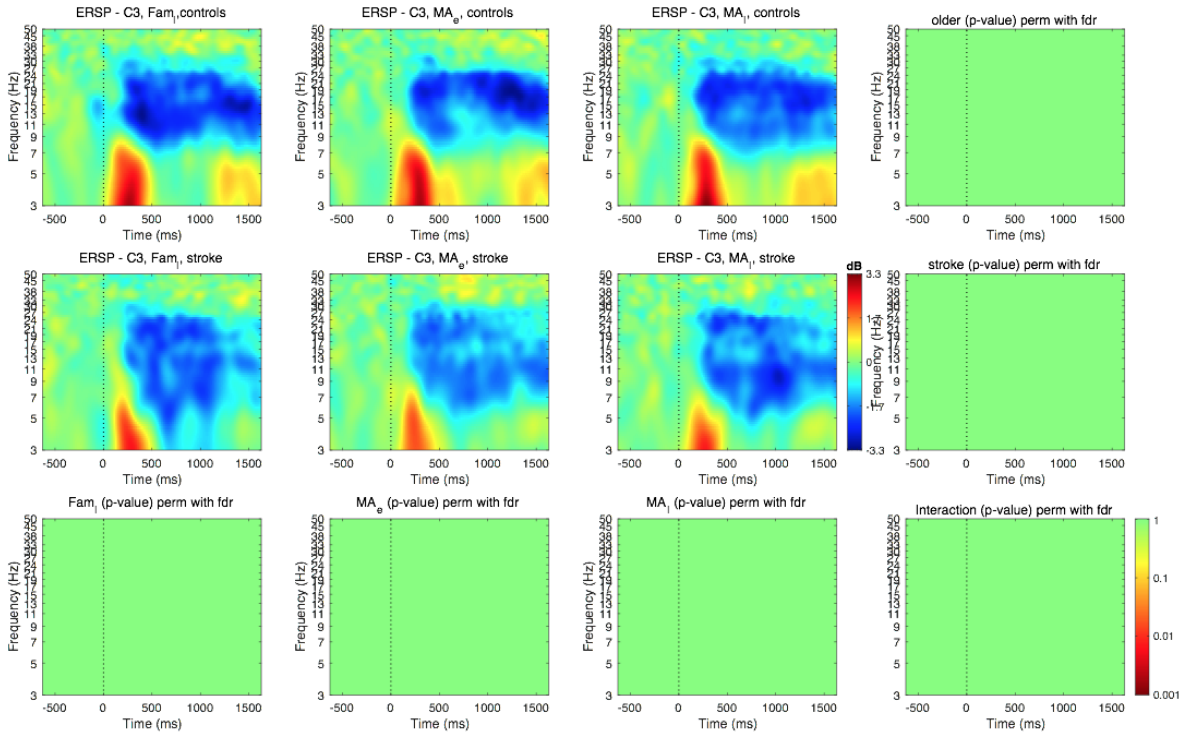


Figure 5.7. Time-frequency plot in C3 electrode of interest.

The plot represents all frequencies obtained from the convolution procedure. Bottom row and right column represent p-values for each time-frequency point (no significant differences between groups and conditions).

A specific ANOVA model for the C3 electrode beta band power binned in different time windows yielded only a main effect of window, $F(1.351,21.609) = 9.883$, $p = 0.002$, $\eta^2 = 0.382$, with no main effect of group ($F(1,16) = 0.372$, $p = 0.550$, $\eta^2 = 0.023$) nor condition ($F(2,32) = 0.353$, $p = 0.705$, $\eta^2 = 0.022$). The second time window - first post movement onset (300-600 ms) again showed the lowest ERSP values (figure 5.8).

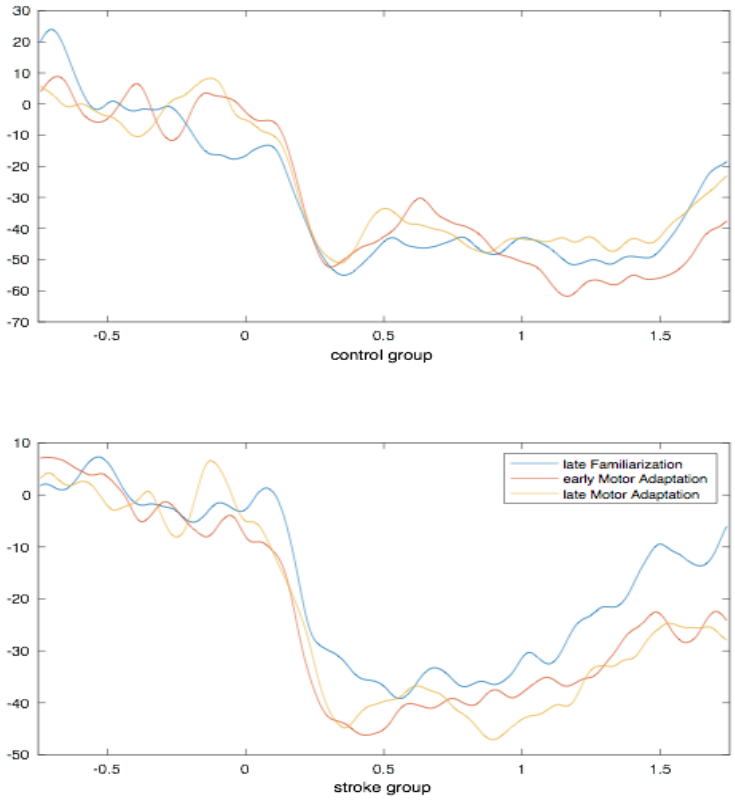


Figure 5.8. Beta band power (13-30 Hz) evolution in time in C3 electrode in stroke vs control group.

The lines represent different conditions.

Additionally, I conducted an analysis for averaged channels over the frontocentral area in the time window of interest around the movement onset. Again, the ANOVA model did not yield any significant factors in the of condition by group.

5.4. Discussion

In the current time-frequency analysis, I demonstrated a characteristic desynchronization pattern in all conditions in all groups of participants, that did not show differences between familiarization and motor adaptation conditions. The movement-related desynchronization was present in beta and alpha bands and located as expected over bilateral primary motor cortex electrodes. The beta band is a well known classic rhythm associated with motor function, showing attenuation induced by voluntary movements (Baker, 2007; Engel & Fries, 2010; Klostermann et al., 2007; Sanes & Donoghue, 1993), and motor imagery (Pfurtscheller et al., 2013; Toni, 2008).

It seems thus that the experimental paradigm was able to produce classic movement effect, but the ERSP measure was not sensitive to the differences in motor adaptation. Recently, literature on motor adaptation suggested, that it is rather post movement beta synchronization measured at the single trial level that could be sensitive marker of the change in motor behaviour associated with error processing (Tan, Jenkinson, & Brown, 2014; Torrecillos, Alayrangues, Kilavik, & Malfait, 2015). The current study reports the changes spanning only over the movement period as analysed previously in the stroke time-frequency literature (Rossiter et al., 2014) and did not allow for detailed post-movement analysis. The choice of time-window for

preprocessing and analysis in the current study was motivated by literature showing that the signature of movement preparation happens shortly after a cue to move -within the first second - and peaks around 300 ms post cue, even in motor-imagery only paradigms (Pfurtscheller, Scherer, Müller-Putz, & Lopes da Silva, 2008).

There was no differences in the time-frequency domain between stroke patients and healthy controls, which is probably explained by the fact that they were as able as healthy controls to produce the desired movement - illustrated by no differences in the kinematic measures and high Fugl-Meyer cut-off score. Research analysing beta band response attenuation in stroke showed correlations of that measure with the residual hand function (Bartur et al., 2019; Carino-Escobar et al., 2019; Rossiter et al., 2014), which would explain no differences when participants have good residual hand function. ERSP however may still be valuable target in stroke research for rehabilitative interventions, for example utilising brain-computer interface (Carino-Escobar et al., 2019; Fazli et al., 2012), with more focus on patients that are not as well recovered as in the current study.

This chapter suggests that movement-related time-frequency characteristics does not show distinctive features in motor adaptation and fails to provide novel results, replicating only results of studies showing well researched movement related spectral desynchronisation. Perhaps broadening the analysis window to include post movement period would bring more conclusive results in that domain in the future.

6. Connectivity

6.1. Introduction

Studies analysing relations between different brain regions employ typically two approaches: functional and effective connectivity. The first - which is within the scope of this chapter - focuses on observing non-directional temporal associations between brain systems usually based on correlation or phase synchrony measures. According to the communication through coherence hypothesis (Fries, 2005, 2015), neuronal populations communicate by synchronous firing that expresses waves of inhibition and excitation in the brain. In EEG, a phase locking value (PLV) is one of the metrics of variability of the phase difference at different electrodes and as such, it depicts functional connectivity between those (Lachaux, Rodriguez, Martinerie, & Varela, 1999).

Movement execution studies have revealed a robust pattern of the PLV in delta-theta frequency bands over the primary motor cortex contralateral to the movement, regardless of the moving hand laterality or whether the movement was cued or self-initiated (Popovych et al., 2016). The PLV employed in this study demonstrated distinct patterns that were different to the time-frequency and time domain results, which led the authors to think that it is the phase-locked motor cortex oscillations that are crucial for movement preparation and execution (Popovych et al 2016). Phase locking in the delta-theta band was also found to be an age-independent phenomenon, present in younger and older study participants, but to a different extent - older adults presented a more wide-spread activation network (Rosjat et al., 2018). This phenomenon, coupled with the fact that the authors did not find a correlation between the PLV and movement time,

suggests that the additional connections serve to compensate the age-related changes in brain functions underlying movement execution to maintain performance (Rosjat et al., 2018).

Studies employing EEG functional connectivity in motor learning revealed increases in resting state functional connectivity between M1 and cerebellum and within cerebellum in the mu (= motor alpha) and beta bands after one session of training (Mehrkanoon, Boonstra, Breakspear, Hinder, & Summers, 2016). Resting state beta coherence in C3 electrode over the primary motor area was found to be a predictor of future motor improvement after a single training session (Wu, Srinivasan, Kaur, & Cramer, 2014). Resting state beta coherence between C3 and Fp1 and C3 and Fpz electrodes over left prefrontal cortex predicted the ability to adapt a hand movement to a force-field, suggesting a possible role for higher-level cognitive-motor control in motor adaptation employing the active inference theory (Faiman, Pizzamiglio, & Turner, 2018). To our knowledge, however, there was no task-related connectivity studies in motor adaptation.

We recently extensively reviewed functional connectivity changes that occur after having a stroke (Desowska & Turner, 2019). The dominant trend was found to be a decrease in connectivity early after stroke, both in resting state and task-related connectivity; in both EEG and fMRI measures and expressed by simple functional connectivity, causality and network topology measures. These supposed "dysfunctions" in brain networks normalised with recovery time. A few of the sampled studies found higher functional connectivity in a small number of brain structures after stroke, but when analysed further higher functional connectivity was accompanied by a decrease in

clustering coefficient of the wider network, a result that lead to a conclusion that the motor network may become more randomised with recovery (Wang et al., 2010). Connections crucial for hand function after stroke were identified between M1-M1, M1-PM and M1-SMA (Carlowitz-Ghori et al., 2014; Volz et al., 2015; Bajaj, Adhikari, Friston, & Dhamala, 2016; Bajaj, Housley, et al., 2016; Lazaridou et al., 2013; Wu et al., 2015). Lastly, in the reviewed EEG studies, connectivity was analysed mostly in beta and theta bands (Nicolo et al., 2015; Wu et al., 2015).

In this study, I explored functional connectivity correlates of motor adaptation. Although the nature of this chapter is exploratory, it was hypothesized according to the three steps framework that a) there will be movement-related phase locking over primary motor cortex (step 1) b) there will be increase in phase locking in the motor adaptation condition as a result of learning activity (step 2) c) that there will be differences in functional connectivity after stroke (step 3). Specifically, I expected, based on literature review, a reduction in functional connectivity after stroke.

6.2. Method

6.2.1 Participants

Detailed description of participants and recruitment process can be found in General methods chapter. In brief, 29 healthy participants with a broad range of age and nine stroke patients volunteered to participate in the study. Of the healthy participants, 9 were subsampled as age matched controls for the stroke patients. None of the participants had previous history of neurological, neuromuscular or orthopaedic disease (except of the stroke in case of stroke patients). All participants were right hand dominant. Stroke patients had a stroke that initially affected their right hand function but were well

recovered by the time they participated in the study (Fugl-Meyer score >= 55 points). The study was approved by the University of East London Ethics Committee and NHS ethics committee (UREC 1516_25; IRAS 195798) and conducted in accordance with the Declaration of Helsinki.

The PLV features were analysed first to explore the pattern of motor adaptation in healthy young adults and their development over age. The results for healthy participants will be presented in division between younger and older group. Once the healthy pattern of PLV measures was established, I moved on to explore the same variables using the same paradigm in well recovered stroke patients.

6.2.2 Apparatus and procedure

The apparatus and procedure was exactly the same as in previous chapters, the participants task was to perform 288 reaching movements in the northwest direction, of which 96 were performed in a velocity dependent force field. EEG and kinematic data was recorded.

6.2.3 Data analysis

Offline data analyses were carried out with MatLab 2015b (The MathWorks, Inc.), with the support of EEGLab and FieldTrip open-source toolboxes for the analysis of EEG data (Delorme & Makeig, 2004; Oostenveld, Fries, Maris, & Schoffelen, 2011).

6.2.3.1 EEG pre-processing

A pre-processing pipeline for EEG data has been developed with EEGLab toolbox (Delorme & Makeig, 2004) and has been described in more detail in chapter 2. In brief, data were band-pass filtered between 0.5 Hz and 100 Hz, notch filtered at 50 Hz and 25 Hz to remove the power line noise and harmonics, epoched between -1000 to

2000ms around visual cue with baseline between -1000 and 0 ms. After bad channel and epoch removal, the data were subjected to ICA, removed channels interpolated and re-referenced to common average.

For more specific analysis, sub-epochs were extracted from the epochs, timelocking the signal -500 to 800 ms around the movement onset.

6.2.3.2 Functional connectivity and brain network behaviour in motor adaptation

A novel approach was developed to further analyse the EEG findings beyond simple ERP and ERSP approaches detailed in Chapters 4 and 5. Phase locking value (PLV) as a measure of functional connectivity between electrodes and was calculated per each pair of electrodes per each time point in all frequency bins (defined as delta, theta, alpha, beta, gamma) by first filtering the data to the specific band (FIR filter), then taking a Hilbert transform of the signal and assessing the variability of the difference between the instantaneous phase of the pair of the electrodes at each time point, following the procedure outlined in Lachaux et al. (1999). The values were calculated for each condition in late familiarization, early motor adaptation and late motor adaptation, in analogy to the conditions analysed in the time domain and standardised for each timepoint (mean subtracted and divided by the standard deviation of each channel pair at frequency band and condition).

6.2.4.3 Statistical analysis

As in previous chapters, I focused on identifying differences between the groups and for initial analysis I defined the time of interest at 270-330 ms post visual cue and the main electrodes of interest as C3 - over the primary motor cortex contralateral to the moving

hand and frontocentral FCz - over the SMA, consistent with electrode choice in the movement related PLV literature (Rosjat et al., 2018). I first analysed the whole-brain functional connectivity pattern with C3 as a seed region in the time of interest (TOI) in each frequency band, testing PLV averaged for the time window of interest with a t-test corrected with FDR (Benjamini & Hochberg, 1995) in theta, alpha and beta bands. These frequency bands were chosen as the ones identified in literature as important for error processing and motor control (Cohen, 2016; Pfurtscheller, Graimann, Huggins, Levine, & Schuh, 2003; Popovych et al., 2016). Based on the functional connectivity pattern that emerged at the initial TOI that additionally validated focusing on the two specific electrodes of interest, I proceeded to analyse the timecourse of connectivity for each electrode pair of interest (C3-C4, C3-FCz) in theta, alpha and beta band, testing statistical significance of differences between groups with t-tests at each time point adjusted with FDR correction. To further understand the nature of increase of the connectivity around the movement onset, I performed the same timecourse analysis on the data timelocked to the movement onset. As a final zoom I tested the movement onset timelocked data for each pair of interest with a repeated measures ANOVA model: 3 (condition, within: late familiarization, early motor adaptation and late motor adaptation) x 3 (timing, within: baseline, -400 -300ms, premovement -100 0ms, post movement onset 0 100ms) x 2 (group, between). PLV for each timepoint within each timing window was averaged before entering it into the ANOVA model. I also performed simpler post-hoc ANOVAs per each timing level to understand the moderation of the timing window on the changes in PLV dependent on the condition. I finally analysed simple main effects as t values, corrected with Bonferroni correction. I

report here all significant effects of the ANOVA models, with values reported with Greenhouse-Geiser correction when the assumption of sphericity was not met. Occasionally I cite specific statistics for insignificant factors, where it informed the conclusions (e.g. no significant main effect of group or no effect of condition in one time window as opposed to a different one).

6.3. Results

6.3.1 Healthy young versus older groups

I first looked at the differences in the connectivity of C3 as a seed electrode over the primary motor cortex contralateral to the movement with all other electrodes in the TOI around the movement onset, as identified in previous chapters. In both younger and older group there was a robust pattern of increased connectivity between C3 and especially with the frontocentral, contralateral motor and posterior regions that was not different between the age groups in theta, alpha and beta bands (figure 6.1, figure 6.2, figure 6.3).

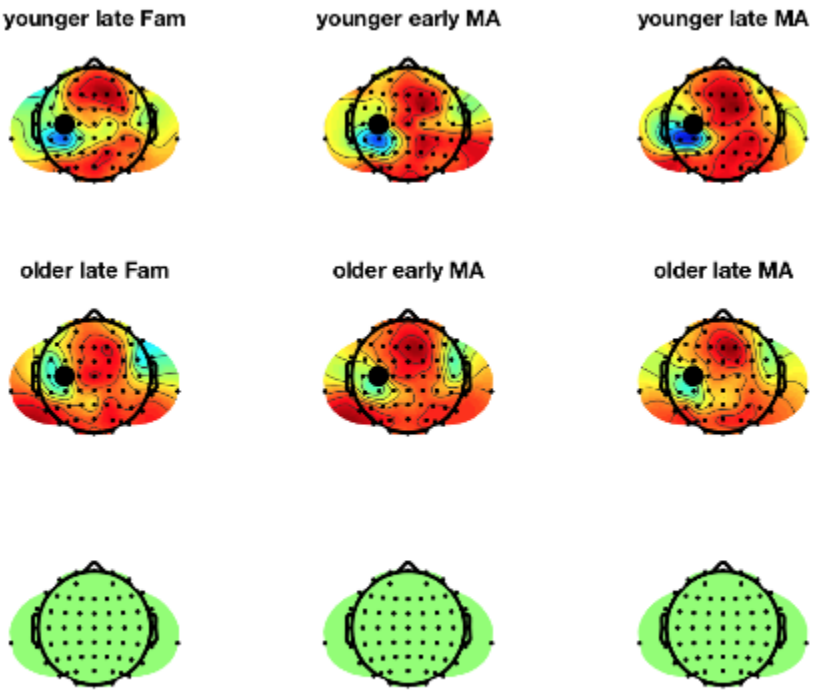


Figure 6.1. Topographical map of theta PLV between C3 electrode and all other electrodes, averaged for the time of interest 270-330 post visual cue.

P values in the lowest row represent the result of t-test at each electrode between the younger and older group, adjusted with fdr correction masked for significance (green represents no significance, any colour - p-values below the significance threshold after multiple comparisons correction).

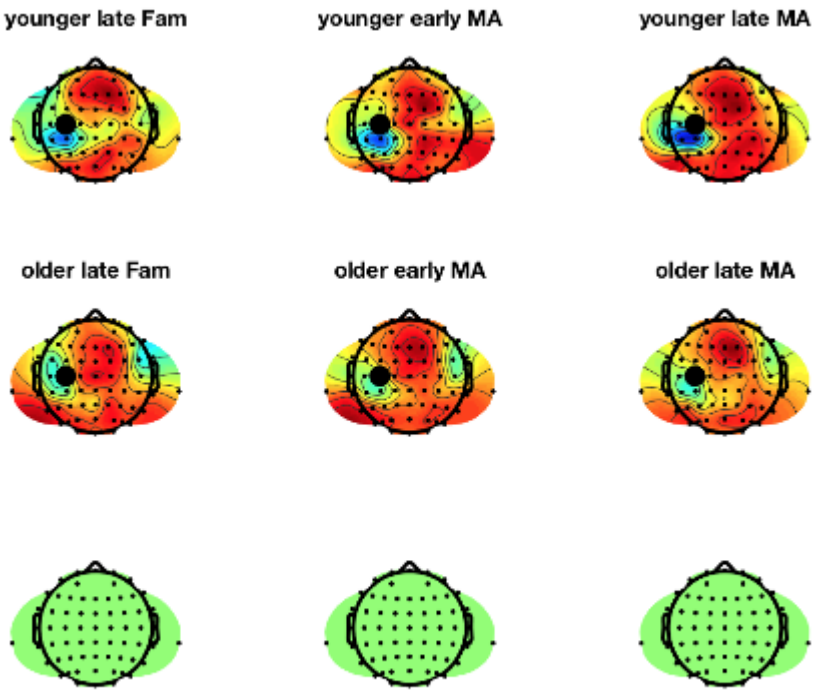


Figure 6.2. Topographical map of alpha PLV between C3 electrode and all other electrodes, averaged for the time of interest 270-330 post visual cue.

P values in the lowest row represent the result of t-test at each electrode between the younger and older group, adjusted with fdr correction masked for significance (green represents no significance, any colour - p-values below the significance threshold after multiple comparisons correction).

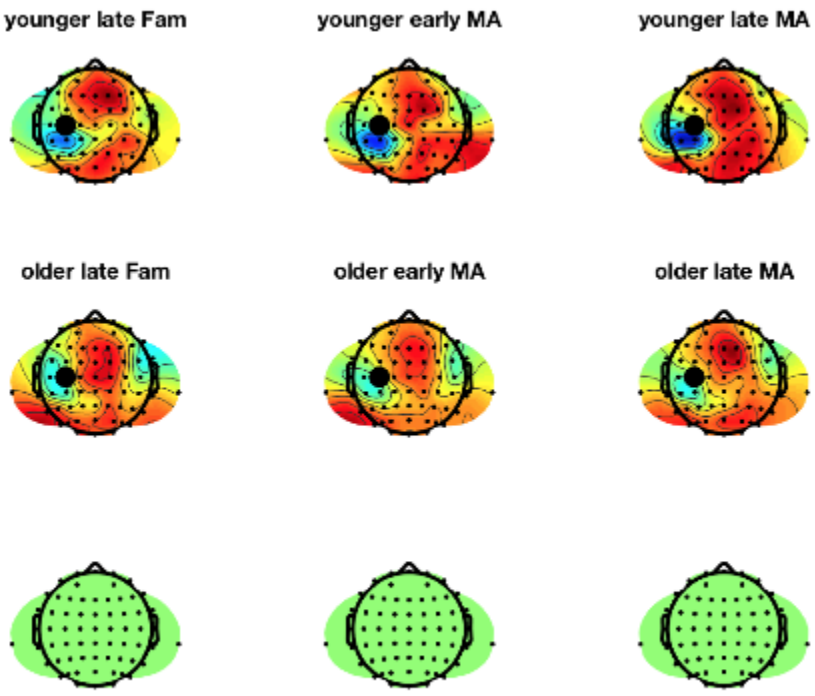


Figure 6.3. Topographical map of beta PLV between C3 electrode and all other electrodes, averaged for the time of interest 270-330 post visual cue.

P values in the lowest row represent the result of t-test at each electrode between the younger and older group, adjusted with fdr correction masked for significance (green represents no significance, any colour - p-values below the significance threshold after multiple comparisons correction).

When looking at pairs of electrodes of interest, C3-C4 and C3-FCz, there was a visible increase in connectivity around the movement onset in all three bands, with no statistical differences between groups (figure 6.4, figure 6.5). To analyse the nature of that increase and the specific relationship with the timing of movement, I extracted shorter epochs timelocked around the movement onset for each participant and tested the data in a timing (baseline, premovement, post movement onset) x condition x group ANOVA model. Since all three frequency bands followed a similar pattern of connectivity change, I focused on alpha band for more detailed analysis.

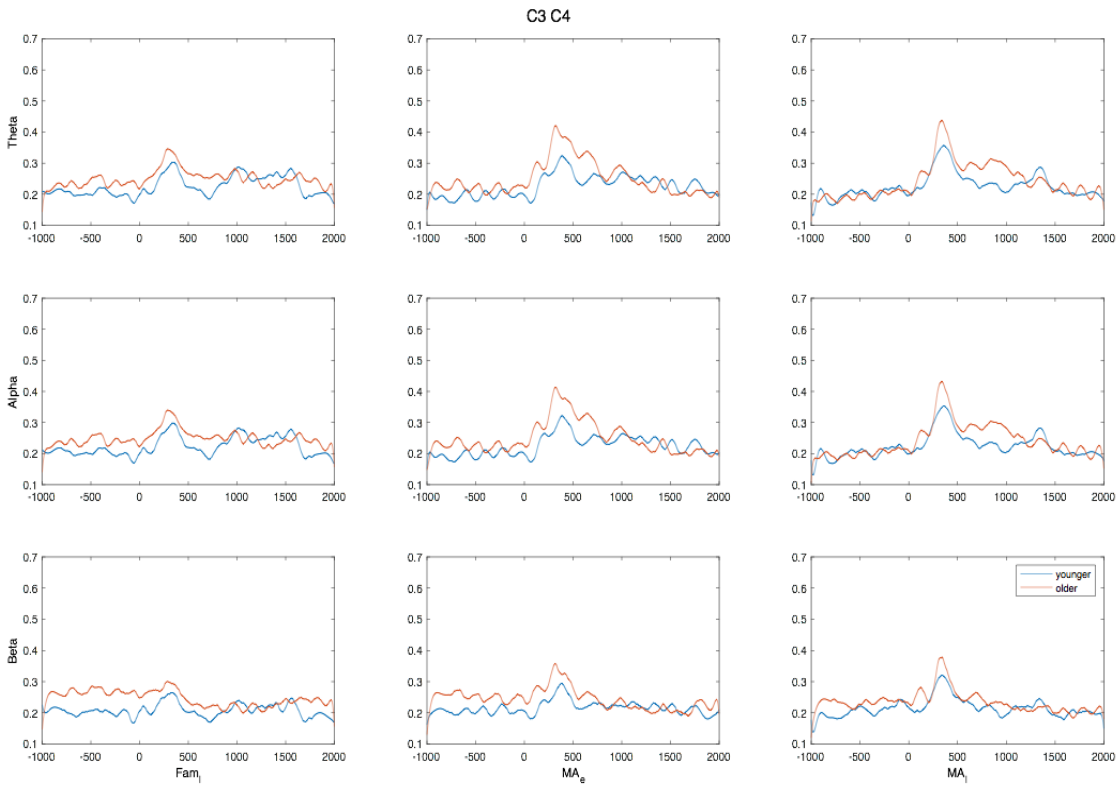


Figure 6.4. C3 - C4 PLV in theta, alpha and beta frequency bands in all conditions. 0= visual cue. There were no significant differences between the groups tested at every timepoint with a t-test, FDR corrected.

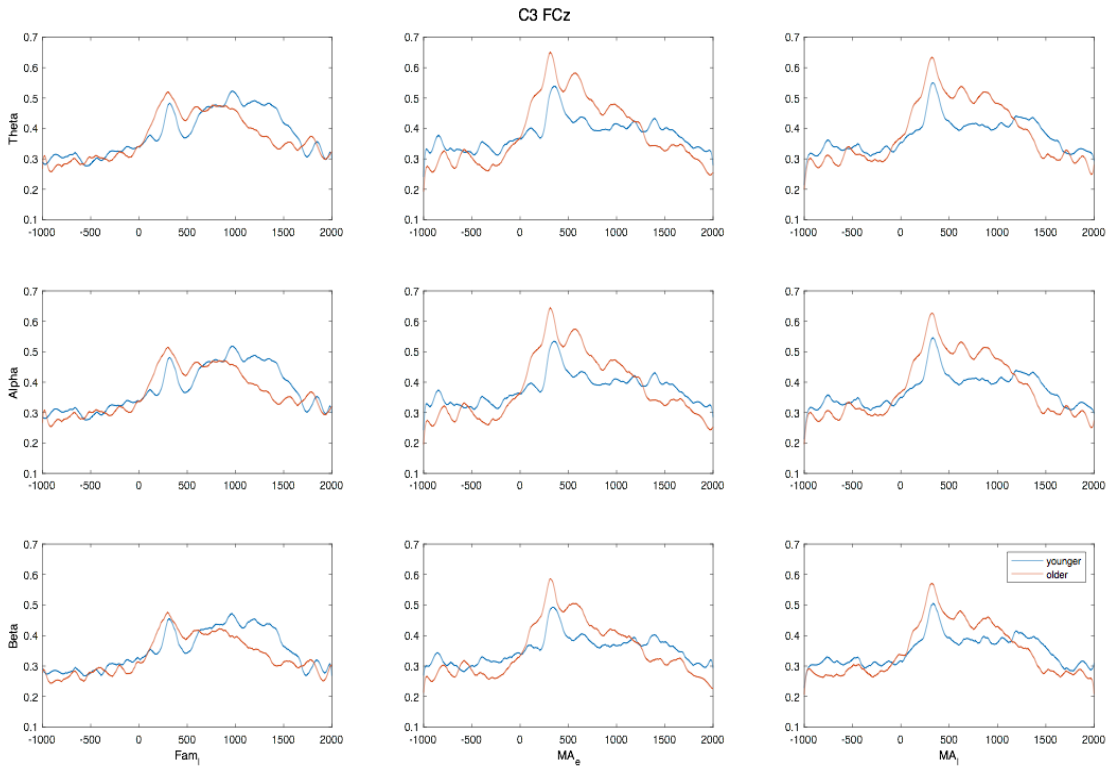


Figure 6.5. C3 - FCz PLV in theta, alpha and beta frequency bands in all conditions. 0 = visual cue. There were no significant differences between the groups tested at every timepoint with a t-test, FDR corrected.

For the C3 - C4 connectivity in the alpha band, the effect of group was not significant ($F(1,27) = 1.105$, $p = 0.303$, $\eta^2 = 0.039$), there was a significant main effect of timing ($F(1.654,44.664) = 10.710$, $p < 0.001$, $\eta^2 = 0.284$) and an interaction effect between condition and timing ($F(4,108) = 3.772$, $p = 0.007$, $\eta^2 = 0.123$) - all timing groups were different from each other. I further tested how the effect of condition on the C3 - C4 connectivity was moderated by TOI chosen and found that there was no main effect of condition in the baseline time window (400-300 ms before the movement onset, $F(2,54) = 0.618$, $p = 0.543$, $\eta^2 = 0.022$) or directly before the movement onset ($F(2,54) = 0.880$, $p = 0.421$, $\eta^2 = 0.032$), but there was a significant main effect of condition right after the movement onset, $F(2,54) = 3.633$, $p = 0.033$, $\eta^2 = 0.119$. In summary, there was a difference in connectivity between electrodes over the bilateral primary motor cortex evoked by the movement onset (figure 6.6).

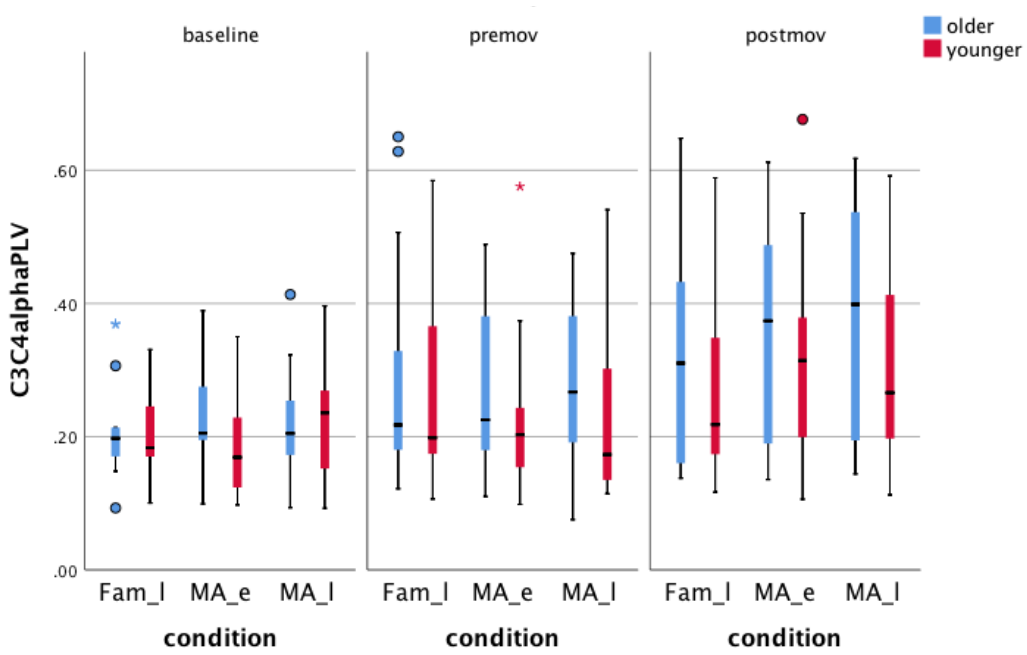


Figure 6.6. PLV in alpha band between C3 and C4 electrodes.

PLV averaged for three 100 ms time windows analysed in timing x condition x group ANOVA model. Baseline = -400 -300ms before movement onset, premov = -100 0ms before movement onset, postmov - 0-100ms post movement onset. Circles and start represent outliers.

In the other pair of electrodes of interest, C3-FCz, a similar model yielded a main effect of both timing ($F(1.429,38.596) = 27.432$, $p < 0.001$, $\eta^2 = 0.504$) and condition ($F(2,54) = 5.807$, $p = 0.005$, $\eta^2 = 0.177$), no main effect of group ($F(1,27) = 0.646$, $p = 0.429$, $\eta^2 = 0.023$) and an interaction effect between condition and timing ($F(4,108) = 5.727$, $p < 0.001$, $\eta^2 = 0.175$), that further explored again demonstrated differences between the conditions in the post-movement onset time window only ($F(2,54) = 12.833$, $p < 0.001$, $\eta^2 = 0.322$).

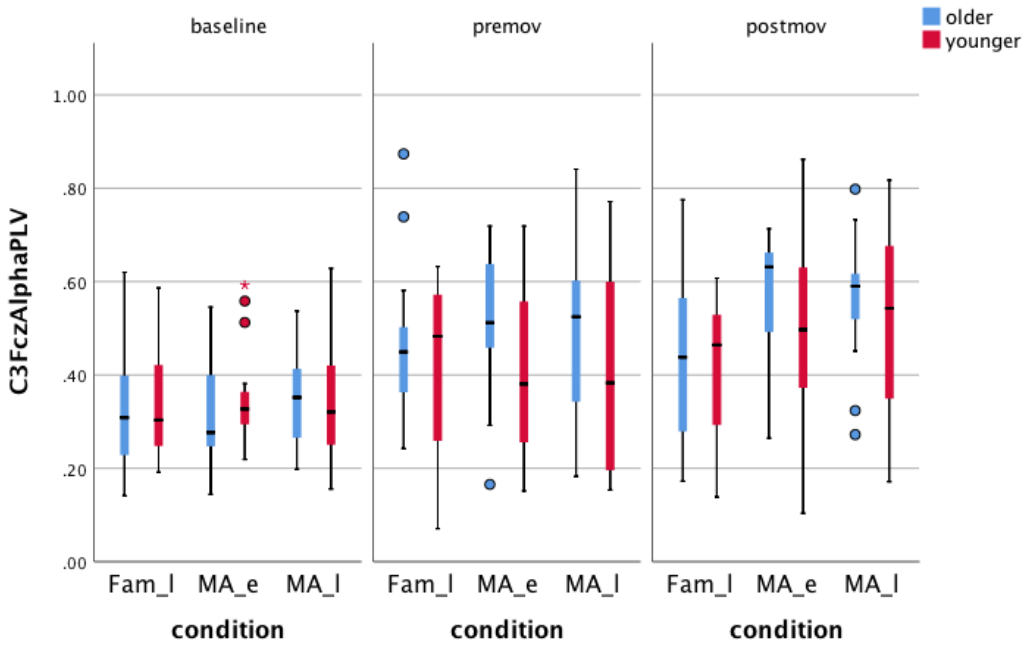


Figure 6.7. PLV in alpha band between C3 and FCz electrodes.

PLV averaged for three 100 ms time windows analysed in timing x condition x group ANOVA model. Baseline = -400 -300ms before movement onset, premov = -100 0ms before movement onset, postmov - 0-100ms post movement onset. Circles and start represent outliers.

6.3.2 Stroke group versus controls

I first looked at the differences in the connectivity of C3 as a seed electrode over the primary motor cortex contralateral to the movement with all other electrodes in the TOI around the movement onset. In the control (healthy older) group there was a robust pattern of increased connectivity as previously seen in the healthy younger and older participants with the frontocentral, contralateral motor and posterior regions showing increased connectivity with C3. There were no differences between the groups in the familiarization condition, but in the motor adaptation there was a different pattern of connectivity in the stroke group, with the posterior parietal, contralateral motor and frontocentral electrodes showing lower connectivity in the stroke group. Again, the pattern was similar for all three frequency bands except for beta band where the was no change in posterior parietal electrodes in stroke group in the early MA condition (figure 6.8, figure 6.9, figure 6.10).

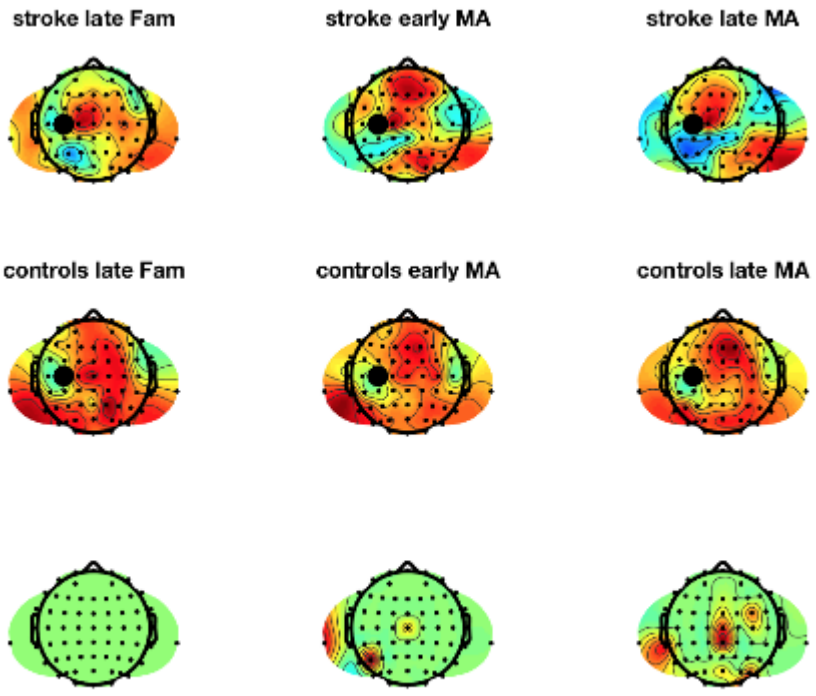


Figure 6.8. Topographical map of theta PLV between C3 electrode and all other electrodes, averaged for the time of interest 270-330 post visual cue.

P values in the lowest row represent the result of t-test at each electrode between the control and stroke group, adjusted with fdr correction masked for significance (green represents no significance, any colour - p-values below the significance threshold after multiple comparisons correction).

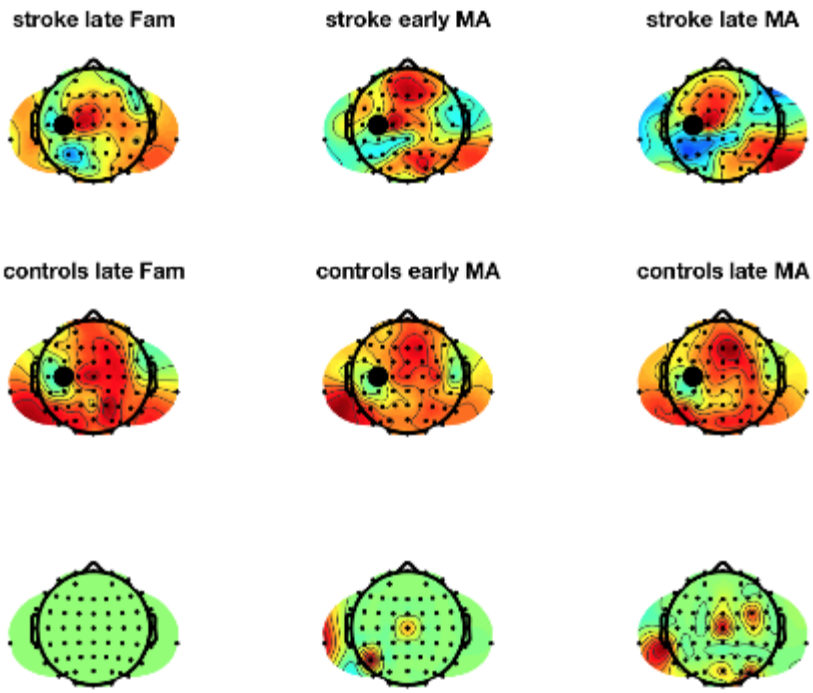


Figure 6.9. Topographical map of alpha PLV between C3 electrode and all other electrodes, averaged for the time of interest 270-330 post visual cue.

P values in the lowest row represent the result of t-test at each electrode between the control and stroke group, adjusted with fdr correction masked for significance (green represents no significance, any colour - p-values below the significance threshold after multiple comparisons correction).

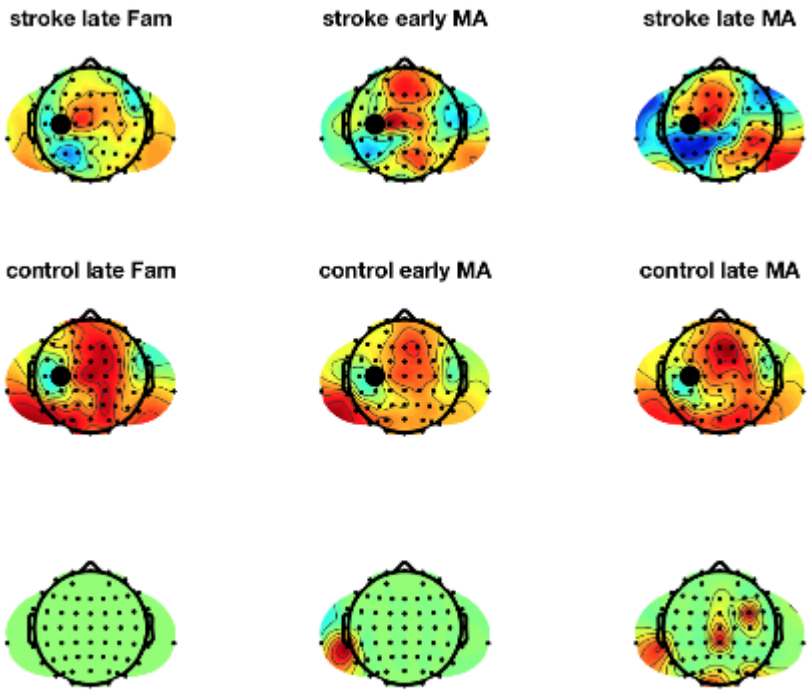


Figure 6.10. Topographical map of beta PLV between C3 electrode and all other electrodes, averaged for the time of interest 270-330 post visual cue.

P values in the lowest row represent the result of t-test at each electrode between the control and stroke group, adjusted with fdr correction masked for significance (green represents no significance, any colour - p-values below the significance threshold after multiple comparisons correction).

When looking at pairs of electrodes of interest, C3-C4 and C3-FCz, the increase in connectivity around the movement onset did not seem to be as visible in the stroke group as opposed to the control group in all three bands, however testing for statistical significance at all timepoints did not yield any differences between the groups after multiple comparisons correction (figure 6.11, figure 6.12). For the stroke participants, I also included an analysis of the differences in the C3-P3 electrode pair, but it did not follow the peak pattern seen in the other pairs of interest and also showed no significant differences between the groups (figure 6.13). To analyse the specific relationship with the timing of movement, I extracted shorter epochs timelocked around the movement onset for each participant and tested the data in a timing (baseline, premovement, post movement onset) x condition x group ANOVA model. Since all three frequency bands followed a similar pattern of connectivity change, the alpha band is illustrated for a more detailed analysis.

Figure 6.11. C3 - FCz PLV in theta, alpha and beta frequency bands in all conditions. 0 = visual cue.

There were no significant differences between the groups tested at every timepoint with a t-test, FDR corrected.

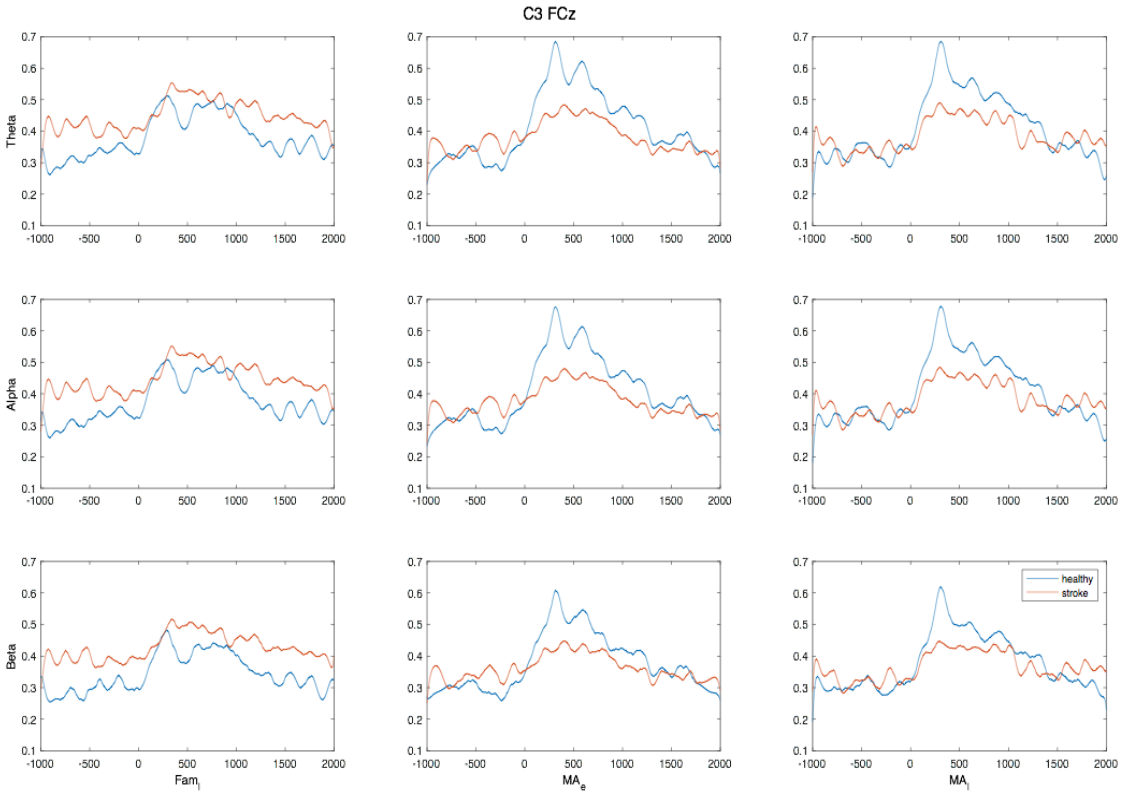


Figure 6.12. C3 - FCz PLV in theta, alpha and beta frequency bands in all conditions. 0 = visual cue. There were no significant differences between the groups tested at every timepoint with a t-test, FDR corrected.

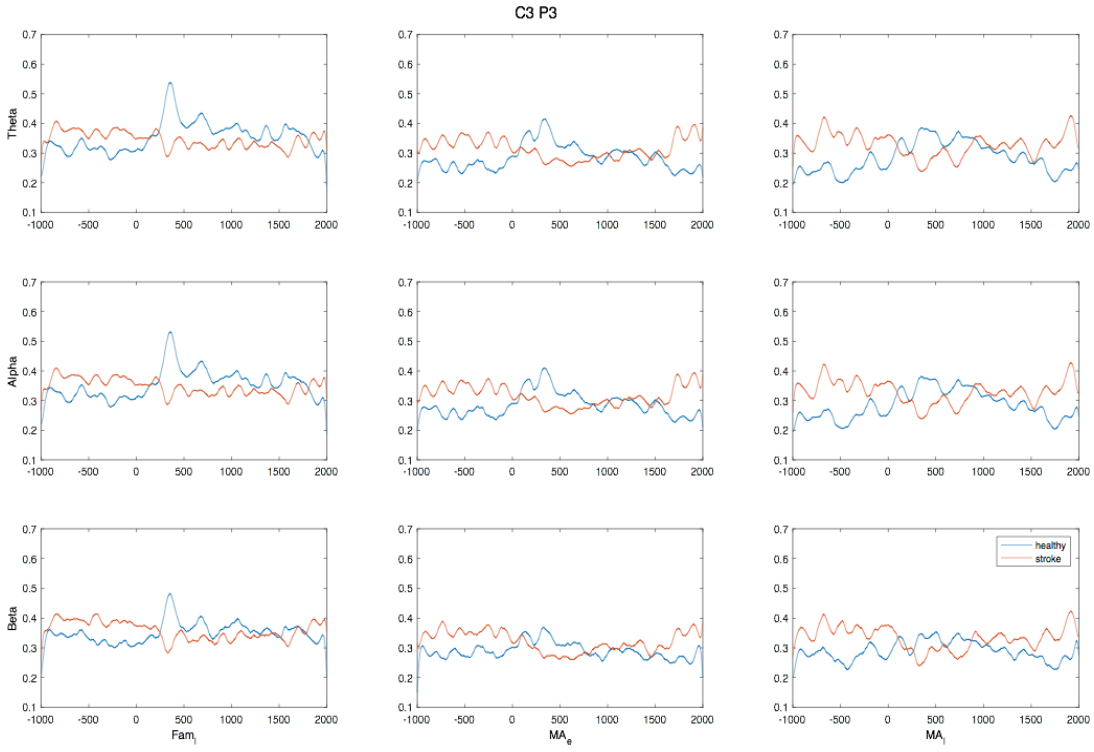


Figure 6.13. C3 - P3 PLV in theta, alpha and beta frequency bands in all conditions. 0 = visual cue. There were no significant differences between the groups tested at every timepoint with a t-test, FDR corrected.

In the alpha band, ANOVA analysing PLV between C3 and FCz electrode revealed a main effect of timing ($F(2,32) = 23.475$, $p < 0.001$, $\eta^2 = 0.595$) and a significant interaction between condition, group and timing ($F(4,64) = 3.806$, $p = 0.008$, $\eta^2 = 0.192$). Analysis of simple main effects showed that connectivity during the baseline (300-200 ms before movement onset) was significantly lower than in the 100 ms directly preceeding and following movement onset. When C3-FCz connectivity in alpha band was analysed separately for the groups, there was a significant interaction between the timing and condition in the control group ($F(4,32) = 3.087$, $p =0.029$, $\eta^2 = 0.278$), illustrating the increase in connectivity around the movement onset, but not in the stroke group ($F(4,32) = 1.353$, $p =0.272$, $\eta^2= 0.145$), which - in the context of significant main effects of timing in both groups (controls: $F(2,16) = 18.067$, $p <0.001$, $\eta^2 = 0.693$ stroke: $F(2,16) = 6.500$, $p =0.009$, $\eta^2 = 0.448$) and no significant main effect of condition (controls: $F(2,16) = 2.787$, $p = 0.092$, $\eta^2 = 0.258$, stroke: $F(1.216,9.726) = 1.389$, $p =0.278$, $\eta^2 = 0.148$) - suggests the connectivity in different time windows did not differ between conditions in stroke, but the difference between conditions was evident in the different time windows in the healthy controls group (figure 6.14).

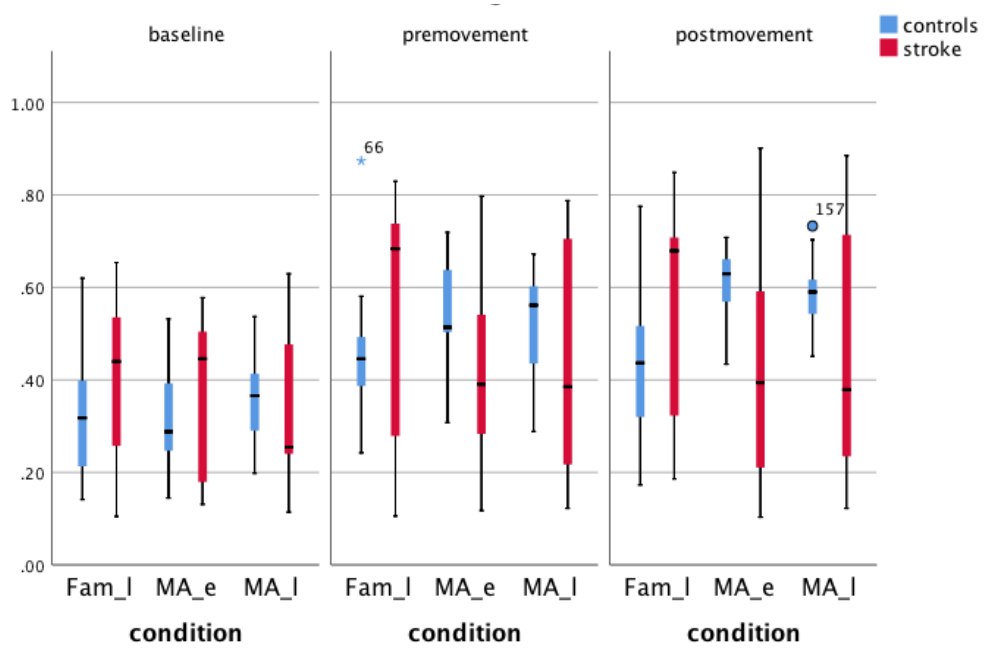


Figure 6.14. PLV in alpha band between C3 and FCz electrodes, averaged for three 100 ms time windows analysed in timing x condition x group ANOVA model.

Baseline = -400 -300ms before movement onset, premovement = -100 0ms before movement onset, postmovement = 0-100ms post movement onset. Circles and start represent outliers.

A similar connectivity pattern between groups over time emerged in PLV between C3 and C4 electrode in the alpha band. The same model (group by condition by timing) ANOVA yielded a main effect of timing ($F(1.449,23.190) = 12.094$, $p < 0.001$, $\eta^2 = 0.430$) and an interaction effect of timing by stroke ($F(1.449,23.190) = 4.215$, $p = 0.038$, $\eta^2 = 0.208$) and when timing by condition model was analysed for each group separately, it yielded a main effect of timing for the stroke group ($F(2,16) = 12.229$, $p = 0.001$, $\eta^2 = 0.605$) but not for the control group, ($F(1.204,9,635) = 1.360$, $p = 0.285$, $\eta^2 = 0.145$) (figure 6.15).

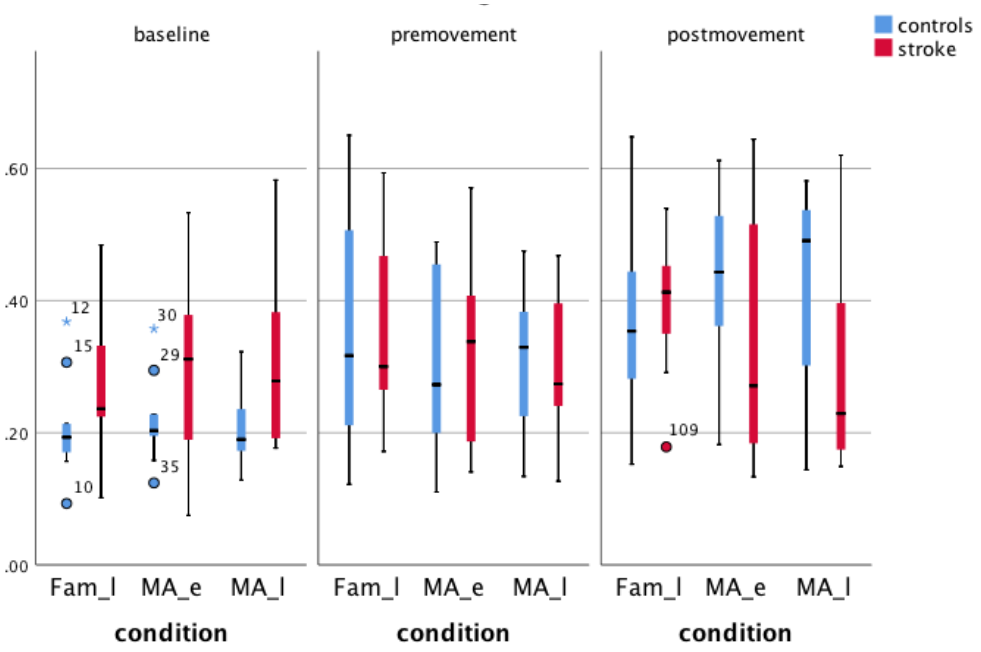


Figure 6.15. PLV in alpha band between C3 and C4 electrodes, averaged for three 100 ms time windows analysed in timing x condition x group ANOVA model.

Baseline = -400 -300ms before movement onset, premovement = -100 0ms before movement onset, postmovement = 0-100ms post movement onset. Circles and start represent outliers.

6.4. Discussion

In the healthy participants in the electrode pairs of interest (C3-C4 and C3-FCz) I found a characteristic increase in functional connectivity only in motor adaptation conditions after the movement onset that was not present in the familiarization condition, which can be interpreted as a functional connectivity signature of motor adaptation. This effect was robust over age and yielded no statistically significant differences between the age groups in any analysis I performed.

Group differences however emerged in the analyses between the stroke and healthy older control group. In the initial time window of interest encompassing the time around the movement onset, significant differences can be seen between the groups mainly between C3 and the electrodes over the motor cortex and between C3 and frontocentral electrodes, but only in the motor adaptation condition, with no group differences in familiarization. The significant electrode pairs were the one identified in previous chapters and literature as important connections for motor planning, execution and error processing (Cohen, 2016; Naranjo et al., 2007; Nicolo et al., 2015; Wu et al., 2015, 2014) and these findings support the use of the PLV and and the analysis model. Moreover, the areas over which the significant electrodes were found, were often identified as crucial regions in functional connectivity studies in stroke recovery, showing dynamic connectivity changes over time and meaningful connections interpreted as restorative mechanisms (Desowska and Turner 2019; Bajaj, Housley, et al., 2016; Lazaridou et al., 2013; Nicolo et al., 2015; Rosso et al., 2013; Volz et al., 2015; Westlake et al., 2012; Wu et al., 2015) . The follow-up analysis of the timecourse

of the electrode pairs in stroke patients of interest depicted a lack of the characteristic increase in functional connectivity during motor adaptation that was seen in healthy participants.. The effect of motor adaptation on connectivity measure was moderated by timing in control, but not in the stroke group. This observation of stroke patients relying less on the network functionality characteristic for the healthy motor adaptation is in line with the concept of network randomization after stroke (Wang et al., 2010). This concept posits that with time and recovery of function, the brain network supporting the function does not go back to the initial state, but learns to rely on weaker, more spurious connections. This notion was further supported in fMRI studies using network topology measures and spatial component analysis (Cheng et al., 2015; Lee, Lee, Kim, & Kim, 2015; Wadden et al., 2015; Wang et al., 2010).

The results, to our knowledge, show for the first time the characteristic functional connectivity pattern accompanying motor adaptation, and moreover, show lack thereof in the stroke group. These results are especially interesting in the context of the kinematic data analysis, that did not show statistically significant differences between the stroke and control group motor performance. The stroke patients in this study were well recovered, able to perform the motor adaptation task at the same level as healthy age matched controls, but still showed a distinct connectivity pattern, a difference that was seen when analysing phase locking (a parameter of functional connectivity), but not in the amplitude/power results in the time-frequency domain (see chapter 5).

7. Relationship between EEG and behavioural measures

7.1 Introduction

This chapter aims at summarising different measures described separately in the previous experimental chapters in order to attempt at building a landscape of different methods of assessing motor adaptation in healthy and disease. In clinical neuroscience, a multimodal approach allows building better predictor models for rehabilitation and summarising correlates of recovery has recently gained a significant interest with systematic reviews focusing on collating different measures together in hope to find guidelines for predicting and treating motor deficits after stroke (Boyd et al., 2017; Desowska & Turner, 2019; Tedesco Triccas et al., 2019; Ward, 2015). The requirement for predicting those patients who may recover and/or respond to treatment is becoming more urgent as many recent very large trials have not been successful (Rodgers et al., 2019). By nature, and because the previous chapters provided already theoretical bases, this chapter focuses mainly on empirical findings.

The purpose of this chapter was to find relationship between kinematic and EEG variables associated with motor adaptation, since it is not necessarily one measure, but a complex relationship between many measures that can explain a behaviour (eg. seminal work by Baron & Kenny (1986)).

7.2. Method

The procedures to obtaining the data used in this chapter were completely described in the previous chapters.

7.2.1 Participants

In brief, 29 healthy participants with a broad range of age and nine stroke patients volunteered to participate in the study. Of the healthy participants, 9 were subsampled as age matched controls for the stroke patients. None of the participants had previous history of neurological, neuromuscular or orthopaedic disease (except of the stroke in case of stroke patients). All participants were right hand dominant. Stroke patients had a stroke that initially affected their right hand function but were well recovered by the time they participated in the study (Fugl-Meyer score >= 55 points). The study was approved by the University of East London Ethics Committee and NHS ethics committee (UREC 1516_25; IRAS 195798) and conducted in accordance with the Declaration of Helsinki.

7.2.2 Apparatus

Brain activity was recorded through a 64-channel Waveguard cap and amplified by a TMSi Ref-Ext amplifier (ANT Neuro, Enschede, Netherlands), digitized at 1024 Hz and band-pass filtered from 0.1 to 500 Hz. During the recording, data were referenced to the Fz electrode and impedances were kept below 5 kΩ.

The kinematic data were recorded by the encoders embedded within the joystick of the MIT-Manus2 (InMotion Technologies, Cambridge, MA, USA) robotic manipulandum.

Additional motor tests were employed: grip force, where the participants' task is to squeeze the dynamometer as hard as they can for three seconds following one practice trial. The test was administered to both dominant and non-dominant hand (procedure adapted from the NIH Toolbox strength measure (Reuben et al., 2013) for assessing

neurological patients) and the measure of grip asymmetry between the strength of two hands was further analysed. Pinch force is an assessment of the finest motor skills is similar to the grip strength measure procedure but using a pinchmeter (Biometrics Co Ltd UK).

A selection of psychometric tools were used as screeners of the functions crucial for successful study completion and included the Fugl-Meyer Assessment – Upper extremity (Fugl-Meyer, Jääskö, Leyman, Olsson, & Steglind, 1975) which is an experimenter-lead scale of motor function impairment designed for post-stroke hemiplegic patients. The participant's task is to perform specific movements of the upper and lower arm and hand. In this thesis I only used the upper extremity assessment. The Brief Fatigue Inventory (BFI, (Mendoza et al., 1999) is a simple self-assessment paper-pen tool to assess the severity of fatigue in the last 24 hours and the impact that it has on the daily functioning in 6 items. The Oxford Cognitive Screen (OCS, (Demeyere, Riddoch, Slavkova, Bickerton, & Humphreys, 2015) and is a rapid cognitive screen that was designed specifically for the stroke population. It reports scores in different cognitive domains, screening also for aphasia and visual neglect. The Montreal Cognitive Assessment (MoCa, (Nasreddine et al., 2005) which is a cognitive screen used also in healthy population.

7.2.3 Procedure

After signing the consent form, the participant's grip and pinch force was measured alongside a medical questionnaire, and fatigue inventory. The battery of screening psychometric tests was usually performed in a separate session. In the case of stroke participants that session happened at their home.

The experimental protocol was based on 3 conditions, each composed of 96 reaching trials. The familiarization condition was performed in a null force-field to familiarize the participant with the reaching task and served as a baseline for comparisons. During the motor adaptation condition, the robot applied a velocity-dependent force-field in the clockwise direction of 25 N/m/s absolute intensity, perpendicular to the trajectory of the end-effector joystick.

7.2.4 Data analysis

Offline data analyses were carried out with MatLab 2015b (The MathWorks, Inc.), with the support of EEGLab and FieldTrip open-source toolboxes for the analysis of EEG data (Delorme & Makeig, 2004; Oostenveld, Fries, Maris, & Schoffelen, 2011).

7.2.4.1 EEG pre-processing

A pre-processing pipeline for EEG data has been developed with EEGLab toolbox (Delorme & Makeig, 2004) and has been described in more detail in chapter 2. In brief, data were band-pass filtered between 0.5 Hz and 100 Hz, notch filtered at 50 Hz and 25 Hz to remove the power line noise and harmonics, epoched between -1000 to 2000ms around visual cue with baseline between -1000 and 0 ms. After bad channel and epoch removal, the data were subjected to ICA, removed channels interpolated and re-referenced to common average. ERP, ERSP and PLV measures were calculated as described in detail in chapter 2 and subsequent chapters dedicated to each measure.

7.2.4.2 Reaching kinematics

Kinematic data from the robot were interpolated to match the sampling rate of 1 kHz. The kinematic measures included movement onset, offset, maximum velocity, perpendicular distance of the effector to the line joining the start and end point of

movement at the time of maximum velocity, summed error, and performance index , calculated as described in chapter 2.

Dynamometer and pinchmeter recordings were summarised into a grip and pinch asymmetry values, as a ratio between the right peak force and left peak force for both types of measurement.

7.2.4.3 Statistical analysis

A multiple linear regression approach was used to model the relationship between the variables. To initially reduce the number of entered predictors, the values were averaged from both motor adaptation conditions together. To obtain a uniform level of values, the values were standardised to the z-score (subtracted mean from each value and divided by standard deviation). Stepwise multiple linear regression models (with forward and backward algorithms; inclusion/exclusion probability levels: $\alpha Enter<0.05/\alpha Exclude>0.1$) were used to select predictors from the following list: age, ERP in central ROI in the perimovement time of interest (270-330ms; see chapter 4) in motor adaptation, beta time-frequency in the same ROI and time of interest in motor adaptation (see chapter 5), alpha connectivity between C3 and FCz in baseline time of interest (-400 -300ms before movement onset; see chapter 6) in MA, alpha connectivity between C3 and C4 in the same time of interest and condition (see chapter 6), pinch asymmetry and stroke, with summed error averaged for motor adaptation conditions and performance index (see chapter 2 and 3 for defintion) as dependent variables in separate models.

More detailed correlations post hoc were also performed. Since some of the variables were not normally distributed as tested with a Shapiro-Wilk test, nonparametric Spearman's rho correlations were performed. Multiple comparisons were corrected with FDR adjustment.

7.3. Results

7.3.1 Regression model

In order to gain insight into the relationship between the motor performance and neurophysiological measures, a stepwise multiple linear regression approach was first employed to explain values of summed error measure averaged for both motor adaptation conditions. This approach yielded a model with two predictors, ($F(2,35) = 19.220$, $p<0.001$). The first predictor was alpha connectivity between C3 and C4 at baseline before stimulus presentation in motor adaptation conditions, expressed as z-scored PLV averaged for both MA_e and MA_l, ($\beta = 0.502$, $p < 0.001$). The second was pinch asymmetry ($\beta = -0.360$, $p = 0.008$). The two predictors together explained 49,6% of summed error variance. The positive coefficient value suggests that the more connectivity at baseline was present between the electrodes over bilateral motor cortices, the further was the movement from the perfect straight trajectory to target - the bigger the total error in motor adaptation. The negative coefficient of pinch asymmetry suggests that the stronger the right hand relative to left hand was, the less error in movement performed by that hand. No ERP or ERSP measure nor age or presence of stroke were predictors of summed error . Interestingly, the connectivity between C3 and FCz at the same alpha frequency in baseline time window also did not prove a

significant predictor of the error measure in the regression analysis. To understand the model further and to analyse the complex pattern of relationships between the measures, more detailed post hoc correlations were performed.

7.3.2. Relationship between motor performance and connectivity measures

The most significant predictor of summed error at motor adaptation was the connectivity measure. The connectivity in alpha band between C3 and FCz electrode did not correlate with motor measures, except of an association between connectivity at baseline time (-400 -100ms before movement onset) at MA_l with movement Offset at MA_e (rho(38) = -0.421, p = 0.009). However when the same measures were tested against interhemispheric connectivity between electrodes over left and right primary motor cortices, summed error in both motor adaptation conditions strongly correlated (i.e. survived FDR corrections) with C3-C4 PLV in MA_e, but only in the baseline period, 400-300ms before movement onset, just before/at visual cue (table 7.1). These associations seem to be driven by the stroke group (figure 7.1), however stroke did not prove a significant grouping predictor for summed error.

		C3C4 PLV								
		baseline			premovement			postmovement		
Offset		Fam_l	MA_e	MA_l	Fam_l	MA_e	MA_l	Fam_l	MA_e	MA_l
Fam_l	rho	-0.061	-0.141	-0.156	-0.139	-0.017	0.12	-0.101	-0.128	-0.084
	p	0.718	0.399	0.35	0.406	0.917	0.473	0.546	0.444	0.616
MA_e	rho	0.246	-0.068	0.06	-0.045	-0.127	0.104	-0.054	-0.062	-0.14
	p	0.137	0.685	0.722	0.79	0.446	0.536	0.747	0.711	0.402
MA_l	rho	0.375*	0.014	-0.084	0.191	-0.013	0.098	0.068	0.017	-0.086
	p	0.02	0.933	0.617	0.25	0.936	0.559	0.685	0.917	0.608
Summed Error										
Fam_l	rho	-0.072	0.149	0.129	-0.024	0.043	-0.105	-0.008	0.005	-0.122
	p	0.666	0.372	0.44	0.889	0.799	0.532	0.962	0.978	0.464

MA_e	rho	0.093	0.394*	0.29	0.24	0.179	0.195	0.101	0.114	0.128
	p	0.58	0.014	0.077	0.147	0.283	0.242	0.548	0.494	0.443
MA_l	rho	0.143	0.435*	0.307	0.254	0.18	0.227	0.127	0.093	0.108
	p	0.393	0.006	0.061	0.124	0.278	0.171	0.449	0.579	0.518
PI										
	rho	-0.217	-0.34	-0.22	-0.097	-0.266	-0.254	0.182	-0.125	0.053
	p	0.192	0.037	0.183	0.56	0.107	0.125	0.274	0.454	0.753
Pinch asymmetry										
	rho	0.1	0.187	0.349	0.095	0.088	0.15	0.204	-0.001	0.043
	p	0.552	0.261	0.032	0.572	0.6	0.367	0.22	0.996	0.797

Table 7.1. Correlations between PLV and behavioural motor measures.

All correlations reported with Spearman's rho, N = 38. *Correlation is significant after applying FDR correction for multiple comparisons.

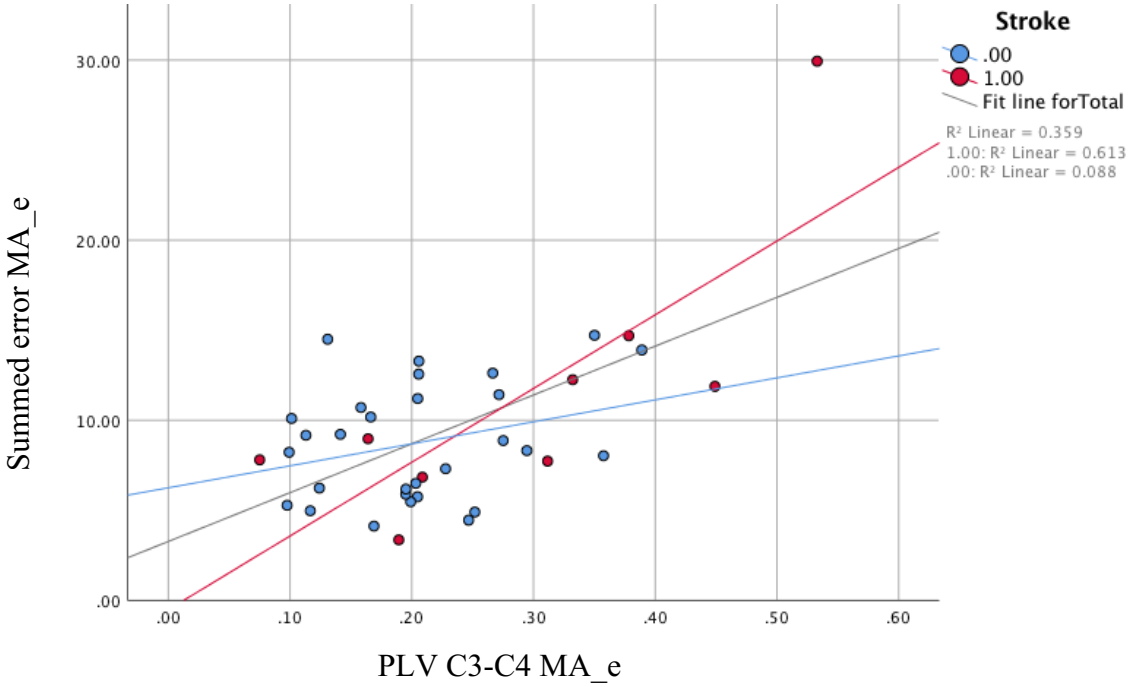


Figure 7.1. Relationship of interhemispheric connectivity between C3 and C4 with summed error in different groups.

There is a significant negative correlation between PLV at baseline and summed error in early motor adaptation, but it is driven by the stroke group.

7.3.3. Motor performance measures

Since pinch strength asymmetry proved a significant predictor of summed error, I looked further into its relationship with kinematic measures. It correlated with maximum velocity and error at maximum velocity in late motor adaptation only, and with movement offset in motor adaptation conditions, but not movement onset (table 7.2). It also correlated with summed error, also only in motor adaptation conditions (figure 7.2). Interestingly, it did not correlate with any of the measures in the familiarization condition. After applying FDR correction for multiple comparisons accounting for all three conditions, only the association between pinch asymmetry and summed error in both motor adaptation conditions stayed significant.

	Fam_l	MA_e	MA_l
Pinch asymmetry	Maximum velocity		
rho	-0.287	-0.119	-0.338
p	0.081	0.477	0.038
	Error at maximum velocity		
rho	0.128	-0.308	-0.351
p	0.444	0.06	0.031
	Summed Error		
rho	-0.113	-.421*	-.382*
p	0.498	0.008	0.018
	Movement Onset		
rho	-0.217	-0.208	-0.2
p	0.191	0.211	0.229
	Movement Offset		
rho	0.197	-0.385	-0.33
p	0.236	0.017	0.043
	Grip asymmetry		
rho	.493*		
p	0.002		

Table 7.2. Significant correlations between pinch strength and behavioural motor measures.

All correlations reported with Spearman's rho, N = 38. *Correlation is significant after applying FDR correction for multiple comparisons.

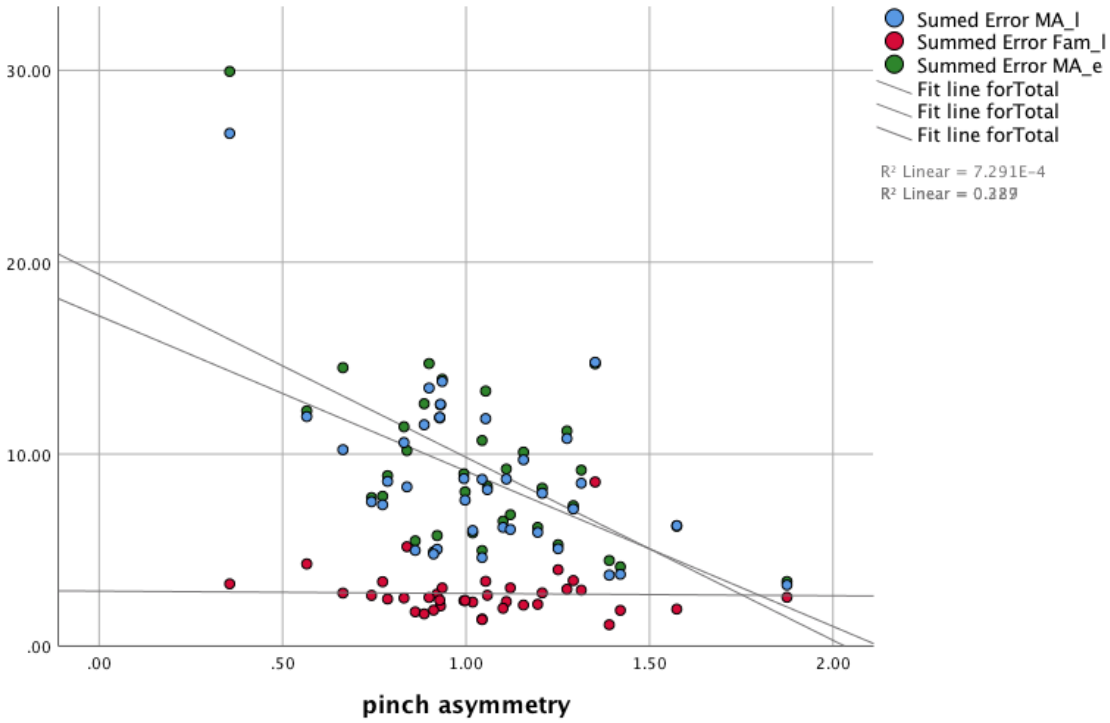


Figure 7.2. Relationship of pinch asymmetry with summed error in different conditions. There is a significant negative correlation between pinch asymmetry and summer error in both motor adaptation conditions, but not in the familiarization condition.

Grip strength asymmetry did not prove as strongly correlated with kinematic measures, with significant correlations only with maximum velocity and error at maximum velocity in late motor adaptation (table 7.3), that did not hold after applying FDR correction.

	Fam_l	MA_e	MA_l
Grip asymmetry	Maximum velocity		
rho	-0.283	-0.294	-0.346
p	0.085	0.073	0.033
	Error at maximum velocity		
rho	0.08	-0.103	-0.374
p	0.631	0.539	0.021
	Summed Error		
rho	-0.061	-0.103	-0.143
p	0.714	0.54	0.392
	Movement Onset		
rho	-0.077	0.058	-0.085
p	0.646	0.728	0.612
	Movement Offset		
rho	0.134	-0.01	-0.013
p	0.423	0.955	0.94

Table 7.3. Correlations between pinch strength and behavioural motor measures. All correlations reported with Spearman's rho, N = 38. *Correlation is significant after applying FDR correction for multiple comparisons.

The additional behaviour variables were also tested for the differences between the stroke and the age matched control group to find out that it was the grip asymmetry ($t(16) = 2.211$, $p= 0.042$) but not pinch asymmetry ($t(16) = 1.115$, $p = 0.281$) that

diversified the groups. The difference in performance index did not reach significance ($t(16) = -2.038$, $p = 0.58$), confirming again there was no significant differences in motor performance as opposed to the differences found in EEG measures.

7.3.4. Relationship with ERP and time-frequency measures

For ERP measured at the central ROI at the time of interest around movement onset 270-330 ms, and looking at data timelocked to the visual cue as the basic ERP measure, significant correlations were found with kinematic measures only at late motor adaptation condition. Thus, movement offset in MA_l was related with ERP value at Fam_l, and summed error at MA_l correlated with ERP at MA_E and MA_l. Correlation between summed error at MA_e and ERP at MA_e did not survive multiple comparisons. Performance index strongly correlated with ERP at all conditions and there was no relationship between ERP and pinch asymmetry (table 7.4).

		ROI ERP at 270-330ms		
Offset		Fam_l	MA_e	MA_l
Fam_l	rho	0.112	0.266	0.134
	p	0.505	0.107	0.424
MA_e	rho	0.182	-0.058	-0.009
	p	0.275	0.731	0.957
MA_l	rho	.395*	0.189	0.268
	p	0.014	0.255	0.104
Summed Error				
Fam_l	rho	-0.015	0.144	0.187
	p	0.93	0.389	0.262
MA_e	rho	0.267	0.331	0.324
	p	0.105	0.043	0.047
MA_l	rho	0.302	.361*	.350*
	p	0.065	0.026	0.031
PI	rho	.361*	.570*	.523*
	p	0.026	0	0.001

Pinch asymmetry	rho	-0.145	-0.141	-0.226
	p	0.386	0.398	0.173

Table 7.4. Correlations between ERP and behavioural motor measures.
All correlations reported with Spearman's rho, N = 38. *Correlation is significant after applying FDR correction for multiple comparisons.

Interestingly, in a stepwise regression model to explain performance index, which is a measure of change in summed error over the motor adaptation period, the only significant predictor was the z-scored ERP in the TOI around movement onset in the central ROI averaged for both motor adaptation conditions ($F(1,36) = 13.570$, $p = 0.001$) explaining 25.4% of performance index variance with $\beta = 0.523$ ($p = 0.001$). This positive value of the coefficient suggests that the higher the ERP amplitude around the movement onset, the bigger the reduction in error over the training period, meaning a better adaptation process.

None of the scarce correlations between motor measures and time-frequency measures held multiple comparisons adjustment. Age was not associated with any of the measures.

7.4. Discussion

The most important predictor of summed error and thus motor adaptation was the connectivity between C3 and C4 electrode at the baseline prestimulus period in the motor adaptation condition. Higher prestimulus interhemispheric primary motor cortex connectivity was associated with larger deviation from the optimal trajectory. Pinch asymmetry also predicted the same kinematic measure. When looking at summed error

dynamic derivative as a dependent variable - performance index - it was ERP at the central error-related ROI that explained the most variance.

Stronger EEG connectivity predicted worse performance measure, which - coupled with significant differences between the stroke and healthy control group in EEG, but not kinematic measures, creates an interesting behaviouro-neural landscape. One could hypothesize that the changes in stroke EEG have a compensatory value to support the hand motor function, and that the stroke participants presenting with weaker connectivity - as in this study - should show worse function - as not in this study - and that increase in connectivity can boost the function - again association that was not present in this study. However, the intergroup differences in connectivity appeared in the period directly after the movement onset, and the prediction of motor performance was valid for connectivity only in the baseline period making the predictive interhemispheric connectivity more similar to resting connectivity trait.

It is a typical finding in general that stroke patients show decreased connectivity as compared to healthy controls (Desowska & Turner, 2019). However, increased interhemispheric connectivity is not necessarily a positive trait as I showed here that this was associated with more movement error during adaptation and as studies in stroke show, the connectivity between bilateral motor cortices may have an excessively inhibitory character, and if it stays increased for too long in the recovery process, can be associated with persistent deficit (Rehme, Eickhoff, Wang, Fink, & Grefkes, 2011).

Different EEG measures predicting two different aspects of motor performance - one more stable error averaged over the whole motor adaptation and other capturing the increment in performance between the initial and final adaptation stages - can also

reflect two temporally different neurophysiological traits. One is a more fast-pace changing ERP, and the other - more stable level of baseline interhemispheric connectivity. This emerging difference in temporal dynamic traits can perhaps make ERP a more interesting measure for closed-loops time-varying BCI interventions (Linden & Turner 2016; Sitaram et al. 2017), whereas the baseline connectivity might be more useful in predicting recovery potential (Boyd et al., 2017).

The novelty of this approach lies in combining different EEG domain measures and kinematics in one model to infer how the neural correlates predict the kinematic output. This led to formulating clinically relevant conclusions and opens the exciting door to further, more tailor-made research, e.g. precision medicine or personalised rehabilitation programmes.

8. Conclusions

Understanding neural dynamics during motor adaptation can help design neuroscience-informed rehabilitation programs in the future. This thesis aimed at looking for neural correlates of motor adaptation as a model of rehabilitation after brain injury.

Healthy adults across the lifespan and stroke patients were tested in a force-field learning paradigm. EEG and kinematic data were recorded.

I chose a combination of hypothesis-based and data-driven approaches, scanning EEG data first on a general, whole head level, to look for literature-informed regions of interest (ROIs) and times of interest (TOIs). I subsequently zoomed in to analyse specific electrode data and employed advanced statistical procedures to test hypotheses. To describe each domain in detail, I focused first on finding group differences between older and younger healthy adults in a similar manner as I did later with stroke patients versus healthy age-matched controls. The analyses were finalised by looking for relationships between the EEG and motor performance data using a multiple linear regression approach.

As candidate EEG biomarkers of motor adaptation, I chose first the time domain data, (ERP), focusing on the time just after movement onset and a frontocentral ROI (chapter 4). In the time-frequency domain, I focused on movement related beta band synchronisation perturbation, looking at the electrodes over the primary motor cortex and the frontocentral ROI found significant in the time domain (chapter 5). Finally functional connectivity was analysed in chapter 6, focusing first on electrodes over the primary motor cortex contralateral to the movement as a seed region, to narrow down the analysis to bilateral motor cortex connectivity and connectivity between primary

motor cortex contralateral to the movement and the frontocentral region identified as important in the ERP analysis.

8.1.Key findings

All kinematic measures showed significant differences between the conditions of motor adaptation illustrating increases of kinematic error and change in velocity in the motor adaptation condition but with no significant group differences across young vs older vs stroke patients.

There were no differences between the groups and no interactions of group x condition in most of the measures, with the exception of maximum velocity that was significantly higher in all conditions in stroke patients. A dynamic derivative of the error measure, the performance index illustrating a reduction in kinematic error from start to end of motor adaptation did not differ between groups either, suggesting that neither age nor stroke is a factor crucial for reaching desired outcome performance in this specifically-designed motor adaptation protocol. I concluded that the stroke participants used velocity increase as a compensating strategy that worked well judging by the fact that intergroup differences in error measures did not reach significance. Based on the kinematic results I concluded that stroke patients can still adapt their movement well to perturbation. This ability to learn a motor skill addresses long held hypothesis that "learning" per se is affected by a stroke. In case of this study, in well recovered stroke patients this is not true as the stroke lesion per se was disassociated from motor impairment as a sequala caused by the stroke.

The effect of stroke, however seamless in the kinematic data, came at a cost in neural data.

The crucial ERP component differentiating motor adaptation from simple the reaching condition was a frontocentral negative deflection peaking around 300 ms post visual cue, just after movement onset. This component resembles the temporal and topographic characteristics of the ERN, a brain ERP component related to error processing. Since the difference between the conditions was most pronounced after the movement onset and not before, I concluded that this ERP component is a reflection of sensory feedback processing rather than predictive model formation. Importantly, there were significant differences in that component between the recovered stroke and the healthy age matched control group. The adaptation related ERP component did not seem to be present in the stroke group, with a weaker deflection in general, less pronounced differences between conditions, and significant differences between stroke and healthy group in the motor adaptation but not in the familiarization conditions.

After the analysis of data in the time-frequency domain, a classic movement related spectral desynchronisation was noted, but the ERSP measure was not sensitive to the condition or group differences in motor adaptation.

Even though the amplitude in the time-frequency did not bear significant differences, the analysis of the phase differences brought informative results. Healthy participants showed a characteristic increase in the connectivity of electrodes of interest after the movement onset only in the motor adaptation conditions. Group differences emerged again in the analyses between the stroke and healthy controls - stroke patients presented with a flat line of connectivity during the course of the trial not only in the familiarization but also in the motor adaptation conditions, lacking the connectivity motor adaptation signature of healthy subjects. The effect of condition on connectivity

measure was moderated by timing in control subjects, but not in the stroke group. I concluded that this observation is in line with the concept of network randomization after stroke (Wang et al. 2010), when a function after an injury gradually becomes supported by more dispersed neural resources.

The crucial part of the project was analysing the relationship between the neural and kinematic measures. The most important predictor of summed error in motor adaptation was the connectivity between C3 and C4 electrode at the baseline prestimulus period in the motor adaptation condition and pinch asymmetry. Higher prestimulus interhemispheric connectivity was associated with bigger deviation from the optimal trajectory. When looking at summed error dynamic derivative as a dependent variable - performance index - it was the ERP at the central error-related ROI that explained the most variance. I concluded that higher baseline interhemispheric connectivity can be a reflection of a maladaptive process, perhaps related to increased bi-directional (as methods to determine causality at this stage were not used) interhemispheric inhibition. It is important to also note that the same connectivity at different timepoints in the movement can be of different significance - differences between stroke patients and controls were present in the post-movement period.

Together, all the measures in kinematics and in different domains of EEG analysis create a complex landscape of relationships that hold a promise to understanding the motor adaptation process in health and disease states better.

8.2 Novelty of the findings

To our knowledge there is no studies that analyse EEG correlates of motor adaptation in stroke patients. This study is the first to show that neural correlates of

motor adaptation in stroke population are different to that of healthy controls, even with the same kinematic performance level. Also EEG, despite its superior temporal resolution, has not been widely used in motor adaptation studies. The only EEG studies in motor adaptation thus far focused on resting state or postmovement activity (Faiman et al., 2018, Ozdenici et al., 2017, Torrecillos et al., 2015, Tan et al., 2014) and they involved only healthy participants. Additionally, this study takes on also a comprehensive approach of analysing the data in different domains, with time, time-frequency and functional connectivity measures integrated with the kinematic data. This comprehensive approach is rarely adopted with papers reporting usually single domain data, however proves especially interesting in showing the utility of EEG measures for different facets of rehabilitation planning.

8.3 Limitations

An important limitation of the study is the fact that all of recruited stroke participants were, for practical reasons, well recovered. One can expect that the kinematic measures would be significantly different for more severely affected participants. They would not be able to meet the temporal expectations of the task, or even not be able to perform the full range of motion. Even the same participants in earlier phases of stroke recovery, could present with different behaviour having still perhaps the same structural and functional motor adapting potential. It seems that the crucial moment for stabilising the connectivity measures is one month post stroke (Desowska & Turner, 2019). Interestingly this time window post-stroke is also assumed as the period in which the most motor recovery in hand function happens (Verheyden et al. 2008). The natural next step would be to analyse changes in neural correlates of

motor adaptation longitudinally and in a group of patients with varied levels of upper limb function.

One of the limitations of the regression approach is also the sample size as often seen in studies involving clinical population. Stroke participants present with greater variability of all results, which makes statistical inference more challenging.

8.4 Clinical applications and future directions

Motor adaptation is a simple but potent physiological phenomenon - when the perturbation appears, we adapt our behaviour. There is however a complex orchestra of neural processes that lies behind it. It has implications for recovery.

The results warrant further research in EEG correlates of motor adaptation and could in the future focus on expanding the time window of analysis to include wider pre- and postmovement margins that might bring more interesting results in time-frequency domain, and continuing connectivity analyses in the resting period. A natural step further would also be to move into the source level data to map more specifically the structures involved in the process. An interesting approach would also include muscle activation data to map the mechanism of corticomuscular coherence in the motor adaptation process.

Finally, including patients of different levels of ability and on different stages of recovery could help pin down when exactly the EEG adaptation signature fails to support effective recovery.

This thesis suggests that two EEG measures seem to be most important to identifying performance success in two different temporal aspects. The more stable

measure of averaged summed error from all motor adaptation conditions was predicted by baseline interhemispheric connectivity, making connectivity at the premovement and pre-preparation period an interesting measure in models predicting hand function or even recovery. On the other hand, the dynamic kinematic measure depicting change between the beginning and end of the condition was predicted by time-based ERP amplitude and in a different region – over the frontocentral area. This measure thus would be recommended for more dynamic purposes, like closed-loop BCI interventions.

Brain derived measures need to play a role in the future design of neurorehabilitation programs – after all the injury that the patients recover from happens in the brain. Traditional physiotherapy focuses on motor interventions. They are valid, based on years of practice and - by principles of hebbian plasticity - they have an effect on the neural structure, but they are missing the brain element. Brain information could be helpful for a start for example for stratifying patients into different intensity programs based on their predicted potential to recover. Moreover, brain information could be utilised to apply closed-loop systems modulating the intensity of tasks to reach the optimal brain state that facilitates learning. Closed-loop neuromodulation by means of magnetic or alternating current stimulation would be another application.

With all the potential in mind, the field of incorporating the brain measures of motor adaptation into rehabilitation programs is exciting for the future.

In terms of motor strength measures, the fact that it was the grip but not pinch asymmetry that differed more between stroke and control groups but it was the pinch asymmetry that was a predictor of motor performance suggests that even though motor

performance can differ, the EEG measures are related to finer, more subtle motor movements. The fact that it did not correlate with any familiarization condition measures, makes it a promising measure that does not seem to capture merely a simple relationship with baseline motor characteristics, but the dynamic behaviour of motor output in challenging conditions (i.e. force-field motor adaptation).

The results summarising relationships between different variables seem to confirm that the combination of neurophysiological, kinematic and demographic measures may be far more complex than simple correlations. It is however an important observation that the hand movement performance is related to bilateral motor cortex connectivity - a result seen especially strongly in stroke recovery and rehabilitation studies (Fallani et al., 2017; Grefkes et al., 2008); (Liu, Tian, Qin, Li, & Yu, 2016; Li, Li, Zhu, & Chen, 2014; Zhang et al., 2016). A differently calculated motor error measure, the performance index, that captures the dynamic aspect of learning, was on the other hand explained not by connectivity but by time domain ERP values over the error-related frontocentral ROI, which is in line with the adaptation literature (MacLean, Hassall, Ishigami, Krigolson, & Eskes, 2015).

One of the limitations of the regression approach is however the sample size and the number of stroke participants was limited in this study. Stroke participants - as it is the case with any clinical population – also present with greater variability of all results, which make definite statistical inference more difficult. Nevertheless, some combinations of multidomain variables offer promise for further development in both

clinical neuroscience mechanisms of pathology and in terms of predicting recovery and responses to interventions following acquired brain injury.

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Appendix 1. UREC ethics approval

EXTERNAL AND STRATEGIC DEVELOPMENT SERVICES
uel.ac.uk/qa
Quality Assurance and Enhancement

06 January 2016

Dear Adela,

Project Title:	**Are there brain-based predictors of the ability to learn a new skill in healthy ageing and can they help in the design of effective therapy after stroke?**
Principal Investigator:	**Professor Duncan Turner**
Researcher:	**Adela Desowska**
Reference Number:	**UREC 1516 25**

I am writing to confirm the outcome of your application to the University Research Ethics Committee (UREC), which was considered by UREC **on Wednesday 18th November 2015.**

The decision made by members of the Committee is **Approved**. The Committee's response is based on the protocol described in the application form and supporting documentation. Your study has received ethical approval from the date of this letter.

Should any significant adverse events or considerable changes occur in connection with this research project that may consequently alter relevant ethical considerations, this must be reported immediately to UREC. Subsequent to such changes an Ethical Amendment Form should be completed and submitted to UREC.

Approved Research Site

I am pleased to confirm that the approval of the proposed research applies to the following research site.

Research Site	**Principal Investigator / Local Collaborator**
UEL Stratford campus	Professor Duncan Turner

Approved Documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	***Version***	***Date***
UREC application form	3.0	05 January 2016

Docklands Campus, University Way, London E16 2RD
Tel: +44 (0)20 8223 3322 Fax: +44 (0)20 8223 3394 MINICOM 020 8223 2853
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Appendix 2. Medical questionnaire, Information sheet, Consent form – UREC

Annexe 1

MEDICAL QUESTIONNAIRE

Project title: Are there brain-based predictors of the ability to learn a new skill in healthy ageing and can they help in the design of effective therapy after stroke?

Date:
Subject Number:
Date of birth:
Gender: **M / F**

This questionnaire is confidential. The data given below will be used only to decide, whether there are any conditions that would exclude your participation in the study:

Do you take any medication ? **Y / N**

If Yes, state below:

……

How many units of alcohol do you consume per week on average:

……

Do you use any illegal drugs? **Y / N**

If Yes, state below:

……

Have you had any surgeries in the past?

……

Do you have a history of head or spinal injury (e.g concussion, car crash whiplash):

……

Do you have any chronic illness? **Y / N**

If Yes, state below:

……

Do you have any neurological disorders (e.g. stroke, spinal cord injury, colour blindness, dyslexia, Parkinson's or Alzheimer's disease, epilepsy/seizures, family history of these)?
Y / N

If Yes, state below:

……

Do you have a psychiatric history (e.g. schizophrenia, bipolar disorder, depression, obsessive compulsive disorders, panic disorder, family history of these) ? Y / N

If Yes, state below:

……

Do you have a cardio-respiratory Disease (asthma, angina, high blood pressure, respiratory distress)? Y / N

If Yes, state below:

……

Do you have a musculoskeletal condition: (bone fracture, muscle or ligament tear)? Y / N

If Yes, state below:

……

……

Do you have metal implantable devices outside of mouth (e.g. pacemakers, intracranial plates, skeletal pins, vascular clips)? Y / N

If Yes, state below:

……

If you are a woman are you pregnant or experiencing altered menstrual cycles? Y / N

If Yes, state below:

……

Lateralization: Hand L / R Leg L / R Eye L / R

Other:

……

Annexe 3

University of East London
Stratford Campus
London E15 4LZ
England

University Research Ethics Committee
If you have any queries regarding the conduct of the programme in which you are being asked to participate, please contact:

Catherine Fieulleteau, Research Integrity and Ethics Manager, Graduate School, EB 1.43
University of East London, Docklands Campus, London E16 2RD
(Telephone: 020 8223 6683, Email: researchethics@uel.ac.uk).

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Investigator/PhD student: Adela Desowska
a.desowska@uel.ac.uk

Consent to Participate in a Research Study
The purpose of this letter is to provide you with the information that you need to consider in deciding whether to participate in this study.

Project Title
Are there brain-based predictors of the ability to learn a new skill in healthy ageing and can they help in the design of effective therapy after stroke?

Project Description

Aim of the study
The aim of the study is to analyse how brain activity changes during learning a new movement. To meet that aim, we will use recording of your brain's electrical activity (EEG) and recording of your muscles activity (EMG), while you play a game using a robot designed to assess and aid arm manipulation. Before that we will assess your memory with a psychological test and ask you to fill a confidential medical questionnaire so we know whether there are any medical conditions that could influence the data.

Duration of the study
The whole study with the preparation phase will take about 3 hours.

Benefits of the study

There are no benefits of the study

Risks involved

There are no medical risks to the participants of our study. Since we are collecting data only form 20 participants in each group of the study, the risk of identifying the data is a little increased, but we will use anonymizing procedures no make sure you will not be identified.

Confidentiality of the Data

You will be given a participant number and the data recorded will be stored under that number. The only time we ask your identifying data is the consent form that will be stored separately. The data will be kept at the research lab for 10 years for future analysis.

Location

The study will take place in the UEL Stratford campus Neurorehabilitation Unit research lab.

Remuneration

There is no renumeration for the participation in the study.

Disclaimer

You are not obliged to take part in this study, and are free to withdraw at any time during tests. Should you choose to withdraw from the programme you may do so without disadvantage to yourself and without any obligation to give a reason. If you decide to withdraw from the study, all the data gathered up to this point will be destroyed.

Annexe 4

UNIVERSITY OF EAST LONDON

Consent to Participate in a Programme Involving the Use of Human Participants.

"Are there brain-based predictors of the ability to learn a new skill in healthy ageing and can they help in the design of effective therapy after stroke?"

I have the read the information leaflet relating to the above programme of research in which I have been asked to participate and have been given a copy to keep. The nature and purposes of the research have been explained to me, and I have had the opportunity to discuss the details and ask questions about this information. I understand what it being proposed and the procedures in which I will be involved have been explained to me.

I understand that my involvement in this study, and particular data from this research, will remain strictly confidential. Only the researchers involved in the study will have access to the data. It has been explained to me what will happen once the programme has been completed.

I hereby freely and fully consent to participate in the study which has been fully explained to me and for the information obtained to be used in relevant research publications.

Having given this consent I understand that I have the right to withdraw from the study at any time without disadvantage to myself and without being obliged to give any reason.

Participant's Name (BLOCK CAPITALS)
…….

Participant's Signature
……..

Investigator's Name (BLOCK CAPITALS)
……..

Investigator's Signature
……

Date: …….

Appendix 3. HRA ethics approval

NHS
Health Research Authority

Ms Adela Desowska
PhD Student
Neurorehabilitation Unit, Scholl of Health, Sports and Bioscience, University of East London
Stratford Campus
Water Lane
E15 4LZ

Email: hra.approval@nhs.net

09 February 2017

Dear Ms Desowska,

Letter of HRA Approval

Study title:	**Are there brain-based predictors of the ability to learn a new skill in healthy ageing and are they altered by having a stroke?**
IRAS project ID:	**195798**
Protocol number:	**n/a**
REC reference:	**16/LO/1975**
Sponsor	**University of East London**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Appendix 4. Medical questionnaire, Information sheet, Consent form – patients HRA

MEDICAL QUESTIONNAIRE

Project title: Are there brain-based predictors of the ability to learn a new skill in healthy ageing and can they help in the design of effective therapy after stroke?

Date:
Subject Number:
Date of birth:
Gender: **M / F**

This questionnaire is confidential. The data given below will be used only to decide, whether there are any conditions that would exclude your participation in the study:

Do you take any medication ? **Y / N**

If Yes, state below:

……
……

How many units of alcohol do you consume per week on average:

……
……

Do you use any drugs or medicines that can affect brain functioning? **Y / N**

If Yes, state below:

……
……

Have you had any operations in the past?

……
……

Do you have a history of head or spinal injury (e.g concussion, car crash whiplash):

……
……

Do you have any chronic illness? Y / N

If Yes, state below:

……
……

Do you have any neurological disorders (e.g. stroke, spinal cord injury, colour blindness, dyslexia, Parkinson's or Alzheimer's disease, epilepsy/seizures, family history of these)? Y / N

If Yes, state below:

……
……

Do you have a psychiatric history (e.g. schizophrenia, bipolar disorder, depression, obsessive compulsive disorders, panic disorder, family history of these) ? Y / N

If Yes, state below:

……
……

Do you have a cardio-respiratory Disease (asthma, angina, high blood pressure, respiratory distress)? Y / N

If Yes, state below:

……
……

Do you have a musculoskeletal condition: (bone fracture, muscle or ligament tear)? Y / N

If Yes, state below:

……
……

……
……

Do you have metal implantable devices outside of mouth (e.g. pacemakers, intracranial plates, skeletal pins, vascular clips)? Y / N

If Yes, state below:

……
……

If you are a woman are you pregnant or experiencing altered menstrual cycles? Y / N

If Yes, state below:

……
……

Dominant:
Hand L / R Leg L / R
Eye L / R

Other:

……
……

Patient information sheet

Version for the patient

The Chief Investigator(s)
Adela Desowska
NeuroRehabilitation Unit
School of Health, Sport and Bioscience,
University of East London,
Stratford Campus,
London E15 4LZ
a.desowska@uel.ac.uk

Brain-based predictors of the ability to learn a new skill after stroke

We'd like to invite you to take part in our research study. Joining the study is entirely up to you, before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through this information sheet with you, to help you decide whether or not you would like to take part and answer any questions you may have. We'd suggest this should take about 20 minutes. Please feel free to talk to others about the study if you wish.

The first part of the Participant Information Sheet tells you the purpose of the study and what will happen to you if you take part.
Then we give you more detailed information about the conduct of the study.
Do ask if anything is unclear.

Summary
Study Description

Why?
The aim of the study is to analyse how brain activity changes during learning a new movement. We predict that this ability is different after experiencing a stroke.
The results of the study may in the future help design better rehabilitation programmes for stroke participants.

What will we do?
1. Arrange a neuropsychological assessment session (this can happen at your home if you wish), during which we will assess your memory, perception and language and how your arm works
2. Invite you to our lab for at the University of East London to a robot session, when we use a safe way to record your brain's electrical activity (EEG) and your muscles activity (EMG), while you play a game using a robot designed to assess and aid arm movement. Your task will be to perform a number of reaching movements and the robot may try to disturb some of them. We will also use the equipment to measure your arm function and strength

Why we invite you?
We would like to see how motor learning is changed after a stroke. We invite patients, who have recovered from stroke and healthy adults to compare the data. Participation in the study is completely voluntary and it is absolutely up to you to decide whether you want to participate or not, or withdraw at any time. We are looking for stroke patients, who:
- had a first-ever stroke affecting their right hand function
- are right handed
- have good command of English so that the test results are not affected by their language skills

Where will it happen?
The main procedure will happen in our research lab, in the University of East London in Stratford. We will reimburse the travel cost. The neuropsychology testing can happen either in the lab or at your home.

Duration of the study
The whole study with the preparation phase will take about 6 hours altogether with this talk, but it will be divided in two sessions (neuropsychology - about 1.5 hours - and robot visit, which can take up to 4 hours).
Further details of what's involved
Purpose and background of the research
The nature and purpose of the study
The aim of the study is to analyse the brain's electric activity (electroencephalography; EEG) during the motor learning process. The main hypothesis is that the brain activity of stroke patients during learning to perform a movement would be different from that of age-matched controls, even if their arm function is fully recovered.

The participants recruited for this study will be 44 patients after their first-ever stroke, affecting initially their right hand function and 22 age-matched controls. For the feasibility of the experimental task, only the patients with recovered arm function will be tested.
The participants will be recruited at a stroke follow-up clinic. They will be invited to take part in a neuropsychology testing session followed by motor adaptation testing session, in which their hand function and the potential to learn new movements will be assessed. The clinical MRIs will be obtained if available. EEG recording of the brain activity will be used during a motor adaptation procedure utilizing a robotic arm manipulandum (Interactive Motion Technologies, Cambridge, USA). The participant's task will be to perform 96 reaching movements (Familiarization phase), followed by 96 reaching movements while the robot adds force against the movement (Motor Adaptation) and finally 96 movements of no-force added condition (Wash Out). The EEG preparation involves fitting an EEG cap on the head and filling each of the 64 electrodes with a conductive gel that has mild abrasive effect. Electric activity (EMG) of the right-hand muscles will also be recorded. EMG preparation involves putting 8 sticky electrodes on the arm muscles.
All the procedures used are safe and non-invasive and there are no risks associated with taking part in the study. There are no direct benefits for the participants of the study.

What is already known and how will this study will help us know more?
Rehabilitation of hand function is thought to be a case of movement learning.
We know that people after suffering from stroke can
Learn new movements with success
present with changes in their brain activity as their brain ‘rewires’ during recovery as measured by fMRI and EEG
What we don’t know is how their brain works when they learn.
This knowledge in the future might help build new rehabilitation strategies and rehabilitation programmes.

Will your participation affect your standard care?
The motor adaptation procedure and the neuropsychology testing planned in the study procedure are additional to the standard care. However, the procedure is purely educational and provides no therapeutic benefits to the participant, because it is observation of the brain activity instead of intervention.

What would participation in the study involve?
it will involve two visits
the first visit will be neuropsychology testing, it will involve a test for language, for cognition (memory, attention, perception), and hand function measurement and it will take about 1,5 hours. This can happen in the UEL lab or at your home
the second visit will be testing motor adaptation using a robot with brain activity and muscle activity measurement. Arm function and grip and pinch strength will be tested. We will use special equipment, so this visit has to happen in our lab. It will take up to 4

hours of which up to 2 hours will be spent on preparation (putting the electrodes correctly).
after the first visit, we will request your MRI from the hospital, if you had that done when you had a stroke
this will be made outside of your standard care and will not affect it in any way.

Information handling
We will record:
your neuropsychology results
your hand function results
your EEG recordings of your brain activity
Your EMG recording of your muscle activity
Your MRI results
Your contact details to arrange the meetings (these will be destroyed 3-6 months after the study)
The data will be stored on locked computers under participant numbers characteristic for the study. Only the research team will have access to the data. If you decide at any time to withdraw from the study, the data will be destroyed.
The results from group analysis of the study will be published in scientific journals, but it will be not possible to identify you in any way from these publications.

Benefits from the study
There are no direct benefits of the study. The most likely benefits might be experienced by others with a similar condition, in the future, rather than the participants themselves, as a consequence of discovery through research.

Risks and disadvantages involved
There are no medical risks to the participants of our study. We will use anonymizing procedures to make sure you will not be identified.
There is a small risk for the participant to feel some arm fatigue after the study, similar to the effects of mild exercise routine, since it involves repetitive reaching movement.
There is a small risk of rash from the sticky electrodes we use to record the activity of your arm muscles (EMG) that, if occurred, should disappear within a few hours. The electrodes are a medical device and do not pose serious risks. Before the application of the EMG electrodes, we will rub the skin with alcohol cleansing wipes.
After the procedure, you will have some gel in the hair that we use in the EEG cap preparation. Most of the participants prefer to wash their hair right after. We will provide shampoo and a towel.
The disadvantage of the study is giving a few hours of your time with no medical benefits.
Visit 2 involves sitting in the lab for up to 4 hours, so it can be boring, especially during preparation.

Screening procedures
We will screen your hand function, language and perception and if we feel it is still affected from stroke in a way that would affect working with our equipment we will

exclude you from the study. It is important we are sure that our equipment measures what we planned so we need to proceed with screening, otherwise we will not be sure what condition has produced the results. If we exclude you, we will not proceed to the motor adaptation procedure, we will not obtain your MRI from the hospital and the data that we have gathered will be destroyed.

Incidental findings
The procedures we are using are not diagnostic of any medical condition. In a very unlikely event that we find something that is not typical, we will contact your hospital care team and ask them to clinically assess the finding, if you agree. In case your care team decides additional test should be made, they will contact you. Since the study you are invited to participate in is purely research oriented, the research team is unable to interpret and thus to communicate such findings directly.

Confidentiality of the Data
You will be given a participant number and the data recorded will be stored under that number. The only time we ask your identifying data is the consent form. The data will be kept at the research lab for 10 years for future analysis. To be able to follow you up, we will ask you for your telephone number, and if you wish to arrange a session at your home, we will need to take note of your address. We can arrange the session in our lab instead. The information about your telephone number and address will be destroyed after we perform the assessment, no longer than 6 months after the completion of the study. This information will be stored separately from your other data.
We will provide you with a letter to your GP describing the study if you want to let him/her know that you participate. The participation will not change your medical care in any way.

Supporting information
What if something goes wrong?
If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this by contacting
Professor Duncan Turner,
Director, NeuroRehabilitation Unit,
School of Health, Sports and Bioscience,
University of East London,
Stratford Campus,
London E15 4LZ
Telephone 020 8223 4514, Email: d.l.turner@uel.ac.uk
or
Catherine Fieulleteau,
Research Integrity and Ethics Manager,
Graduate School, EB 1.43
University of East London, Docklands Campus, London E16 2RD
(Telephone: 020 8223 6683, Email: researchethics@uel.ac.uk).

What will happen if I don't want to carry on with the study?
You are not obliged to take part in this study, and are free to withdraw at any time during tests. Should you choose to not take part or withdraw from the study, you may do so without disadvantage to yourself and without any obligation to give a reason. Your decision about participation in the study will not influence the quality of your therapy in any way. If you decide to withdraw from the study, all the data gathered by the research team up to this point will be destroyed.

Will my information be kept confidential?
We will keep your contact data for 3-6 months. We will keep and analyse anonymised research data up to 10 years. All the identifiable data will be stored in password protected computers and locked cabinets in the research lab at UEL and no one from outside of the research team will have access to it.
The data controller is University of East London
The data custodian is Professor Duncan Turner, Director of The NeuroRehabilitation Unit at UEL.
We do not intend to ask for further consent nor ethics committee approval for re-use of the data, since the data will be anonymised (this is in accordance with GaFREC and the Data Protection Act (1998))
The identifiable data will not be shared with other institutions.

What will happen to the results of the study?
The results of group analysis of the study will be used in a PhD thesis at University of East London. We intend to publish the results in peer reviewed journals. We will not publish any data that would allow to identify any of the participants in any way.

Who is organising and funding the study?
The study is organised by the University of East London and Queens Hospital, Barking, Redbridge and Havering University NHS Trust. The study is funded by the University of East London.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed by Harrow Research Ethics Committee.

Further information and contact details
For questions about the study, please contact:
Adela Desowska
NeuroRehabilitation Unit
School of Health, Sport and Bioscience,
University of East London,
Stratford Campus,
London E15 4LZ
a.desowska@uel.ac.uk

If you are unhappy with the study, you can also contact:
Professor Duncan Turner,
Director, NeuroRehabilitation Unit,
School of Health, Sports and Bioscience,
University of East London,
Stratford Campus,
London E15 4LZ
Telephone 020 8223 4514, Email: d.l.turner@uel.ac.uk

If you need advice whether you should participate, we encourage you to take this information sheet to your GP and discuss it.

Consent process

We will obtain a record of your consent in writing, by means of a consent form, and you will be given a copy of the Consent Form and Participant Information Sheet to take away with you and refer back to it as often as you need.

Consent to Participate in a Programme Involving the Use of Human Participants.

Brain-based predictors of the ability to learn a new skill after stroke

I have the read the information leaflet relating to the above programme of research in which I have been asked to participate and have been given a copy to keep. The nature and purposes of the research have been explained to me, and I have had the opportunity to discuss the details and ask questions about this information. I understand what is being proposed and the procedures in which I will be involved have been explained to me.

☐

I understand that my involvement in this study, and particular data from this research, will remain strictly confidential. Only the researchers involved in the study will have access to the data. It has been explained to me what will happen once the programme has been completed.

☐

I understand that as part of this study, the researchers will request access to my MRI scan from the hospital archive and will analyse the images solely to meet the aims of this research study. Some images might be used in publication for illustrative purposes, but it will be impossible to identify the participant based on the images published.

☐

I understand that my clinical information and study data may be looked at by responsible individuals from the research staff, study sponsor, NHS Trust, or from regulatory authorities; I give permission for these individuals to have access to my records.

☐

In case of incidental findings, I agree for the research team to present them to my hospital care team to interpret them clinically.

☐

I hereby freely and fully consent to participate in the study which has been fully explained to me and for the information obtained to be used in relevant research publications.

☐

Having given this consent I understand that I have the right to withdraw from the study at any time without disadvantage to myself and without being obliged to give any reason.

☐

Participant's Name (BLOCK CAPITALS)

…….

Participant's Signature

…….

Investigator's Name (BLOCK CAPITALS)

…….

Investigator’s Signature

…….

Date: …….

Appendix 5. Papers published

Pizzamiglio, S., Desowska, A., Mohajer Shojaii, P., Taga, M. and Turner, D. 2017. Muscle co-contraction patterns in robot-mediated force field learningto guide specific muscle group training. NeuroRehabilitation. 41 (1), pp. 17-29.

https://doi.org/10.3233/NRE-171453

Desowska, A. and Turner, D. 2019. Dynamics of brain connectivity after stroke. Reviews in the Neurosciences. 30 (6), p. 605–623.

https://doi.org/10.1515/revneuro-2018-0082