

Sensorimotor Processing in Post-Stroke Fatigue

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This dissertation is submitted for the degree of

Doctor of Philosophy

June 2021

Declaration

I, William De Doncker confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Chronic pathological fatigue is a highly debilitating symptom with a significant impact on quality of life of stroke survivors. Despite its high prevalence, research into the mechanisms that underlie post-stroke fatigue is lacking. This thesis outlines how changes in cortical neurophysiology results in alterations in sensorimotor processing associated with the perception of effort and how prolonged experience of high effort can subsequently result in chronic pathological fatigue. I show that the perception of effort for what are usually low effort activities is altered in non-depressed, chronic stroke survivors with minimal physical impairment. Low effort voluntary contractions are perceived as more effortful in stroke survivors with high fatigue compared to those with low fatigue. Sensory attenuation, the ability to attend away from predictable sensory input, is thought to underlie altered effort perception. If one is unable to attend away from predictable sensory input associated with a voluntary movement, this will give rise to the perception of higher effort afforded to the movement. I show that stroke survivors with high fatigue do not show reduced sensory attenuation of sensory input arising from mechanoreceptors as quantified using a force matching task and suggest that high effort afforded to simple voluntary movements may be a result of reduced sensory attenuation of information arising from within the body, namely proprioceptive afferent information from the contracting muscle. Using TMS, I show that cortical excitability both at rest and during movement preparation is altered in stroke survivors with high fatigue and propose that cortical excitability reflects the degree of sensory attenuation at the level of the sensorimotor cortex. Finally, I show that neuromodulatory techniques such as transcranial direct current stimulation, are potential tools that can be used to reduce fatigue severity by potentially resetting cortical neurophysiology and reducing perceived effort. Overall, the data provides some evidence in support of the sensory attenuation model of fatigue and provides a novel insight into the mechanisms implicated in post-stroke fatigue.

Impact Statement

Chronic pathological fatigue is major but neglected symptom in a number of neurological diseases such as stroke, multiple sclerosis, Parkinson's disease, and traumatic brain injury. Up until recently fatigue was considered to be a secondary symptom to other affective symptoms commonly implicated in these diseases such as depression, anxiety, apathy and sleep disturbances to name a few. Owing to the lack of effective treatments for fatigue, usually aimed at treating other affective symptoms with the hope of also reducing fatigue severity, it is starting to be acknowledge as a primary symptom that should be addressed independently. Before effective interventions targeted at reducing fatigue severity can be developed, an understanding of the biological mechanisms that drive chronic pathological fatigue is needed.

A theoretical framework, previously used to explain brain function, has recently been proposed to explain chronic pathological fatigue. Throughout this thesis, I present evidence in support of this framework, the sensory attenuation model of fatigue, and highlight the neural mechanisms, namely the role of the sensorimotor cortex, in mediating the perception of effort and fatigue. The work in this thesis provides an objective measure of fatigue that can be used in conjugation with the commonly used questionnaires, as well as providing potential targets for the development of successful interventions for this persistent and highly debilitating symptom.

Acknowledgments

This thesis and the work included in it would not have been completed without the help of a large number of people that I would like to thank. By writing this thesis, I have come to realise that an important part of the PhD ‘journey’, is the people you meet and interact with along the way.

Researchers and academics do not remain in one place for too long, which was great for me, as being around 33 Queen Square for 5 years, I had a chance to meet so many people that made going into the lab on a daily basis so much more enjoyable. Rotation #1 of the 4th floor fellows room, Graziella Quattrochi, Svenja Espenhahn, Alejandro Galvez Pol, Louise Marshall and Ella Clark all of which welcomed me with open arms and made me feel so comfortable starting off as ‘boy’ in his academic career. Rotation #2 of the 4th floor fellows room, Carys Evans, Eve Georgiou, Haya Akkad, Angelo Dawson, Lydia Mardell, Jenny Lee, Catharina Zich, Ainslie Johnstone and Jane Rondina for the interesting conversations over lunch and in the office. Imran Sayed, the king of finance, for constantly dealing with my numerous emails. Of course there are so many other people within the Rothwell Lab that I would like to thank for the post-lunch coffee and the intellectually stimulating conversations both at the journal club and the pub. Jaime Ibañez, Danny Spampinato, Lorenzo Rocchi, Duncan Austin, Vish Rawji, Karen Bunday, the Italian Crew (Francesca Ginatempo and Nicoletta Manzo), Po-Yu Fong, Kate Brown, Lingdi Fu, Ricci Hannah; thank you all.

The Effort Lab, both current and past members. I would like to thank Dr Sasha Ondobaka, with whom we started our journey in the Effort Lab together, for his constant advice and support that made me develop into a better scientist and person. Cameron Cook, although a late addition to the team, your help with recruitment was invaluable and I would have not been able to test over 400 stroke survivors across a range of different experiments without your help. I would like to thank Calvin Cheung, a BSc student, for his help with data collection and all other students and collaborators including Dr Lucie Charles for the intellectually stimulating discussions during our lab meetings. I would also like to thank Dr Chi-Hsu Wu, a recent addition to the Effort Lab.

Of course, I have to thank all the stroke survivors that have dedicated their time and effort to participate in research. They have had to put up with all sorts of experiments, back and forth email and telephone conversations. I have really met some wonderful people that I will stick to my mind.

Finally, there are a few more key people that I would like to thank. I would like to thank my family and my girlfriend, Stella, for their endless support, love and patience. After 9 years at UCL, my journey as a student has come to an end. As is every journey, it was not always smooth sailing, but their support and advice was important to put me back on track and I am extremely grateful.

Prof John Rothwell, my secondary supervisor, for his constant support and advice. Most importantly, it was always done with a smile and a giggle. I am honoured to be in the endless list of PhD students he has supervised over the years.

Paul Hammond, my go to person for all problems throughout my time at Queen Square. Whether it be professional or personal guidance he always there to lend a helping hand and I am extremely grateful for this. Your various mottos and perspectives on life will definitely stay with me for years to come.

The final person I would like to thank, without which none of this would have been possible is my supervisor Dr Anna Kuppuswamy. I am truly honoured to be your first PhD student. We have travelled the world together on various conferences and seminars and have experienced some truly unforgettable moments together. Your support, care and advice during these 5 years has allowed me to develop into a better person and has transformed me into what you might call a 'man'. You have taught me how to be a better scientist, ask the right questions and most importantly how to write. Your constructive criticism over the years has helped me avoid the migraines I got during my upgrade and write my entire thesis with minimal hiccups. Thank you for everything.

Related publications

The below contain some material overlapping with Chapter 1 and Chapter 2

- **De Doncker, W.**, Dantzer, R., Ormstad, H. and Kuppuswamy, A., 2018. Mechanisms of poststroke fatigue. In *Journal of Neurology, Neurosurgery & Psychiatry*

The below publications contain some of the data and results featured in Chapter 3, Chapter 5, and Chapter 6

- **De Doncker, W.**, Charles, L., Ondobaka, S. and Kuppuswamy, A., 2020. Exploring the relationship between effort perception and poststroke fatigue. In *Neurology*
- **William De Doncker**, Katlyn E. Brown and Annapoorna Kuppuswamy, 2021. Influence of post-stroke fatigue on reaction times and corticospinal excitability during movement preparation. In *Clinical Neurophysiology*
- **De Doncker, W.**, Ondobaka, S. and Kuppuswamy, A., 2021. Effect of transcranial direct current stimulation on post-stroke fatigue. In *Journal of Neurology*

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Abbreviations

5-HTRs	Serotonin receptors
ACC	Anterior cingulate cortex
AChRs	Acetylcholine receptors
AMT	Active motor threshold
ARAT	Action research arm test
ATP	Adenosine triphosphate
BOLD	Blood-oxygenation level-dependent
Cam-CAN	Cambridge Centre for Ageing and Neuroscience
CRN	Clinical research network
CRP	C-reactive protein
CST	Corticospinal tract
DA-R	Dopamine receptors
DAMP	Danger associated molecular pattern
DLPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalography
EMG	Electromyography
FDI	First dorsal interosseous
fMRI	Functional magnetic resonance imaging
GABA	γ -Aminobutyric Acid
GPCR	G-protein couple receptors
HADS	Hospital Anxiety and Depression Scale
HASU	Hyper-acute stroke unit
HC	Healthy controls
HF	High fatigue stroke survivors

IIB	Interhemispheric inhibition balance
IL	Interleukin
IOSlope	Recruitment curve slope
IOSlope-A	Recruitment curve slope of affected hemisphere
IOSlope-U	Recruitment curve slope of unaffected hemisphere
IS	Imperative stimulus
KA	Kynurenic acid
KYN	Kynurenine
IDO	Indoleamine 2,3-dioxygenase
LF	Low fatigue stroke survivors
M1	Primary motor cortex
MEG	Magnetoencephalography
MEP	Motor evoked potential
MRCP	Movement-related cortical potential
MS	Multiple Sclerosis
MT	Length of hold
MVF	Maximum voluntary force
NFI	Neurological Fatigue Index
NHPT	Nine-hole peg test
NIBS	Non-invasive brain stimulation
NMDA	N-Methyl D-aspartic acid
NO	Nitric oxide
PD	Parkinson's disease
PE	Perceived effort
PSD	Post-stroke depression
PSF	Post-stroke fatigue
RMT	Resting motor threshold

RMT-A	Resting motor threshold of affected hemisphere
RMT-U	Resting motor threshold of unaffected hemisphere
RT	Reaction time
RT30	30% Reaction time
RT50	50% Reaction time
RT70	70% Reaction Time
SDMT	Symbol digits modalities test
SL	Number of lines reported as long
SMA	Supplementary motor area
SOR	Supra-orbital ridge
T	Force variability
tDCS	Transcranial direct current stimulation
TLR	Toll-like receptor
TMS	Transcranial magnetic stimulation
TNF- α	Tumor necrosis factor
TO	Target overshoot
TRP	Tryptophan
VAS20	Explicit PE in 20% MVF condition
VAS40	Explicit PE in 40% MVF condition
VAS60	Explicit PE in 60% MVF condition
WP	Warning period
WS	Warning stimulus

Chapter 1: Post-stroke fatigue

1.1 Impact of stroke

Stroke is the second leading cause of death worldwide and the leading cause of adult disability with almost 17 million stroke survivors worldwide and 1.2 million stroke survivors in the UK alone (Global Burden of Disease Result tool, 2016; NHS Digital, 2017). Incidence of stroke is on the rise and currently approximately 100,000 people suffer a stroke each year in the UK, one stroke every five minutes (Royal College of Physicians Sentinel Stroke National Audit Programme (SSNAP), n.d.). Care in the acute and hyperacute period of stroke has improved dramatically in the last two decades. Of significant importance are the current treatments for ischaemic strokes, which compromise approximately 85% of all strokes annually, such as thrombolysis and thrombectomy. The development of these treatments amongst others has resulted in half the number deaths as direct consequence of stroke in 2010 when compared to 1990 (Feigin et al., 2014). Lower mortality rates mean that a significant percentage of stroke survivors live with the long-term consequences of stroke. In the next 20 years, it is estimated that the number of stroke survivors aged 45 and over living in the UK with the consequences of stroke will rise by 123% (King et al., 2020). In the UK, almost two-thirds of stroke survivors leave hospital with some sort of disability, of which over one-third of these people depend on others for their care (Adamson et al., 2004). Managing the long-term consequences of stroke is one of the biggest challenges of the future and our attention must now turn to treatments that actively promote stroke recovery. Despite the health and economic burden of stroke, together with the fact that stroke is both a chronic and progressive disorder, funding for research into stroke is far behind that of cancer, coronary heart disease and dementia (Luengo-Fernandez et al., 2015).

The effects of stroke are widespread and result in more disabilities than any other condition. These effects range from physical disabilities to speech and language problems (aphasia), visual disturbances, pain, headaches, emotional disturbances, as well as cognitive and psychological impairment. Of the many sequelae of stroke, the least understood, most difficult to manage, with a significant impact on quality of life are the psychological impacts of stroke. Within this category of symptoms are chronic affective symptoms such as depression, anxiety, and fatigue. Post-stroke fatigue (PSF) is the least understood and most understudied symptom within this cluster of symptoms.

The majority of stroke survivors report PSF as their worst or one of their worst symptoms (Ingles et al., 1999). A stroke survivor I have met over the last 4 years has described fatigue as:

"Being an 'invisible problem', I worry that no-one believes me or can do anything to help"

Management of fatigue has been identified by stroke survivors as their top unmet need and is a top priority for further research (Kirkevold et al., 2012; Pollock et al., 2014).

1.2 Prevalence of Post-Stroke Fatigue

Fatigue after stroke is very common. PSF is highly debilitating and is significantly related to poor quality of life (Naess et al., 2006). PSF limits participation in everyday life and has a significant impact on social participation and return to work (Andersen et al., 2012; White et al., 2012). Stroke survivors suffering from PSF are dependent on others for activities of daily living resulting in institutionalization (Glader et al., 2002). PSF has a major effect on the economy and has been linked to increased mortality rate (Glader et al., 2002; Mead et al., 2011). Given the impact of PSF, understanding the scope of the problem and contributing factors is of major importance. Although it is generally accepted that fatigue is widespread after stroke, there is a large variability between studies in the reported prevalence. The reported prevalence amongst stroke survivors ranges

from 25% to 85% (Cumming et al., 2016). Prevalence of fatigue in stroke survivors is more than three times that of age-matched controls and is a prominent symptom even in those with little disability and mild strokes (van der Werf et al., 2001; Winward et al., 2009). There could be several contributing factors for the reported differences in incidence. Firstly, fatigue is a term that is instantly recognisable and understood by all but defining fatigue for purposes of quantification and comparison across individuals is very difficult. The difficulty lies in the use of confusing terminology when describing fatigue and the distinction between physiological and pathological fatigue. Secondly, PSF has significant overlap with other affective symptoms after stroke such as depression, anxiety, apathy, pain and sleep disturbances. This has previously led to mistaken belief that PSF may be secondary to other primary disorders, however recent work has highlighted the primary occurrence of fatigue after stroke (Wu et al., 2015b). Attempting to control for this complex picture of incidence with other affective symptoms may explain the variable prevalence of PSF reported. Thirdly, fatigue is a subjective experience and is often quantified using self-reported fatigue scales. There are many fatigue scales used within the literature that measure different aspects of fatigue and together with the lack of consensus on a clear cut-off for fatigue, diagnosis and quantification of fatigue is a challenge. Finally, the timing of assessment of fatigue after stroke is likely to contribute to the varied prevalence.

Addressing all these points is therefore essential to identify the true prevalence of PSF and its burden on stroke survivors.

1.3 Physiological and Pathological Fatigue

Fatigue is a term that is instantly recognisable and understood by all. It is however a complex, subjective experience that reflects the subject's interaction with the environment. Fatigue is a non-specific symptom with several underlying causes. Such

causes include physiological states due to excessive muscular or mental activity; medical conditions such as chronic inflammatory conditions, myopathies and viral infections; psychiatric disorders such as major depression and anxiety disorders; and disorders of the central nervous system such as stroke, multiple sclerosis (MS) and Parkinson’s disease (PD). Irrespective of cause, fatigue is a subjective phenomenon and is often described from an individual’s perspective as a weariness, increasing sense of effort or exhaustion (figure 1.1). Given the common nature of fatigue, making a distinction between physiological and pathological fatigue is notoriously difficult. It is however essential to differentiate between the two for the purposes of clinical diagnosis, scientific research, and the development of future interventions.

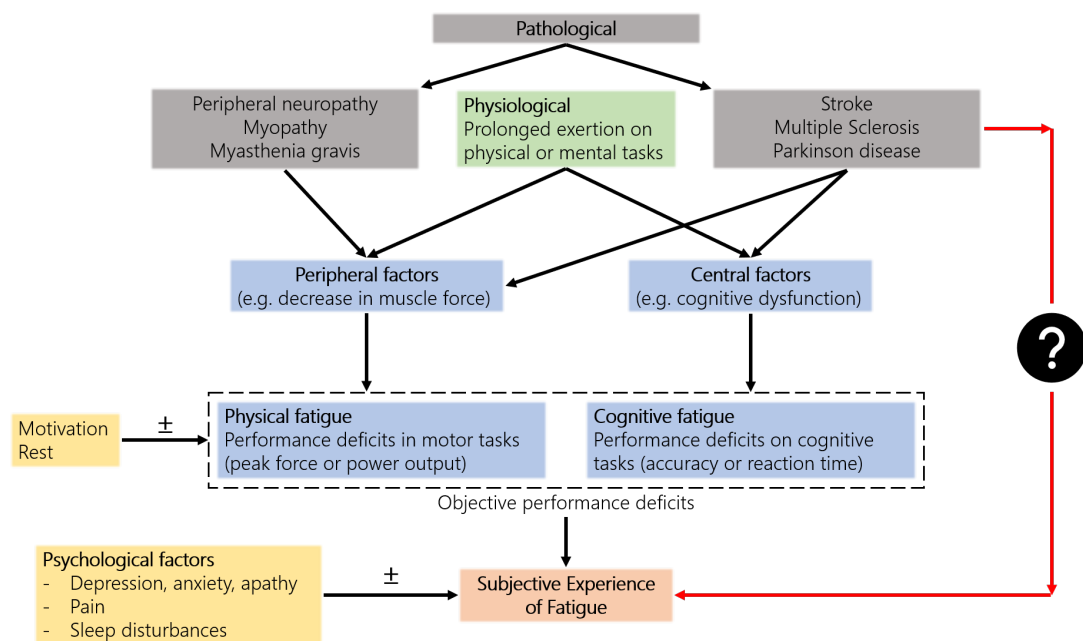


Figure 1.1 – Contributions to the subjective experience of fatigue. Spider diagram depicting the various contributions and influences on the subjective experience of fatigue. Grey boxes indicate a diseased state, blue boxes indicate objectively measured deficits, yellow boxes indicate other influences on the subjective experience of fatigue. The red arrows depict the unknown direct influence of stroke on the subjective experience of fatigue.

Physiological fatigue is the type of fatigue that everyone will experience at some point throughout their life and has been described as a transient phenomenon with an identifiable cause, influenced by motivation, alleviated by rest and with no major impact on quality of life. Physiological fatigue is therefore an objective phenomenon given that

there is clearly defined identifiable cause. Historically, physiological fatigue as an objective phenomenon was studied during the nineteenth century and was triggered by the industrial revolution, as many industrial activities included long hours of hard manual labour under harsh conditions, leaving workers exhausted. These studies in industrial workers gave birth to the study of human physiology and the 'laws of fatigue' as well as the study of athletic performance. One of the pioneers in the study of fatigue at the time was Angelo Mosso who described fatigue in his famous book *La Fatica* as:

'On examination of what takes place in fatigue, two series of phenomena demand our attention. The first is the diminution of muscular force. The second is fatigue as a sensation. That is to say, we have a physical fact that can be measured and compared, and a psychic fact that which eludes measurement. With regard to the feeling of fatigue, the same thing takes place as happens in the case of every stimulus which acts upon our nerves: we being to perceive it only when it has attained a certain intensity'. – Angelo Mosso, La Fatica.

Mosso's description is in the context of physical activity and highlights the role of the periphery and the brain in generating fatigue. There is an organic cause, in this case a diminution of muscular force, that results in the subjective experience of fatigue that can be scaled in intensity. During a physical task, activity from the brain, namely the primary motor cortex, excites motor neurones located in the spinal cord. Action potentials are then conveyed from the spinal cord to the periphery, the neuromuscular junction, which through a cascade of events results in a muscle contraction. The periphery in this instance refers to the neuromuscular junction, the musculature and the associated peripheral nerves. Given the role of the periphery in mediating fatigue this was termed peripheral

physiological fatigue and is often associated with fatigue in the muscle. Peripheral physiological fatigue is commonly referred to in the literature as physical fatigue. Physical fatigue is often quantified by measuring the rate of decline in peak force or power generated during maximum voluntary contraction.

In the middle of the twentieth century, from the study of university lecturers and soldiers fighting in the Second World War, it became obvious that the subjective experience of fatigue could also be triggered by mental and/or cognitive tasks. Prolonged exposure to mental tasks had a subsequent effect on decision-making, attention and concentration. Given the role of the central nervous system, specifically the brain, in performing such tasks, this was termed central physiological fatigue. The exact mechanisms underlying central physiological fatigue after performance of cognitive tasks are still unclear but a model has recently been proposed (Müller and Apps, 2019). Central physiological fatigue however is not only associated with cognitive tasks but also with physical tasks as a failure of the central nervous system to drive the peripheral machinery. In this context, central physiological fatigue is caused at sites proximal to the neuromuscular junction and is often referred to as a progressive decline in the ability to activate the muscles voluntarily. As the muscle becomes more fatigued, there is progressive increase in the voluntary effort to drive the motor output from M1 in order to overcome the muscle fatigue until the physical tasks require maximal effort (Taylor and Gandevia, 2008). Central physiological fatigue is often referred to in the literature as cognitive (or mental) fatigue. Cognitive fatigue is often quantified by measuring the rate of decline in performance (accuracy and/or reaction time) on a cognitive task (Tanaka et al., 2014).

Physical and cognitive fatigue influence each other and have been shown to induce the same feeling of fatigue. Whether fatigue is caused by a cognitively demanding task or a physically demanding task, both physical and mental performance is affected (Marcora,

2009; Van Cutsem et al., 2017). Physiological fatigue is therefore a domain-general process resulting in a transient reduction in engagement of voluntary activities (Krupp et al., 1989).

Physiological fatigue, be it physical or cognitive, is a transient and predictable phenomenon that is alleviated by rest (Helton and Russell, 2015; Meyniel et al., 2014). It is therefore commonly referred to as state fatigue as it describes the state of fatigue at a specific moment in time. It is estimated that approximately 15% to 25% of the general population suffer from periods of fatigue lasting less than one month in duration (Lewis and Wessely, 1992). Incentives have also been shown to counteract the subjective experience of fatigue as a result of physical or cognitive tasks (Boksem et al., 2006; Hopstaken et al., 2015; Meyniel et al., 2014, 2013; Meyniel and Pessiglione, 2014). Whether you are an elite athlete like Chris Froome or a PhD student writing their thesis, prolonged exertion both physical and mental will result in fatigue but knowledge of being rewarded with a Tour de France win or an excellent thesis, allows one to push through the fatigue.

The subjective experience of fatigue can also arise as a result of disease state. When the experience of fatigue becomes chronic, more severe and is associated with other features and functional disability it goes into the realms of pathological fatigue. Pathological fatigue with an identifiable cause can exist in certain disease states but in others it can exist as purely a subjective phenomenon with no clear identifiable cause. Pathological fatigue with an identifiable cause can arise as a result of a number of factors associated with a disease and shares many similarities with what has previously been described as physical and cognitive fatigue. One such factor is that of sickness behaviour. Sickness behaviour is a non-specific response of the body to different stressors such as pathogens that are recognised by the innate immune system or environmental changes. This non-

specific response has metabolic, physiological and behavioural components and the classic symptomology includes fatigue, weakness, malaise, listlessness, inability to concentrate, depression and lethargy, with little interest in their surroundings, eating and drinking (Dantzer and Kelley, 2007). These sickness responses, in most circumstances, are beneficial to the host to overcome the underlying cause of the response. Another factor resulting in pathological fatigue is that of muscle weakness resulting in early muscle fatigability seen in myopathic disorders, myasthenic syndromes, diseases of peripheral nerves, and lower motor neurones. In these cases, pathological fatigue shares many similarities with what has previously been described as physical fatigue, there is an identifiable cause with an objective performance deficit, but with a faster onset and higher severity due to the underlying condition.

Pathological fatigue can also exist as a purely subjective phenomenon with no clear identifiable cause that is often independent of objective or behavioural aspects. This type of pathological fatigue is much more difficult to define and study. It is often described as a chronic phenomenon with a sudden onset and no identifiable cause, which varies in response to incentives, exertion or rest and has a major impact on quality of life. How the brain generates an experience of fatigue in the absence of a stimulus, as is the case in pathological fatigue remains unknown. Historically, pathological fatigue (the subjective experience of fatigue without any clear morphological abnormalities) was termed neurasthenia by the psychopathologist George Miller Beard. Neurasthenia has its origins in the Greek words *neurone* and *asthenes* ('not strong'), meaning weakness of the nerves. Pathological fatigue as a subjective phenomenon is one of the most common features identified in a broad range of neurological conditions, including PD, MS, traumatic brain injury and stroke and does not appear to be associated with the nature or severity of the underlying disease. Stroke survivors with very good recovery and no obvious neurological deficits are often extremely disabled by pathological fatigue (Winward et al., 2009). This

is what is commonly described as PSF, pathological fatigue with no objectively measured performance deficit. Stroke survivors suffering from PSF can often differentiate between the physiological fatigue previously experienced and fatigue after neurologic illness (Flinn and Stube, 2010).

The main features of this type of pathological fatigue are its intensity and its chronic nature. Pathological fatigue, as is the case in PSF, can be both prolonged (lasting between one and five months) or chronic (lasting six months or longer). Additionally, rest does very little to alleviate the symptoms of pathological fatigue and incentives do very little in allowing one to push through their fatigue. When all of the above are taken together, the impairment to an individual's functional activity and quality of life as a result of symptom severity results in seeking clinical advice (Nadarajah and Goh, 2015). This form of fatigue is often termed trait fatigue as it represents the experience and impact of fatigue on day-to-day living.

Given the high prevalence of PSF and its impact on quality of life, how do we go about defining it for the purposes of quantification?

1.4 Defining pathological fatigue

Pathological fatigue as a subjective phenomenon, as is the case in PSF, is very difficult to define given its subjective nature. Given that PSF relies on self-report and is very hard to diagnose as an external observer, the patient's perspective is essential when trying to define fatigue. To get a better understanding of what it is like to live with fatigue and the impact it has on day-to-day living, at the start of my PhD, I asked stroke survivors to describe what it is like to live with fatigue:

“It is a weird feeling that comes over, making me incapable to mentally or physically do anything really, not even get annoyed... Until it passes!” – Patient SO

“I suffer extreme fatigue which follows no pattern whether I rest, exercise or perform daily tasks” – Patient AB

“My fatigue materialises after I do something that involves a lot of concentration and ‘brain’ power – something that would have been relatively easy prior to my stroke. Even though the activity is simple and not physically strenuous, I am left exhausted” – Patient JB

These are powerful descriptions that further endorse the fact that PSF has a sudden onset and is not alleviated by rest. Even simple activities of daily living and simple tasks appear to trigger PSF. These descriptions are invaluable when attempting to define fatigue. A number of studies have used qualitative methods for an in-depth exploration of the patient’s perspective in an attempt to define fatigue. Descriptions that stand out include the following:

“Fatigue is a multidimensional motor-perceptive, emotional and cognitive experience”

“Fatigue is a feeling of lack of energy, weariness, and aversion to effort”

These descriptions of fatigue clearly capture the multidimensional nature of fatigue with common reference to physical, emotional and cognitive aspects. While definitions based on the felt experience define fatigue from a patient’s perspective, others have attempted to define fatigue from a mechanistic perspective.

“We propose to define fatigue as a reversible decrease or loss of abilities associated with a heightened sensation of physical or mental strain, even without conspicuous effort, an overwhelming feeling of exhaustion, which leads to inability or difficulty to sustain even routine activities and which is commonly expressed verbally as loss of drive” (Staub and Bogousslavsky, 2001)

“Pathological fatigue is, thus, best understood as an amplified sense of normal (physiological) fatigue that can be induced by changes in one or more variables regulating

work output. Fatigue could develop during a disease because of dissociation between the level of internal input and that of perceived exertion from applied effort” (Chaudhuri and Behan, 2004)

In the absence of a clear definition, concrete diagnostic criteria and objectively measured performance deficits, neurologists are advised to focus particularly on the initiation and sustainability of physical or cognitive voluntary activities when diagnosing patients with fatigue (Chaudhuri and Behan, 2004). From the abovementioned definitions and the current criteria used to diagnose fatigue, a common feature is the term effort. Could fatigue be a feeling arising from difficulty in initiation or sustaining voluntary effort? This question will be addressed in a later section of this thesis.

1.5 Quantifying Post-Stroke Fatigue

PSF is a subjective experience and cannot be objectively assessed by currently available methods due to the lack of identifiable external criteria. This, along with a lack of a precise definition, presents a challenge when trying to assess and characterize PSF. Currently, the only tools available to assess and quantify the severity and frequency of fatigue across neurological disorders is in the form of self-assessment instruments such as questionnaires (Tyson and Brown, 2014). There are many such scales available, probably a result of the increasing recognition of fatigue as a major clinical problem across neurological disorders. These scales vary widely in how they treat fatigue and measure different aspects of the experience of fatigue, maybe even potentially distinct constructs (Penner and Paul, 2017). Some of the advantages of using such instruments to quantify fatigue is that the majority are easy to understand from a patient’s perspective, they require little or no prior training in order to be administered, they are relatively short and can be administered in a short space of time and they are readily available for use within clinical and scientific practice. The instruments used to quantify fatigue can take on different

structures. Some include unidimensional measures such as the Visual Analogue Fatigue Scale (VAS) which are designed to derive a single score that captures heterogeneous symptoms and behaviours, while others are more complex measures encompassing the multidimensional nature of fatigue such as the Multidimensional Fatigue Inventory which provide a detailed qualitative and quantitative assessment of fatigue. The scaling methods used across the different instruments traditionally include the Likert scale and a response on a VAS. The Likert scaling method asks patients to report the degree to which they agree with a particular item on an ordered scale, while the VAS asks patients to indicate the point on the line of a VAS to which they endorse a particular item.

Fatigue questionnaires vary widely in their assessment focus depending on the questions being asked and the period to which they refer. The period that patients are asked to refer to range from the immediate time of administration (state fatigue), to anywhere between a week and a month leading up to the time of administration (trait fatigue). Therefore, trait fatigue represents the experience and impact of fatigue on day to day living for a pre-determined period leading up to the day of testing, whereas state fatigue characterizes momentary state of fatigue at a given moment in time. The aspects of fatigue measured across these different questionnaires include the frequency and severity of fatigue, the variability of fatigue-related phenomena, the impact of fatigue on everyday life, exacerbating and relieving fatigue as well as the agreement with experiences of fatigue. To measure the severity of fatigue, questionnaires usually ask patients to respond on the degree to which they feel tired, fatigued, sluggish, or worn out. The impact of fatigue is often divided into three categories, physical, mental (or cognitive) and psychosocial. Scales measuring the impact of fatigue on physical activities usually refer to reduced sustained physical functioning, weakness, or a heavy sensation. Scales measuring the impact of fatigue on cognitive activities usually focus on difficulties with concentration, problems with decision-making and confusion. Scales measuring the impact of fatigue on

psychosocial activities usually focus on the social consequences of fatigue and the motivational and affective feelings associated with fatigue.

The range of instruments available are helpful in clinical practice as they capture valuable information with regards to the existence and burden of fatigue in a given individual in a time-effective manner. However, given the aspects of fatigue measured across the different questionnaires varies significantly, the choice of questionnaire depends on the aspects of fatigue the researcher or clinician wishes to measure (Elbers et al., 2012). If the scale is used to make a clinical diagnosis of fatigue, the scale should have clear cut-off points with acceptable levels of sensitivity and specificity to differentiate between positive and negative cases of fatigue. If the scale is to be used to describe the severity or impact of fatigue on every-day life, the scale should be sensitive to the full range of presentations from physical to mental. Finally, if the scale is to be used as an outcome measure within clinical research studies, the scale should have proven sensitivity to change as a result of an intervention or disease progression. Therefore, the quality of the measurement properties, including the reliability, validity, responsiveness and interpretability of the outcome measure, is also an important factor when choosing a suitable questionnaire. The choice of questionnaire is also determined by the clinical population under investigation. The majority of scales have been designed to be used in a specific population. Given that many items referring to the impact of fatigue within these questionnaires are also often directly limited by neurological conditions, it is important to examine the individual items to assess any overlap between fatigue-related and non-fatigue-related symptoms when using the questionnaire in a different population. Until the mechanisms that underlie the subjective experience of fatigue are shown to be common across a range of neurological conditions, it cannot be assumed that a questionnaire that is effective in one condition will be as effective or even suitable for use

in another condition. It is therefore apparent, that many factors should be taken into consideration when choosing a self-assessment tool to quantify fatigue.

One of the best known and most commonly used fatigue questionnaire is Fatigue Severity Scale (Krupp et al., 1989). The Fatigue Severity Scale (FSS) was first used in patients with multiple sclerosis or systemic lupus erythematosus to get an impression of the impact of fatigue on physical activities. It is now also used to measure fatigue in other neurological disorders such as Parkinson's disease and stroke (Elbers et al., 2012). The modified version of the FSS commonly used in stroke survivors, Fatigue Severity Scale-7 (FSS-7), consists of seven items asking patients to rate the degree to which they agree or disagree with the specific statement on a Likert scale ranging from one (strongly disagree) to seven (strongly agree). Patients are asked to respond to the various statements based on how they have been feeling in the week leading up to the time of administration and is therefore a measure of trait fatigue. A cut-off score of 4 is commonly used to define fatigue on the FSS-7. However, it has been argued that using a cut-off of 4 leads to an overestimation of prevalence and categorising FSS-7 scores into three categories (< 4 indicating no/mild fatigue; 4-4.9 indicating moderate fatigue; > 5 indicating severe fatigue) might give a more reliable estimate (Lerdal et al., 2005). The FSS-7 measures the impact of fatigue on physical functioning and does not necessarily measure the intensity of fatigue related symptoms. It is a validated questionnaire that has a high internal consistency, good test-retest reliability, is sensitive to change with time after treatment and has been used in different clinical populations (Johansson et al., 2014).

The progress in fatigue research and improved management of fatigue in clinical care depends on having reliable and valid methods of assessment. Given the inherent subjectivity of fatigue, these methods of assessment should reflect the patient's experience of fatigue. However, having a consistent and reliable objective measure of chronic

pathological fatigue that can be used in combination with these self-assessment scales will shed light on the impact of PSF as well as the effectiveness of various interventions targeted towards treating PSF.

1.6 Post-Stroke Fatigue and related factors

1.6.1 Time post-stroke

Insight into the potential mechanisms that drive PSF can be gained by examining the time course of fatigue post-stroke. In the acute stage of stroke recovery, with acute being within the first three months after stroke, approximately one-third of stroke survivors report symptoms of fatigue. Fatigue in the first few weeks/months following a stroke can be a result of a general non-specific reaction to a major disruptive event and forms part of a cluster of symptoms termed sickness behaviours which has been described previously. Fatigue in the acute stage of stroke recovery can also be a result of hospitalisation, deconditioning and readjustment to life after stroke. Of those that report fatigue in the acute stage of stroke recovery, approximately two-thirds of them continue to suffer from fatigue in the chronic stage of stroke recovery, usually over 6 months after stroke (Wu et al., 2015b). One-third of those with acute fatigue go on to recover from fatigue. A significant percentage of stroke survivors that did not report symptoms in the acute stage of stroke recovery go on to develop symptoms of fatigue at a later stage. Reports of stroke survivors with fatigue in the chronic stage but not in the acute stage range from 12% to 58% (Duncan et al., 2015; van Eijsden et al., 2012; Radman et al., 2012; Schepers et al., 2006). Therefore, fatigue can be divided into three categories based on the temporal profile of symptom presentation. These are persistent fatigue, recovered fatigue and late onset fatigue. It appears that the severity of fatigue in persistent and late onset fatigue remains stable over time (Kjeverud et al., 2020). The more disabling fatigue that has a significant impact on quality of life of stroke survivors is the fatigue that persists

for months or even years after a stroke, in this case the persistent and late onset fatigue. Acute and chronic fatigue can be differentiated by various factors. The severity of the stroke, initial disability and the degree of inflammation are strong correlates of acute fatigue but not of chronic fatigue (Chen and Marsh, 2018; Ormstad et al., 2011; Radman et al., 2012). This is in line with the idea that recovering from neurological impairment requires a large amount of effort that can be physically, cognitively and emotionally exhausting. Chronic fatigue on the other hand is thought to arise from factors unrelated to the stroke itself. These include complex psychosocial interactions and behavioural patterns resulting from residual neurological deficits (Tseng et al., 2010).

A differentiation between early and late fatigue might be indicative of more than a single trigger and possibly several mediating factors that persist beyond the acute stage of stroke recovery. A potential mechanism of persistent chronic fatigue will be explained in a later section of this thesis.

1.6.2 Age and Sex

The influence of biological factors such as type of stroke, age and sex on the prevalence of PSF has been studied extensively with the hope of providing some clues into the origins of fatigue. The association between age and PSF is one of the most commonly studied factors, however the findings remain controversial. Some studies report a higher prevalence of PSF in younger stroke survivors, while others report the opposite, PSF has a higher prevalence in older stroke survivors (Feigin et al., 2012; Glader et al., 2002; Parks et al., 2012; Rudberg et al., 2020). Others report that the association between PSF prevalence and age is U-shaped, with a higher prevalence in both younger (less than 60 years of age) and older (over 75 years of age) stroke survivors (Lerdal and Gay, 2013). A pragmatic approach to age and fatigue is that younger stroke survivors have higher expectations of returning to work that may result in higher reports of fatigue (Naess and

Nyland, 2013). Despite the varied results with regards to prevalence, age explains very little of the variance in fatigue in numerous studies, suggesting that PSF is a direct result of stroke as opposed to a general decline in energy levels with increasing age.

PSF appears to be more frequent in female stroke survivors, however this association is not consistently reported in the stroke population (Choi-Kwon et al., 2005; Dahl et al., 2020; Glader et al., 2002; Ingles et al., 1999; Mead et al., 2011; Schepers et al., 2006). A higher prevalence of fatigue in females has previously been reported in the general population, which might explain the difference in fatigue levels between the two sexes (Loge et al., 1998). Another possible explanation for the observed difference in fatigue levels between the two sexes, is that perception and expression of fatigue in males and females may be different. Female stroke survivors display a greater variability when expressing their fatigue symptoms than male stroke survivors (Falconer et al., 2010).

1.6.3 Stroke type and lesion location

To identify potential stroke resultant factors that might lead to PSF, one needs to consider the direct tissue damage. There is no reported difference in the incidence of PSF between haemorrhagic and ischaemic stroke (Schepers et al., 2006). However, it appears that stroke survivors with large vessel stroke experience a higher severity of fatigue than stroke survivors with small vessel involvement (Chestnut, 2011). This is also true when comparing strokes with transient ischaemic attacks (Winward et al., 2009). The relationship between lesion location and PSF remains controversial. The general consensus is that lesion location does not determine whether or not one will develop symptoms of fatigue; however, some studies suggest there may be a higher incidence of fatigue in subcortical strokes when compared with cortical strokes. Subcortical strokes may be further broadly classified as basal ganglia and cerebellar strokes, with basal ganglia strokes more likely to give rise to fatigue possibly due to disturbances in the limbic–motor

integration networks (Chaudhuri and Behan, 2000; Tang et al., 2010). The limbic-motor integration networks involving the sensorimotor cortices, the anterior cingulate cortex (ACC), the anterior insula and the dorsolateral prefrontal cortex (DLPFC) have been implicated in the development of fatigue like symptoms such as exhaustion as well as the experience of these symptoms (Müller and Apps, 2019). There is not enough information available about detailed distribution of cortical lesions and the incidence of fatigue; however, the lack of association between lesion location and fatigue favours the hypothesis that a distributed network of brain regions across different vascular territories mediates PSF. One such potential network is the attentional network. Any lesion to attention networks could result in fatigue, as poor attention may be a key element of high effort, a feature of fatigue, as described later in the thesis. In fact, posterior cerebral artery strokes resulting in thalamic and brainstem lesions have previously been associated with high levels of fatigue. Focusing on network level disturbances rather than specific lesion locations might provide more insight into the cause of pathological fatigue.

1.6.4 Affective symptoms

PSF may arise as either a primary or secondary phenomenon. PSF as a primary phenomenon is considered part of the underlying condition and emerges independently of other comorbidities. Secondary causes of PSF include medications, physical deconditioning, and other affective symptoms such as depression, anxiety, apathy, pain and sleep disturbances. Similarly to PSF, the majority of affective symptoms result in a reduction in initiation of voluntary activities and can have a negative impact on quality of life. Although there may be clinical overlap and interactions between these affective symptoms and fatigue, they are distinct phenomena and should be addressed independently. Therefore, a comprehensive evaluation of the frequency, severity and

impact of fatigue mentioned previously, should also include the assessment of the aforementioned clinically related factors.

1.6.4.1 Post-Stroke Fatigue and Depression

Depression is defined as depressed mood or anhedonia (loss of interest or pleasure) for a period of at least two weeks. For a definitive diagnosis of depression, depressed mood must be accompanied by a persistent presence of at least four of the following, substantial weight loss or gain, sleep disturbances, psychomotor agitation or retardation, fatigue, worthlessness or inappropriate guilt, reduced concentration and indecisiveness (Association, 2013). Given that the presence of fatigue constitutes one of the many components for the diagnosis of depression it is perhaps not surprising that of all affective symptoms after stroke, post-stroke depression (PSD) is widely recognised as one of the most critical concomitant symptoms associated with PSF. The close association between PSF and PSD has been highlighted in a number of studies with a higher severity of PSF in stroke survivors with a confirmed diagnosis of PSD (Cumming et al., 2016).

This makes it difficult to differentiate between them as independent conditions and has led to the mistaken belief that PSF is a secondary symptom to PSD. Although there may be overlap between PSF and PSD, PSF can also occur in the absence of depression or depression related symptoms. In fact, depression has been shown to be independent of fatigue with only 29% - 38% of stroke survivors with a high severity of fatigue having elevated depression scores (Kjeverud et al., 2020). Recent work has also shown that almost every stroke survivor with PSD reports fatigue but not all with PSF have depression (Kjeverud et al., 2020; van der Werf et al., 2001). This dissociation between depression and fatigue has also been highlighted in other neurological disorders such as multiple sclerosis and Parkinson's disease. However, the strongest evidence for PSF being independent of PSD comes from the lack of effect of anti-depressants on fatigue, with

some making fatigue worse. Commonly used anti-depressants such as fluoxetine, duloxetine, citalopram and sertraline have no significant effect on PSF (Choi-Kwon et al., 2007; Karaiskos et al., 2012).

1.6.4.2 Post-Stroke Fatigue and Apathy

Apathy is a motivational disorder with diminished goal-directed behaviour and cognition. The diagnostic criteria for apathy include persistent diminished motivation for at least four weeks together with two other symptoms from reduced goal-directed behaviour; goal-directed cognitive activity; emotional instability; and functional impairments (Robert et al., 2009). Apathy has phenomenological overlap with depression, and similarly to depression, can be diagnosed by an external observer. This can make the diagnosis of apathy difficult in many situations. Despite the overlap with depression, apathy has distinct biological correlates, clinical course, and treatment. Apathy has a prevalence of approximately 25% post stroke and co-occurs with depression in approximately 40% of stroke survivors (van Dalen et al., 2013; Vlachos et al., 2021). Despite the overlap between apathy and depression and the subsequent overlap between depression and fatigue, apathy and fatigue do not appear to be associated with each other (Douven et al., 2017). Despite the fact that both apathy and fatigue share the same symptom of reduced daily activity, apathy is not characterised by the feeling of exhaustion that is the hallmark of pathological fatigue (Ang et al., 2017).

1.6.4.3 Post-Stroke Fatigue and Pain

Pain, like fatigue, until recently, has been a neglected issue after stroke. The onset of pain is often several months after the stroke and is often categorized into three distinct classes, central post-stroke pain, nociceptive pain mainly in the shoulder and/or arm, and headache. Similarly to fatigue, pain is a subjective experience and has a prevalence ranging from 20% to 50% in stroke survivors. There is an association between pain and fatigue,

with 20% of stroke survivors with PSF also reporting chronic pain (Appelros, 2006). Pain appears to be also related to depression and along with fatigue form a cluster of symptoms that is present in approximately 10% of stroke survivors (Naess et al., 2012a). The relationship between pain and fatigue, and whether pain is involved in the persistence of fatigue over time in certain cases is yet to be explored fully.

1.6.4.4 Post-Stroke Fatigue and Anxiety

Anxiety is defined as anxiety symptoms that are out of proportion to the actual threat or danger presented in a given situation that persist for at least 6 months. The anxiety symptoms must also be accompanied by at least three other symptoms from feeling wound-up, tense or restless; fatigue; difficulty concentrating; irritability; increased muscle tension; and sleep disturbances. The presence of persistent anxiety after stroke ranges from 38% to 76% (Hackett et al., 2014). There is a trend towards an association between PSF and anxiety, but the association is weaker after accounting for the presence of depressive symptoms (Sanner Beauchamp et al., 2020). Anxiety is more closely related to PSD than to PSF, however the association between PSF and anxiety needs to be evaluated further (Barker-Collo, 2007; Campbell Burton et al., 2013).

1.6.4.5 Post-Stroke Fatigue and Sleep Disturbances

Sleep disturbances are common after stroke and approximately 50% of stroke survivors complain of changes to their sleeping patterns. These changes include longer sleeping hours at night, sleep apnoea, poor sleep quality, insomnia and daytime drowsiness (Hermann and Bassetti, 2009). It is perhaps not surprising then that there is a significant overlap between PSF and sleep disturbances with anywhere between 33% and 62% of stroke survivors with PSF reporting sleep problems (Schepers et al., 2006). Similarly to PSD, a key distinction between PSF and sleep disturbances lies in the lack of effect of wakefulness drugs on fatigue in all stroke survivors suffering from fatigue. Studies treating

PSF as a secondary symptom to sleep disturbances have shown no effect of modafinil, a wakefulness promoting agent, on PSF (Brioschi et al., 2009), while others show an improvement in PSF with modafinil (Bajorek et al., 2020; Bivard et al., 2017). Whether the improvement in PSF is a result of treating underlying sleep disturbances or is directly targeting fatigue as a primary symptom remains unclear.

1.6.5 Post-Stroke Fatigue and cognitive and physical impairment

A number of studies have examined the association between PSF and cognitive impairment. Cognitive impairment is seen in many stroke survivors and include impairments in memory, attention, concentration, mental speed, cognitive control, language, visual perception, and executive function. However, the relationship between cognitive impairment and PSF remains unclear (Lagogianni et al., 2016). The majority of the studies looking into the association between PSF and cognitive impairment have all been correlational, with a systematic review of the literature showing a non-significant correlation between the two. However, in the majority of the cases, the tools used to assess cognition are not suitable to be used in stroke survivors and the fatigue questionnaires used to quantify fatigue do not capture the cognitive components of fatigue (Cumming et al., 2013). In order to draw valid conclusions, studies using more appropriate measures of fatigue and cognition need to be carried out. Some studies however, have found a significant correlation between PSF and attention as well as speed of information processing (Appelros, 2006; Hubacher et al., 2012; Radman et al., 2012; Winkens et al., 2009).

Physical deconditioning is another common sequela after stroke and is believed to trigger PSF. Reduced physical activity in the early stages following a stroke results in physical deconditioning and subsequently in exertional fatigue. This results in avoidance of physical activity, further deconditioning and the development of persistent fatigue (Lewis

et al., 2011). A recent systematic review however failed to find an association between fatigue and any other measures of physical activity. The association between PSF and residual disability following a stroke is well established with a higher incidence in stroke survivors with greater disability, particularly stroke survivors with poorer lower limb function. The tests commonly used to identify physical disability are normally questionnaire-based scores of activities of daily living such as Barthel index, Rankin scale and National Institute of Health Stroke Scale, as well laboratory-based tasks to measure motor function such as action research arm test, nine-hole peg test, grip strength and the Fugl-Meyer scale. These measures assess different aspects of motor function from manual dexterity, grip strength to gross motor functions and can therefore identify motor limitations relevant to daily life. Physical disability following a stroke is associated with a reduction in muscle strength due to a failure of the central nervous system to drive the peripheral machinery, the muscles. This reduction in muscle strength leads to an increase in the effort demand to perform voluntary activities and could therefore contribute to the development of PSF (Hubacher et al., 2012; Lerdal et al., 2012). However, it is important to note that PSF is also present in stroke survivors that make a full neurological and neuropsychological recovery. In those patients, PSF may be the only persisting sequela and severely limits day to day life. It is highly likely therefore that fatigue associated with increased physical efforts due to severe neurological deficits is a different construct in itself. There is an objectively measured performance deficit and may therefore be more closely related to physiological peripheral fatigue mentioned previously. This is different to the subjective experience of fatigue in the absence of objectively measured performance deficits seen in stroke survivors with no neurological deficits.

1.7 Mechanism of Post-Stroke Fatigue

Fatigue that persists for months and years after stroke is highly debilitating and significantly affects the quality of life of stroke survivors. To develop successful treatments and interventions for PSF, one must first develop a mechanistic understanding that underlies the symptom of fatigue. One potential mechanism of PSF is that inflammation, the commonest cause of fatigue in the acute stage of stroke recovery, results in altered neurotransmission and neuromodulation which sets in motion a series of changes that include alterations in sensorimotor processing that underlie the perception of effort. Failure of homeostatic mechanisms to reverse these alterations results in the persistent experience of high effort and subsequently in the self-reported symptom of fatigue (figure 1.2).

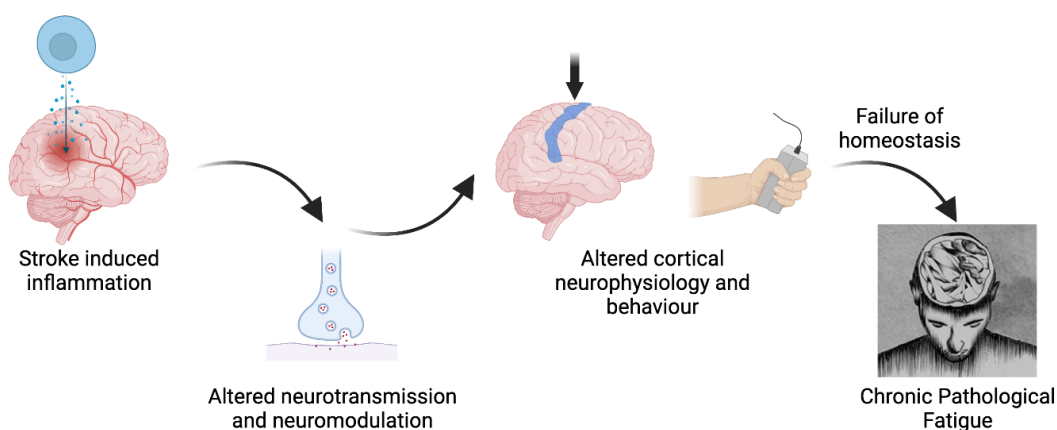


Figure 1.2 – Mechanism of Post-Stroke Fatigue: The proposed mechanism of PSF, where stroke induced inflammation results in changes in neurotransmission, neuromodulation, cortical neurophysiology and behaviour and failure of reversal of these changes results in chronic pathological fatigue¹

¹The animation is a result of collaboration, which I was involved in, between scientists, artists and stroke survivors titled “Experiencing Fatigue”. The aim of the project was to make visible the invisible condition of PSF with the hope of informing scientific research and increasing awareness of the physical and emotional challenges associated with fatigue. This was achieved through a series of workshops in which stroke survivors explored the multi-sensory nature of fatigue and expressed it via metaphors, narrative and various artistic media. Credit to Sofie Layton and Babis Alexiadis for producing the animation.

1.7.1 Inflammation and Post-Stroke Fatigue

A stroke results in the death of the affected and surrounding brain tissue as the metabolic demands of the cells are not met. Stroke causes hypoxia, lack of oxygen, and lack of glucose to the affected brain area and therefore hinders adenosine triphosphate (ATP) production. ATP is essential for the normal functioning of the cells and a depletion of ATP results in cell damage and eventually cell death. Dead or dying cells release molecules called danger associated molecular patterns (DAMPs). These molecules are recognised by pattern recognition Toll-like receptors (TLR) located on the surface of microglia. Microglia are cells found within the central nervous system and form an essential component of the innate immunity in the brain (Kaur and Ling, 2009). Upon binding of DAMP to TLR, the DAMP-TLR complex initiates a cascade of events known as the NF- κ B signalling cascade. This cascade initiates the synthesis and secretion of interleukin1 β (IL-1 β) into the extracellular space of the cells (Yao et al., 2013b, 2013a). When IL-1 β binds to IL-1 receptors located on adjacent cells it induces its own synthesis as well as that of other inflammatory cytokines, chemokines and proteases. These include IL-6, tumor-necrosis factor alpha (TNF- α), nitric acid (NO) and reactive oxygen species (Moskowitz et al., 2010; Rothwell et al., 1996). Brain injury and the breakdown of the blood brain barrier, as well as the production of cytokines, results in infiltration of peripheral immune cells, such as monocytes, neutrophils and T-lymphocytes, to the affected area. These cells secrete additional inflammatory cytokines that further exacerbate inflammation within the affected area (Shichita et al., 2012). The inflammatory response can affect the brain in a number of ways. Firstly, pro-inflammatory cytokines located within the brain influence the synthesis and activity of monoamine neurotransmitters such as serotonin, dopamine and noradrenaline. They do this via several mechanisms. These include the synthesis, packaging into micro-vesicles, release

and reuptake of these neurotransmitters (Dantzer et al., 2014). Dysregulation of monoamine neurotransmitters is closely associated to the development of affective symptoms in the acute stages post-stroke. Secondly, inflammation as a result of a pro-inflammatory cytokines can also induce oxidative stress within the brain which, if anti-inflammatory and anti-oxidant processes are deficient, can lead to neurodegeneration that primarily affects dopaminergic neurones in the meso-striatal and mesolimbic pathway (Hirsch and Hunot, 2009). Thirdly, inflammation can activate the kynurenine (KYN) pathway. Inflammation upregulates the indoleamine 2,3-dioxygenase (IDO) enzyme which is responsible for catalysing the rate limiting step for the production of KYN from tryptophan (TRP) (Fujigaki et al., 2001; Pemberton et al., 1997). Activation of IDO can be measured by increased plasma/serum KYN levels relative to TRP. TRP is essential for the synthesis of serotonin. KYN has a dual role. It can act as a ligand of the aryl hydrocarbon receptor resulting in the production of regulatory T cells or it can be further metabolised. KYN is further metabolised into Kynurenic acid (KA), which has a neuroprotective role, or into 3-hydroxykynurenine and quinolinic acid, which have a neurotoxic role. In the presence of activated microglia and ongoing inflammation, the formation of neurotoxic KYN metabolites is favoured to the detriment of neuroprotective KYN metabolites as it results in the extracellular release of glutamate. Therefore, prolonged inflammation also affects glutamate production, release and metabolism.

The inflammatory response does not remain local to the central nervous system but propagates from the brain to the periphery and vice versa. Damage to the CNS activates resident microglia and astrocytes which transmit injury signals that activate endothelial cells resulting in the release of microvesicles into the circulation which initiate the acute phase response. The primary purpose of the acute phase response by the liver, the principle organ involved in this response, is considered to be to effect a return to

homeostasis, by removing inflammatory stimuli, attenuating local inflammation, and promoting tissue repair and regeneration (Anthony and Couch, 2014). In acute stroke, elevated levels of IL-1 β , IL-1 α , TNF- α , IL-6, IL-8, soluble TNF receptor 1, IL-10, IL-1ra and C-reactive protein (CRP) are seen in the circulation, liver, gut, bone marrow and spleen (Brambilla et al., 2013; Denes et al., 2011; Meisel et al., 2005). Whether this global inflammatory response both within the central nervous system and the periphery is deleterious or beneficial to brain recovery is still a matter of discussion (Kriz and Lalancette-Hébert, 2009; Wang et al., 2007). In the short-term, cytokine induced sickness behaviour is thought to be advantageous for survival following infection or tissue damage because it results in withdrawal from activity, allowing for rest and recovery as mentioned previously (Dantzer and Kelley, 2007). However, prolonged production of inflammatory cytokines does not appear to serve any evolutionary advantage and is associated with the development of chronic affective symptoms such as fatigue.

In some stroke survivors, inflammation persists for months and in some instances up to two years or more following a stroke. Stroke survivors have significantly higher serum levels of IL-1 β , IL-1ra, IL-6, IL-8, IL-10, IL-12 and IL-18 than healthy controls 72 hours post-stroke (Ormstad et al., 2011). They also have higher serum levels of CRP, a biomarker of inflammation usually associated with poorer outcomes (VanGilder et al., 2014). From the above-mentioned inflammatory markers, there appears to be a significant positive association between levels of IL-1 β in the acute stage following a stroke and the severity of fatigue 6 months post-stroke. There is also a significant negative association between IL-1ra and IL-9 levels and the severity of fatigue 12 months post-stroke (Ormstad et al., 2011). The role of IL-1 β and fatigue has been further examined in both animal and genetic studies. Animal models of stroke show that rats exhibit sickness-like behaviour including fatigue-like behaviour (Kunze et al., 2014) while single nucleotide

polymorphisms in the gene coding for the IL-1 receptor were associated with high levels of fatigue (Becker et al., 2015). Activation of the KYN pathway and different plasma levels of neuroprotective and neurotoxic KYN metabolites could play a role in post-stroke sequela (Brouns et al., 2010; Darlington et al., 2007; Mo et al., 2014; Ormstad et al., 2013). In fact, TRP levels are significantly lower in stroke survivors with high severity of fatigue compared to those with low severity of fatigue at 12 months post-stroke. In addition, serum levels of KA (the neuroprotective metabolite of KYN) are also significantly higher in those with higher severity of fatigue at 18 months post-stroke (Ormstad et al., 2014). Interestingly, there is no association between the KYN/TRP ratio and fatigue severity in the acute stages post-stroke (Bensimon et al., 2014).

Fatigue is a common symptom in several neurological diseases in which inflammation is a determining feature. These include Parkinson's disease, traumatic brain injury and multiple sclerosis (Jassam et al., 2017; Krupp, 2006; Scalzo et al., 2009). In addition, fatigue is also common among otherwise healthy individuals who suffer infectious illness (Harrison et al., 2009). This evidence, when taken together with what has previously been mentioned in stroke survivors, suggests that inflammatory cytokines contribute to the development of fatigue. In the case of stroke, this association between inflammation and fatigue holds true in the acute stage but does not explain the chronic nature of fatigue that persists for years in the majority of stroke survivors. An interesting finding across all studies investigating pro-inflammatory cytokines and fatigue was a lack of correlation between post-stroke depression and inflammatory markers. This lends further support to the idea that depression and fatigue are independent phenomena. Animal studies show that exposure to pro-inflammatory cytokines have long-lasting effects on behaviour (Ming et al., 2015). The precise mechanisms by which cytokines and subsequent inflammation result in pathological fatigue remain unclear. This is important because a theory of fatigue based on molecular changes does not explain how the clinical symptoms

associated with pathological fatigue arise. A circuit-level description however, based on molecular changes, is the closest one can get to describe behavioural changes and the subjective experience of fatigue. As previously mentioned, inflammation impacts neurotransmitters such as dopamine, serotonin and glutamate, which are essential for the normal function of the central nervous system. Some studies indicate a direct effect of pro-inflammatory cytokines on cortical neuronal excitability by inhibiting voltage-gated sodium currents in cortical neurones (Zhou et al., 2011). Could inflammation result in changes in neurophysiology, namely alterations in sensorimotor processing, and subsequent behaviour and perception, that might explain persistent pathological fatigue?

1.7.2 Neurophysiology and behaviour in Post-Stroke Fatigue

A challenging aspect of investigating persistent fatigue is the difficulty in differentiating the causes from the effects. Persistent symptoms such as fatigue result in significant neurophysiological and behavioural changes, which may then further exacerbate fatigue resulting in a vicious cycle. Identifying the mechanism that first establishes persistent fatigue is therefore not straightforward. As previously mentioned, inflammation has been shown to inhibit voltage-gated sodium currents in cortical neurones and is closely associated with the dysregulation of several neurotransmitters. These both impact measures of cortical neurophysiology when assessed using non-invasive brain stimulation (NIBS) techniques such as transcranial magnetic stimulation (TMS). Studies have examined the neurophysiological and behavioural perturbations seen in PSF with the aim of providing insight into the direction of causality between physiology, behaviour and fatigue.

1.7.2.1 Assessing Neurophysiology

In humans, TMS can non-invasively assess changes in excitability in the cortico-spinal system (Barker et al., 1985). TMS involves passing a current through one or more coils

made of wire to generate a magnetic field based on the principles of electromagnetic induction. The coil is placed on the surface of the scalp and induces a magnetic field pulse perpendicular to its plane. This magnetic field penetrates the skin, scalp and skull before it reaches the brain. The magnetic field is not impeded by the scalp and is therefore a largely painless technique that is well tolerated by most subjects and patients (Rossi et al., 2009). Upon reaching the brain, the magnetic field pulse induces an electric current perpendicular to the magnetic field, parallel to the plane of the coil. The magnetic field is typically 1-2.5 Tesla, has a rise time of approximately 50-200 μ s, and decays rapidly over distance (Sauvé and Crowther, 2014). The fast decay time means that TMS is mostly effective in stimulating superficial layers of cortical tissue. Coils can have different shapes that determine their power as well as their focality. The most commonly used magnetic coil and the one most relevant to this thesis is the figure-of-eight coil. The figure-of-eight coil consists of two round components, producing maximal current at the intersection of the two round components, making it more focal than other magnetic coils. The electric field and associated current density induced in the brain acts primarily on axons and elicits action potentials in neurones of the targeted brain region. TMS can therefore target various cortical areas. The most common cortical area targeted by TMS is the primary motor cortex (M1). At appropriate stimulation intensities, stimulating the M1 results in a clearly observable and recordable response in the electromyography (EMG) of the target muscle known as the motor evoked potential (MEP). TMS stimulation intensities resulting in MEPs above a pre-defined amplitude are known as suprathreshold whereas stimulation intensities that do not result in an MEP of a specific amplitude are known as subthreshold. MEPs are most readily induced in intrinsic hand muscles (figure 1.3).

The MEP is a compound signal that consists of a series of descending corticospinal volleys that summate at the spinal level (Di Lazzaro and Rothwell, 2014). Suprathreshold TMS evokes a series of descending corticospinal volleys that can be directly recorded via

epidural electrodes placed over high cervical cord. The earliest wave that originates from direct activation of the axons of fast-conducting pyramidal tract neurones and is hence known as the direct (D-) wave and is followed by several I-waves (1 ms apart from the D-wave and each other) that reflect indirect depolarization of axons comprised of excitatory and inhibitory neurons (Ziemann and Rothwell, 2000). I-waves can have both monosynaptic (early I-waves) and polysynaptic (late I-waves) projections to the output corticospinal neurons (Ziemann and Rothwell, 2000). Polysynaptic projections include connections from other brain regions such as the premotor cortex, supplementary motor area (SMA), cingulate motor areas, basal ganglia and cerebellum. In other words, the MEP is a global readout that reflects the intrinsic excitability of corticospinal cells, including the summation of distinct neural inputs that project to the corticospinal tract and the activity of spinal circuits that contributes to the overall signal.

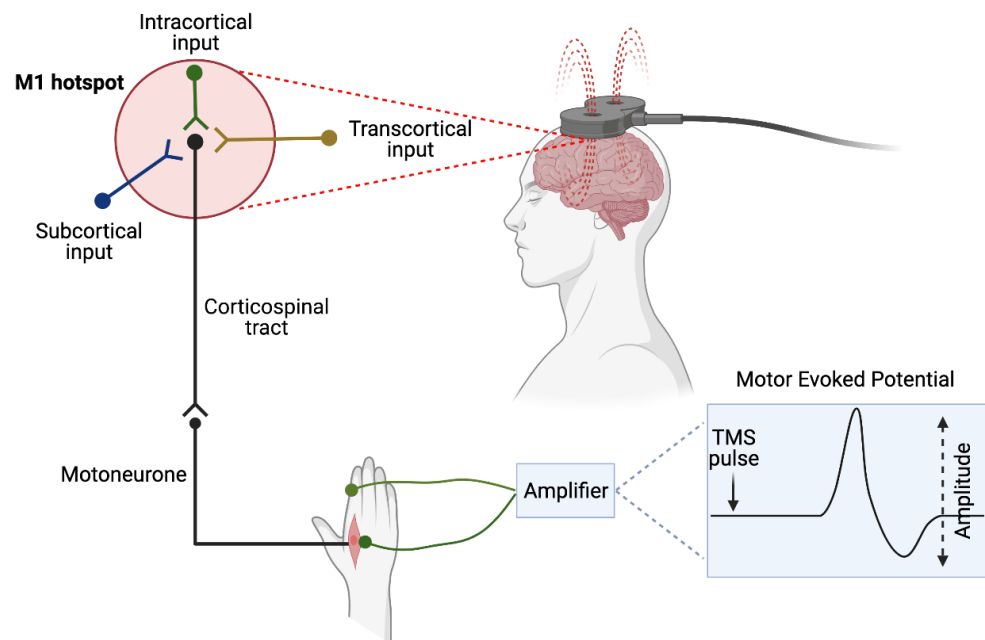


Figure 1.3 – Transcranial Magnetic Stimulation: The mechanism by which TMS results in a motor evoked potential.

In summary, descending volleys are influenced by multiple intra-cortical excitatory and inhibitory neurones with axons of varying size, location, orientation and functional properties, as well as various spinal mechanisms, that can be ‘selectively’ targeted using specific stimulation protocols.

1.7.2.2 Cortical excitability

A number of TMS measures of the M1 assessed using various stimulation protocols can evaluate different aspects of cortical excitability. Condition specific changes in MEP amplitude, and therefore cortical excitability, are useful in understanding changes in brain physiology and how they might relate to specific disease states, subsequent behaviour and perception.

One commonly used measure of cortical excitability is the motor threshold. Measures of motor threshold can be obtained in two different brain states, when the target muscle is at rest or when the target muscle is active and are termed resting motor threshold (RMT) and active motor threshold (AMT) respectively. RMT is usually defined as the minimum intensity of stimulation required, given as a percentage of maximum magnetic stimulator output, required to elicit at least a 50 μ V MEP in the resting target muscle in 5 out of 10 consecutive trials. AMT is usually defined as the minimum intensity of stimulation required, given as a percentage of maximum magnetic stimulator output, required to elicit at least a 200 μ V in 5 out of 10 consecutive trials during an isometric contraction of ~10–20% MVC in the target muscle. The motor threshold tends to be lower in the voluntarily contracting target muscle than in the resting muscle, and so AMT is usually lower than RMT by about 10% of maximum stimulator output. Motor threshold reflects the excitability of corticospinal projections to the target muscle with the lowest excitation threshold. This reflects the influence of mainly I_1 waves (Di Lazzaro and Ziemann, 2013, p. 200). Since motor threshold can be influenced by drugs affecting sodium and calcium

channels, it is thought to reflect membrane excitability. Voltage-gated sodium channel blockers, tend to increase motor threshold, making the corticospinal system less excitable (Ziemann, 2013).

The average resting and active motor thresholds in the general population are approximately 50% and 40% of maximum stimulator output respectively. However, these values are highly variable in the general population with a number of different factors contributing to this variability (Wassermann, 2002). Structural factors such as scalp thickness can influence motor thresholds (List et al., 2013; Stokes et al., 2007, p. 201). As the magnetic field decays quickly over time, increasing the coil to cortical surface distance will affect the strength of the magnetic field and hence the current density induced in the underlying brain tissue. Other structural factors that affect motor thresholds include white matter microstructure, cortical thickness and cortical sulcation. Physiological factors also contribute to the variability in motor thresholds. These include the excitability of axon membranes as well as synaptic excitability, with pharmac-TMS studies showing that drugs targeted at blocking ion channels or synaptic neurotransmitters significantly alter motor thresholds (Ziemann, 2004).

The use and interpretation of cortical excitability varies significantly. Cortical excitability has been used as a surrogate marker for disease-related impairment in the quality of the motor output. In pathological conditions such as stroke, if cortical excitability reflects the degree of spared descending cortico-spinal projections, one would expect cortical excitability to closely track the degree of impairment. This has shown to be true in a number of studies (Ward et al., 2007, 2006). Cortical excitability can also reflect the state of the motor cortex at the time of stimulation. Different experimental manipulations and disease states are known to change the state of the motor cortex which is then reflected in changes in cortical excitability. Cortical excitability has been directly correlated to a

number of motor behaviours such as force, speed and precision of movements (Pearce and Kidgell, 2009; Perez and Cohen, 2009a; Uehara et al., 2011). Excitability changes might not reflect the quality and integrity of the motor output but given the strong connections between M1 and other cortical and subcortical regions, might reflect the input into M1. A number of cognitive processes such as attention, action planning and selection, decision making have been shown to affect cortical excitability (Bestmann and Krakauer, 2015). Therefore, changes in cortical excitability might reflect changes in corticospinal tract integrity, changes within M1, and top-down influences on M1 from other brain regions.

1.7.2.3 Altering neurophysiology and cortical excitability

As well as using NIBS techniques to measure cortico-spinal excitability, these techniques can also be used to induce long-lasting changes in excitability. The use of electrical stimulation to induce changes within the brain goes back as far as the Roman Empire, in which live torpedo fish were placed over the scalp to deliver strong electric currents to relieve headaches (Largus, 2020). There have also been reports of the use of electric stimulation from live electric catfish in the treatment of epilepsy in the 11th century. In the 18th century, with the introduction of the electric battery, the use of electrical stimulation to induce physiological changes became more popular (Zago et al., 2008). Electrical stimulation to the scalp was used at the time for the treatment of mental disorders. In the middle of the 20th century, transcranial electrical stimulation was shown to induce changes in brain activity and increase excitability in animals and at the turn of the century, the same results were shown in humans (Bindman et al., 1964; Nitsche and Paulus, 2000).

A commonly used method of applying transcranial electrical stimulation is known as transcranial direct current stimulation (tDCS). TDCS is a safe technique and has been

tested in thousands of subjects, both healthy and clinical populations to date. A number of studies have looked into the safety of tDCS and report that the most common side effects of tDCS include mild tingling sensations, itching sensation, headache, moderate fatigue and a metallic taste in the mouth (Poreisz et al., 2007). Modern tDCS involves the use of two (or more) electrodes, at least one of which needs to be placed on the head. The electrodes include at least one anode (positively charged electrode) and one cathode (negatively charged electrode). The electrodes are connected to a battery which applies a current, usually ranging from 1-2 mA, that flows between the anode and the cathode. The electrodes are often coated with a conductive paste or NaCl solution when placed on the scalp to allow the current to flow through the scalp. The stimulation current used in tDCS is not sufficient to cause the depolarisation of the neuronal membrane and cause neuronal firing. Rather, tDCS modulates spontaneous neuronal network activity via a polarity-dependent polarization of the resting membrane potential. This accounts for the immediate effects of tDCS, however longer-lasting effects have also been previously reported. There are a number of mechanisms that can explain the long-lasting effects of tDCS including change in synaptic strength implicating both NMDA and GABAergic synaptic connections, modulation of intracortical and corticospinal neurones as well as by inducing prolonged neurochemical changes implicating various neurotransmitters within the central nervous system (Nitsche et al., 2005; Stagg et al., 2009). The abovementioned mechanisms directly affect the area of the brain being stimulated, and tDCS can also have indirect effects on brain regions remote to the area being stimulated via alterations in connectivity between cortical and subcortical areas as well as alterations in spontaneous neuronal oscillations (Lang et al., 2005).

The effects of tDCS vary widely and are dependent on several different parameters. Such factors include the positioning of electrodes, the intensity and duration of stimulation, the number of sessions per day and the interval between sessions. Different amounts of

current can be delivered to the targeted brain region by modifying these parameters and can therefore induce diverse physiological effects. When stimulating motor regions, one electrode is often placed over the M1 with the second electrode (often referred to as the reference electrode) placed over the contralateral supra-orbital ridge (SOR) or extraencephalically, such as the shoulder. Placing the anode over the M1 and using the cathode as the reference, called anodal tDCS, tends to enhance cortical activity and increase cortical excitability in the M1 while cathodal tDCS, where the cathode is placed over the M1 and the anode is used as the reference, has the opposite effect and tends to decrease cortical excitability.

The intensity of stimulation and the size of electrodes used will determine the current density that reaches the brain tissue and influence the effects of tDCS. Using a stimulation intensity of 1-2 mA and the most common electrodes with a size ranging from 25-35 mm², should result in a current density ranging from 0.28-0.80 A/m². However, the current that effectively reaches the neuronal tissue of the brain is influenced by other anatomical and physiological factors. Anatomical factors include skin resistance, skull resistance, the resistance of brain tissue, brain lesions and skull defects, while physiological factors include baseline cortical excitability. Therefore, controlling for such individual factors and ensuring that the same current density reaches the underlying neuronal tissue is important when carrying out tDCS studies to reduce the variability in the effects observed (Evans et al., 2020). The duration of stimulation impacts the duration of after-effects reported after tDCS. Short applications, typically lasting a few seconds to a few minutes, of tDCS result in excitability changes during the period of stimulation with no long-term effects. For clinical purposes such effects are often not clinically useful and longer-lasting effects are crucial. Increasing the duration of stimulation beyond 10 minutes, can elicit prolonged after-effects, which are sustained for over an hour (Nitsche

et al., 2008). The exact duration of after-effects of tDCS depends on the brain region being targeted and the type of variable being assessed.

TDCS provides a safe, cost-effective, and easy to administer method to induce long-lasting physiological changes in different locations within the human brain. It is therefore not surprising that the therapeutical application of tDCS has been widely explored in a range of clinical populations ranging from physical disability after stroke, to chronic pain, PD and other movement disorders, to epilepsy, depression, schizophrenia and other psychiatric disorders, MS and chronic pathological fatigue.

1.7.2.4 Cortical excitability and Post-Stroke Fatigue

Given the association between inflammation and PSF and the subsequent impact of inflammation on ion channels which are essential for the normal functioning of brain neurophysiology, one would expect to see changes in neurophysiology in PSF. In fact, neurophysiological changes such as reduced cortical excitability have previously been demonstrated in MS fatigue (Liepert et al., 2005). It is important to reiterate that MS also has a strong inflammatory component and like stroke, persistent fatigue is not associated to the degree of inflammation in this condition. Cortical excitability is in fact lower in stroke survivors with high severity of fatigue, reflected by higher RMTs assessed using TMS (Annapoorna Kuppuswamy et al., 2015). The association between cortical excitability does not reflect changes in corticospinal tract integrity given that the investigated cohort of stroke survivors had minimal physical impairment. Therefore, lower cortical excitability in PSF is due to changes within M1 or due to top-down influences on M1 from other brain regions. What are the behavioural and perceptual consequences of low cortical excitability and how might this give rise to the subjective experience of fatigue?

1.7.2.5 Behaviour and perception in Post-Stroke Fatigue

Cortical excitability is intrinsically linked to behaviour and perception. Whether changes in cortical excitability are at all causal to certain behaviours, for example, movement speeds, or just an epiphenomenon that can suitably be read-out from TMS over M1 remains unclear. Stroke survivors with high severity of fatigue have a significant reduction in self-selected ballistic movement speeds on the hemiparetic side when compared to stroke survivors with low severity or no fatigue (A. Kuppuswamy et al., 2015). These differences in movement speeds are present despite minimal motor functional deficits. It is unclear whether those with high fatigue were capable of achieving higher movement speeds and simply chose to move slower than their maximum speed. Why might those with high fatigue choose to move slower? Those with slower self-selected movement speeds also perceived the upper limb on the hemiparetic side to be heavier (Kuppuswamy et al., 2016). Could the perception of limb heaviness result in slower movement speeds? The perception of limb heaviness is suggestive of a central sensory processing problem. The perception of limb heaviness is often thought of as a manifestation of muscle weakness, with peripheral muscle weakness resulting in an overestimation of weight perception (Brodie and Ross, 1984). Perceived heaviness of an object arises as a result of central processing of re-afferent activity from muscle spindles in the contracting muscle. With repeated muscle contractions, the peripheral muscle weakens resulting in the recruitment of more muscle fibres to maintain muscle force compared to the pre-weakened state. The recruitment of more muscle fibres subsequently results in increased re-afferent activity that is subsequently processed by the central nervous system and the object perceived as being heavier (Luu et al., 2011). Given that the investigated cohort of stroke survivors, as mentioned previously, had minimal physical impairment and therefore no or little muscle weakness is suggestive that the perception of limb heaviness

seen in PSF is due to alterations of central processing of normal re-afferent activity from the peripheral musculature.

When taking into consideration all the factors described so far in this introduction: poor attention, slower processing speed, reduced self-selected movement speed, perceived limb heaviness and lower cortical excitability, in the absence of physical impairment and affective symptoms, and irrespective of lesion location and other biological factors, one can start to propose a model for chronic, persistent fatigue.

1.7.3 Perceived Effort

How might the above deficits then give rise to fatigue in the absence of sustained exertion, as is the case in PSF? To answer this, one must first understand how sustained exertion gives rise to fatigue. In what has previously been described as physiological fatigue, sustained exertion results in a decrease in task performance and the subjective experience of fatigue. However, before a decrease in performance is observed, subjects often report the need for higher effort to maintain task performance and at task failure, the inability to exert the required effort to perform the task (Barry and Enoka, 2007). It is well established that task performance and the subjective experience of fatigue, as well as the experience of effort are not closely associated (Enoka and Duchateau, 2008). In the context of exercise-induced physiological fatigue, the increase in perception of effort during prolonged exercise can be seen in the absence of physiological changes such as loss of muscle strength. Increasing the difficulty of the task at hand results in a faster decrease in performance and an increase in the perception of effort. From the abovementioned, it appears that the notion of higher effort precedes and is inextricably linked to the subjective experience of fatigue, while drop in task performance and task failure can be considered as behavioural consequences of fatigue. It has previously been shown that physically effortful tasks and cognitively effortful tasks induce the same

feeling of fatigue (Marcora et al., 2009; Van Cutsem et al., 2017). Also, performing a cognitively demanding task affects subsequent performance on either a physical or cognitive task and vice versa. The fact that performance in one task affects subsequent behaviour in another task that relies on distinct processes is suggestive that common processes are involved and affected over time. A suitable candidate that might underlie this process is the perception of effort.

Perceived effort has been extensively studied within the motor system, mainly in the context of physiological fatigue. When executing a voluntary movement or performing a motor task, there are a number of computations taking place both within the central nervous system and the periphery. These computations involve signals from brain regions such as the prefrontal cortex, pre-supplementary and supplementary motor areas, the premotor cortex, the primary motor cortex and posterior parietal cortex, as well as signals from the periphery originating from various sensory receptors and the muscles themselves. These computations are not explicitly experienced and what is consciously perceived is a sense of effort assigned to a muscular contraction. In the beginning of the 19th century, Maine de Biran, a French philosopher, argued that the perception of effort associated with voluntary actions is the criterion of self. The perception of effort assigned to a muscle contraction is an important aspect of our subjective experience of volition and contributes to the feeling of conscious will (Frith et al., 2000). Without the subjective experience of effort, there is no feeling of agency or causality. Not all actions are carried out with the conscious feeling of exerting a certain amount of effort, the majority of movements performed on a day-to-day basis are 'automatic' and effortless. However, the perception of effort associated with voluntary movements is always available to consciousness and can be reported if the agent attends to it. Therefore, the perception of effort enters conscious perception and is reported by the agent once a specific threshold is reached. Based on the above, the perception of effort associated with a muscle

contraction and the resulting voluntary movement can be scaled in intensity. This is in line with what Angelo Mosso had described towards the end of the 19th century. Studies have shown that both central and peripheral factors contribute to perceived effort and the property of intensity is determined by selective attention to either central or peripheral factors.

1.7.3.1 Central and peripheral contributions to effort perception

Central and peripheral factors contribute to the sense of effort, force and heaviness. These terms are related in their meaning and are descriptions of the subjective experiences one can experience. The sense of effort, force and heaviness are transformed at the level of the central nervous system to perception, namely the perception of effort. Despite resulting in the same percept, a distinguishing feature of these sensations however is their origin.

Bain, von Helmholtz, Wundt and Lewes were the first to argue that the sense of effort associated with a voluntary muscle contraction does not result from the activity of the muscle alone but also from the neural activity preceding the muscle contraction. This has led to the proposal of the corollary discharge model in which the sense of effort arises from corollary discharges of the central motor command to the peripheral musculature (Marcora, 2009; Pageaux, 2016). In this case, the term corollary discharge is used to describe the internal signals that arise from centrifugal motor commands that influence perception and the central motor command is defined as a discharge pattern within the central nervous system that leads to the excitation of spinal α -motor neurones. Anecdotally, there are reports that support the hypothesis that the sense of effort is centrally generated. An anaesthetised patient waking up from surgery reports an increased sense of heaviness of their limbs when they try to lift them. This is a result of a larger

motor command required to overcome the effect of the circulating muscle relaxant given during surgery, resulting in an increased sense of effort.

There are also many experimental findings supporting the hypothesis that the sense of effort is centrally generated. Electrophysiological studies using electroencephalography (EEG) have examined the effect of the sense of effort prior and during physical tasks on the movement-related cortical potential (MRCP). The MRCP is a slow negative potential that appears over the scalp usually 1-2 seconds before the onset of voluntary movement and is thought to represent excitatory post-synaptic potentials in the apical dendrites of cortical pyramidal neurones. Before movement onset, the MRCP propagates from the bilateral pre-supplementary and supplementary motor area to bilateral premotor cortices and eventually to contralateral premotor and primary motor cortex. The MRCP continues to be evident during movement execution and is thought to reflect activity in the primary motor and sensory cortices as well as the supplementary motor area, premotor cortex, cingulate cortex and the parietal cortex. The MRCP therefore reflects efferent and afferent processes and has therefore been considered as a neural substrate of the corollary discharge (Shibasaki and Hallett, 2006). The amplitude of the MRCP both prior to movement initiation and during movement execution reflects the sense of effort of the subsequent movement (de Morree et al., 2012; Slobounov et al., 2004). Other studies using TMS to reduce activity within M1 shown an increase in perceived effort (Takarada et al., 2014). The increase in perceived effort is not due a decrease in activity in M1 but more likely an increase in activity in areas that input into M1 to compensate for the reduced activity. In fact further studies in which the activity within the supplementary motor area was disrupted show a reduction in the sense of effort associated with the subsequent movements (Zénon et al., 2015a). This result suggests that activity within the SMA might determine the amount of effort perceived. Activity in the SMA has previously been associated with grip force intensity and online disruption of the SMA results in

increased grip force (Spraker et al., 2007; Ward et al., 2007; White et al., 2013). The SMA has direct projections to somatosensory cortex and is suggested to be involved in predicting the sensory consequences of voluntary actions, which will be expanded on in a later section of this thesis (Haggard and Whitford, 2004; Jürgens, 1984). In fact, functional alterations within the SMA have previously been reported in patients complaining of fatigue, possibly by alterations in effort perception (Filippi et al., 2002).

Further studies in patients with partial paralysis or studies in which paralysis is induced experimentally using neuromuscular blockers suggest that the sense of effort associated with lifting a weight and its perceived heaviness are increased, compared to unparalysed conditions (Gandevia and McCloskey, 1977; GANDEVIA and McCLOSKEY, 1977). This is suggestive of a larger motor command required to overcome the paralysis which subsequently results in the increased sense of effort and heaviness. Similar observations are seen in healthy volunteers following fatiguing exercise. Weights supported by fatigued muscles feel heavier than when supported before muscle fatigue is induced (Gandevia and McCloskey, 1978). All these studies support the notion that the sense of effort is centrally generated and is a result of the corollary discharge from the central motor command.

It has also been argued that the perception of effort arises from afferent feedback from the muscles, the heart, and/or lungs. The afferent feedback from the various sensory organs is processed by the brain to generate the perception of effort. Several studies suggest that the perception of effort is significantly altered by manipulating afferent feedback from the muscles. Muscle spindles are one of the main sensory receptors located within the muscles. They contribute to the unconscious, automatic control of posture and locomotion and are the principal kinaesthetic sensors, responsible for the sensation of limb position and movement (Merton, 1964; Proske and Gandevia, 2012). In the absence

of feedback from muscle spindles, the central nervous system would be unable to monitor the progress of movement (Proske, 2006). Therefore, the muscle spindles along with other receptors both within the muscle and periphery, such as Golgi tendon organs and skin receptors, are suitable candidates in giving rise to the perception of effort. In fact disturbing these senses using vibration or following fatiguing exercise has shown to alter the sense of effort and force (Monjo et al., 2018; Savage et al., 2015). Pharmacological studies aimed at blocking the neuromuscular junction show that when a muscle is recovering from paralysis, objects feel lighter than their actual weight (Luu et al., 2011). This is a result of a decrease in discharge activity from the muscle spindles, supporting the hypothesis that peripheral signals contribute to the sensation of effort (Brooks et al., 2013). These results cannot be interpreted by purely a central mechanism and are suggestive of contributions from the periphery to the sense of effort.

Further studies in patients with a large-fibre sensory neuropathy, which have no skin or muscle receptors served by large diameter afferents, show that deafferented patients have an impaired sense of muscular effort and the consequences of active movement (Sanes and Shadmehr, 1995). The impaired sense of effort is attributed to the inability to correlate psychophysical decisions associated with voluntary movement with concomitant muscle activity. These patients however still experience a sense of effort. In fact, deafferented patients showed that a sense of heaviness in a force matching task has a one-to-one relationship with the sense of effort. This is again suggestive of central origins to the sense of effort (Lafargue et al., 2003; Luu et al., 2011). It is important to note that deafferented patients did not report any feelings of fatigue nor awareness as to how much effort they had to exert. Therefore, although there is evidence in support of both central and peripheral contributions to the sense of effort in these patients, it appears that the motor command is mediated by afferent input from the periphery.

When taken together, the above results suggest that both central and peripheral sources of information contribute to the sense of effort, heaviness, and force. Although if appropriately instructed subjects can distinguish between a sense of effort arising centrally and a sense of force arising from the periphery (McCloskey et al., 1974), in everyday activities this information does not always reach conscious awareness. This means that we do not feel that simple tasks of daily living require a high sense of effort or force. Afferent (peripheral origin) and efferent (central origin) information is therefore integrated to give rise to a single percept, the perception of effort, that can reach conscious awareness and be consciously perceived once a certain intensity is reached. Perceived effort is the psychophysical output of the process that integrates afferent and efferent information.

1.7.4 Effort perception, sensory attenuation, and active inference

The active inference framework of sensorimotor control provides a simple framework that integrates efferent and afferent input to explain movement initiation, motor control and perception (Adams et al., 2013a). Attention, the process previously suggested to underlie the property of intensity in the perception of effort, is a fundamental feature of active inference. With that in consideration, the perception of effort may be the perceptual consequence of active inference.

1.7.4.1 Predictive coding and Bayesian inference

The idea that the brain performs statistical inference originates from Hermann von Helmholtz in the 1860s and his studies on vision and optics. He was the first to propose that the brain does not represent sensory images per se, but the causes of those images. As the causes of the images cannot be perceived directly, they must be inferred from sensory information. Sensory information however, both from the external environment as well as from within the internal environment (within the body), is ambiguous with

multiple causes contributing to the sensory information making it difficult to determine the true cause of the sensory data. Therefore, to perceive the brain must be able to infer the most likely causes of its sensory data based on prior experiences. To solve this inverse problem the brain is thought to perform inference using predictive coding (Rao and Ballard, 1999). Within predictive coding frameworks a generative model is used which incorporates prior beliefs about how different causes interact to produce an approximation of what the sensory information should look like if the causes are correct. The process of incorporating prior hypothesis (beliefs in the case of the brain) about probable causes of the data is the basis of Bayesian statistics. Therefore, this Bayesian approach is thought to underlie the basis of predictive coding and enables us to understand and act on the world around us. In fact, there are a number of studies across different sensory modalities that provide evidence in support of the idea that the brain uses Bayesian inference (Kersten et al., 2004; Körding and Wolpert, 2004).

A key component of Bayesian statistics and hence predictive coding frameworks is the ability to formally quantify uncertainty in a noisy and ever-changing world to make near ‘optimal’ inferences. In order to achieve this, prior beliefs about the probability of a given sensory state are combined with the estimates of the likelihood of sensory input given possible states of the world to give rise to an optimal estimation of the state under the current sensory evidence. This optimal estimation of the state under the current sensory evidence is known as the posterior expectation. Both the prior beliefs and likelihood of sensory input are associated with some degree of uncertainty. For example, the sensory input (‘likelihood’) we receive when running in the woods in the dark is more uncertain compared to when running during the day and on the contrary, our model of the world (‘prior’) is more uncertain when entering a completely novel environment, such as space, compared to a familiar environment. Within Bayesian inference, these two sources of information, as well as the posterior expectation, are represented as probability

distributions such that the variance of these distributions gives an estimate of the uncertainty surrounding the mean values. The relative uncertainty (or variance) associated with the prior beliefs and the likelihood of sensory input determines which estimate the posterior distribution will more readily reflect.

Bayesian inference takes advantage of the hierarchical structure of the brain whereby the outputs of one level provide inputs to the level below, which send reciprocal projections back up the cortical hierarchy. This architecture employs empirical Bayes whereby the posterior expectation from one level will form the prior expectation for the level below, providing a better estimate of the true cause of the sensory evidence. Backward projections from one hierarchical level to a lower level convey the top-down predicted sensory state which is compared with the afferent input at each level of the cortical hierarchy to generate a prediction error. Prediction errors represent the mismatch between the predicted sensory state and the actual sensory state. Prediction errors are passed from lower levels of the cortical hierarchy back up to higher levels via reciprocal forward projections. The cells that encode the reciprocal forward projections conveying prediction errors are thought to be superficial pyramidal cells located in the upper layers of the cortex (Feldman and Friston, 2010). This message passing across the different levels of the cortical hierarchy continues until prediction error is minimized, representing how accurately the generative model was able to predict the true cause of the sensory evidence. As mentioned previously, the posterior expectation (prediction error) is associated with a degree of uncertainty which will subsequently influence its impact on higher levels of processing. The uncertainty associated with prediction errors can be modulated by adjusting the gain (or precision) of prediction errors, which reflects how meaningful the prediction error is. To put it more simply, within Bayesian inference, the evidence for a hypothesis is reported by precision-weighted prediction errors.

1.7.4.2 The free energy principle and active inference

Predictive coding frameworks play a fundamental role in explaining how humans perceive stimuli across different sensory modalities both within the internal and external environment. Active inference uses the principles of predictive coding and Bayesian inference to not only explain perception but also to explain sensorimotor control and action within a single framework. Active inference is embedded within the free-energy principle originating from information theory. Under the free-energy principle, any adaptive change made by a biological system must minimize its long-term surprise in order to maintain self-organization and homeostasis, a characteristic feature of all biological systems (Friston, 2010). In the context of Bayesian inference and predictive coding, sensory surprise and prediction error are closely related, and minimizing prediction error subsequently reduces sensory surprise. The brain can minimize prediction error by changing the observed sensory input through action to match the predicted sensory input or by changing the predicted sensory input to match the observed sensory input through perception. The process of minimizing prediction error determines how we perceive and behave in the world around us. The perceptual and motor systems should not be regarded as separate but instead as a single active inference machine that tries to predict its sensory input across all sensory domains.

As previously mentioned, active inference provides a unifying framework that can explain perception and sensorimotor control. The active inference framework posits that the output of the of the motor system does not convey a motor command but instead specifies the predicted sensory state. Therefore, prediction errors occur at any point where top-down predictions from the motor system and bottom-up sensory input converge. This is evident across all levels of the cortical hierarchy such as the spinal cord, the thalamus and the sensorimotor cortex. In the context of movement, the output of the

motor system is in the form of proprioceptive predictions about the sensory consequences of the movement itself. The proprioceptive prediction is compared with proprioceptive input from muscle afferents at the level of the spinal cord to generate a proprioceptive prediction error. Prediction error minimization subsequently occurs via activation of the classical motor reflex arc within the spinal cord in order to fulfil the proprioceptive prediction (Feldman and Friston, 2010). Once the proprioceptive prediction is fulfilled the bottom-up proprioceptive input will closely match the top-down proprioceptive prediction and can therefore explain movement initiation and motor control. However, top-down predictions from the motor system are not only in the form of proprioceptive predictions but also in the form of other somatosensory consequences such as predicted cutaneous reafference. These top-down predictions are compared to bottom-up sensory input at higher levels of the cortical hierarchy, at the level of the sensorimotor cortex, which allows for perceptual inference in the somatosensory domain. Within this framework, the motor cortex does not act as a purely motor area as previously suggested in other frameworks of sensorimotor control but instead acts as a multimodal sensory area sending top-down predictions of proprioceptive and exteroceptive consequences of movement (Hatsopoulos and Suminski, 2011). Based on the neuronal architecture of the sensorimotor system, it is neurobiologically plausible that the brain operates under the principles of active inference (Adams et al., 2013a).

1.7.4.3 Sensory attenuation

The precision afforded to prediction errors across all levels of the cortical hierarchy is essential in determining whether a movement occurs or whether stimuli originating in the external environment are perceived. The gain (or precision) of prediction errors is a factor that quantifies the effect of pre-synaptic input on post-synaptic output. Changes in synaptic gain are primarily thought to be mediated by the effects of neurotransmitter on

specific receptors located within the brain. The receptors that determine synaptic gain are NMDA receptors, dopamine receptors (DA-Rs), acetylcholine receptors (in particular muscarinic AChRs), and serotonin receptors (5-HT₂R). The key feature of all these receptors is that they are all G-Protein coupled receptors (GPCRs) and through a cascade of events alter neuronal excitability via changes in the production, surface expression or activity of voltage or ligand-gated ion channels (Durstewitz, 2009; Frank, 2005; Pasquale and Sherman, 2012). As mentioned previously, the active inference framework considers the hierarchical structure of the brain in which precision-weighted prediction errors update predictions at each level of the cortical hierarchy. Therefore, the type of receptors involved will vary depending on the level of the cortical hierarchy.

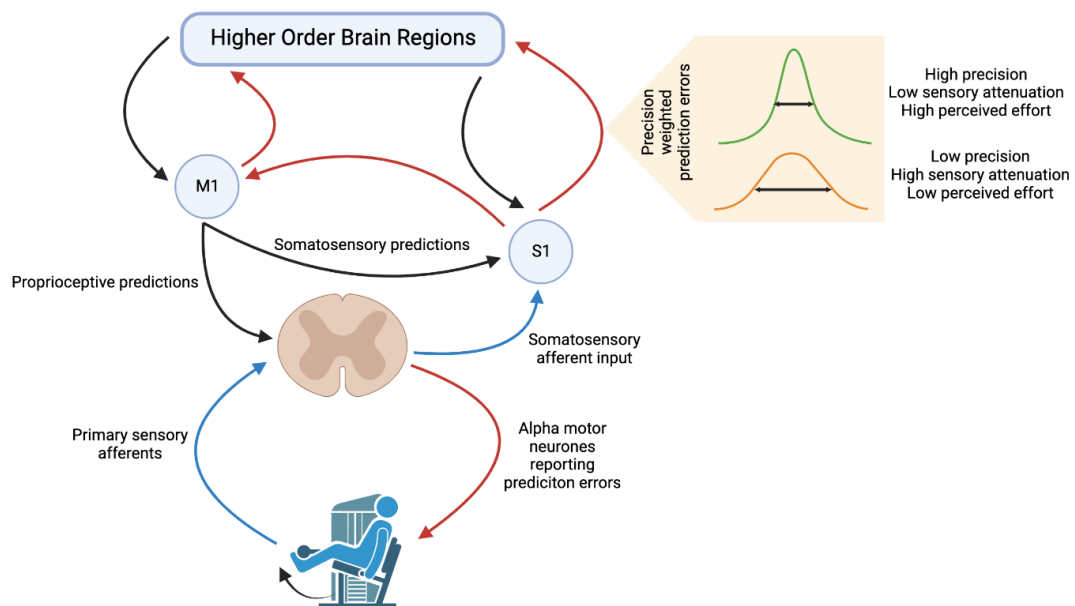


Figure 1.4 – Sensory attenuation model of fatigue: Simplified schematic of active inference. M1 and S1 signify the primary motor and sensory cortex. Red arrows denote bottom-up prediction errors, black arrows denote top-down predictions and blue arrows denote afferent somatosensory projections. Prediction errors are precision-weighted, displayed as Gaussian probability distributions with the width of the distribution corresponding to the variance. Within the sensory attenuation model of fatigue higher precision (inverse of variance) represents low sensory attenuation and high perceived effort.

The function of altering the gain of prediction errors is commonly referred to as sensory attenuation and is inherently related to attention (Brown et al., 2011). In fact, sensory attenuation is the inverse of attention. In other words, prediction errors can either be

attended to or ignored by altering their associated precision or gain (Feldman and Friston, 2010). At the level of the spinal cord, an organism can either temporarily increase the precision afforded to prediction errors (low sensory attenuation) in order to update the top-down predictions to better match bottom-up sensory input, this is known as perception, or it can change the sampling of the environment through action by temporarily decreasing the precision afforded to prediction errors (high sensory attenuation) that one is not moving such that the resulting bottom-up sensory input matches the top-down predictions. There is experimental evidence to demonstrate that sensory attenuation occurs across all sensory modalities from vision, hearing and proprioception (Brown et al., 2011; Cardoso-Leite et al., 2010; Hughes et al., 2013; Hughes and Waszak, 2011; Reznik et al., 2015). It is apparent that precision afforded to prediction errors, the degree of sensory attenuation, at any level of the hierarchy is not fixed but can be altered by modulating the gain.

Given that attention underlies the property of intensity in the perception of effort and sensory attenuation is a core feature of active inference, it is plausible that sensory attenuation underpins the perception of effort (Kuppuswamy, 2017). If one were to consider a simple muscle contraction, under normal circumstances sensory attenuation, the precision associated with bottom-up prediction errors that drive the muscle contraction is suppressed (low gain or high sensory attenuation). This leads to the inference of low or no effort associated to the muscle contraction. When sensory attenuation is reduced, there is higher precision associated with the bottom-up prediction error for the same muscle contraction that can only be explained by the brain if the muscle contraction requires more effort than previously predicted (figure 1.4). The association between active inference, sensory attenuation and the perception of effort is further strengthened by studies in schizophrenia patients with delusion beliefs (Adams et al., 2013b). A number of psychotic symptoms in this group of patients can be explained by

using active inference as a failure of sensory attenuation. Specifically, a failure to represent the precision of top-down predictions, corresponding to abnormal neuromodulation of the post-synaptic gain of superficial pyramidal cells in cortical hierarchies, resulting in delusions and hallucinations (Adams et al., 2013b; Brown et al., 2013; Edwards et al., 2012). One example of delusions is the attribution of control of movements to an external agent or having no control of their actions, a lack of agency. To experience a sense of agency, one must have a feeling of exerting control over an action and the perception of effort plays an important role. In fact, greater effort has been associated with higher sense of agency (Chambon et al., 2014; Demanet et al., 2013). In this group of patients, studies show that sensory attenuation is abolished, and they report little or no effort when performing motor tasks.

1.7.5 Sensory attenuation model of fatigue

Could pathological fatigue be a result of reduced sensory attenuation and altered effort perception? The repeated references to effort in the various definitions of fatigue, both from a mechanistic and patients' perspective, as well as the effort-related statements in the various questionnaires used to quantify fatigue suggest that PSF may be a result of altered effort perception. Stroke survivors suffering from fatigue usually report the simple day to day activities as more effortful. Activities of daily living usually require little or no effort, however, with reduced sensory attenuation, everyday tasks require higher effort than normally required. This is a result of the brains inability to attend away from the sensory consequences of the movement itself, poor sensory attenuation. In fact, sensory attenuation is stronger in low force muscle contractions than stronger muscle contractions (Walsh et al., 2011). When a system is working at its maximum, like when performing a maximal voluntary contraction, one cannot attend away from the sensory consequences of the movement and hence the report of high effort. It is also important

to note that perception of effort is not directly related to force produced. The fact that PSF persists in the absence of physical disability and muscle weakness further strengthens this hypothesis. In the presence of physical disability, simple activities require high effort levels. Therefore, in the absence of physical disability the abovementioned lends support to the idea that reduced sensory attenuation results in higher perceived effort associated with what are usually considered low effort activities. The persistent experience of high effort for simple tasks gives rise to fatigue. This idea of altered effort perception fits in well with the anecdotal evidence from stroke survivors, as well as the clinical symptoms of PSF, such as fatigue in the absence of prior exertion that does not respond to rest and limits everyday activities. The higher effort associated with voluntary movements might explain why stroke survivors suffering from fatigue have slower self-selected movement speeds (A. Kuppuswamy et al., 2015). However, when asked to respond as quickly as possible, they are able to overcome the effort associated with the movement and are capable of responding as quickly as those without PSF. This is evident from the lack of association between reaction times and fatigue.

The abovementioned inflammatory, neurophysiological, perceptual, and behavioural perturbations in PSF, provide evidence in support of the sensory attenuation model of fatigue. As mentioned, the synaptic gain of prediction errors is inextricably linked to neuromodulation and the activity of specific neurotransmitters, which are known to be affected by inflammation post-stroke as previously mentioned. This subsequently affects neuronal excitability. Therefore, neuronal excitability is closely associated with sensory attenuation, specifically the neurones located within the primary cortex given the importance of sensory attenuation in motor control. Cortical excitability at rest is reduced, indicated by higher RMTs, in stroke survivors with high severity of fatigue which might reflect reduced sensory attenuation and a higher perception of effort (Annapoorna Kuppuswamy et al., 2015). Repetitive stimulation of M1 using TMS, which acts to

transiently reduce cortical excitability, reduces the magnitude of sensory attenuation in healthy subjects (Therrien et al., 2011; Voss et al., 2007). This suggests that M1 is involved in determining the level of sensory attenuation.

The perception of limb heaviness seen in those with PSF can also be explained by the sensory attenuation model of fatigue (Kuppuswamy et al., 2016). Body heaviness has previously been thought of as a result of poor sensory suppression of muscle afferent information arising from resting muscle tone or from the contracting muscle. Meaning that prediction errors reaching the brain are not attenuated. Whether this is a result of lower precision-weighted to top-down predictions of expected sensory input or increased precision of bottom-up predictions errors remains unclear. Both these mechanisms are a result of reduced sensory attenuation and can explain the perception of limb heaviness seen in PSF (reduced sensory attenuation of bottom-up prediction errors) and the attribution of control over one's movements to an external agent (lower precision-weighted top-down predictions).

The sensory attenuation model of fatigue is a disease independent mechanism that might underlie the symptom of fatigue in several other neurological disorders. In fact, there is evidence in support of the sensory attenuation model of fatigue in both MS and PD. Fatigue in both MS and PD does not appear to be maintained by the underlying cause of the disease itself, but instead is maintained by neural network-level dysfunction implicating a number of brain regions. These brain regions include sensorimotor cortices, thalamus, anterior insula, superior temporal gyrus, anterior cingulate cortex, inferior frontal gyrus and inferior parietal lobe (Buyukturkoglu et al., 2017; Chalah et al., 2015; Cho et al., 2017; Hidalgo de la Cruz et al., 2017; Li et al., 2017; Palotai et al., 2019; Pravata et al., 2016). These areas are implicated in sensorimotor control, interoception (the processing of internal bodily signals) as well as motivation and cognitive control.

Interestingly activity in these areas has also been implicated in effort perception. Connectivity within the sensorimotor cortex is compromised and cortico-muscular coherence increases in MS patients with fatigue during performance of a motor task (Dell'Acqua et al., 2010; Tecchio et al., 2008; Tomasevic et al., 2013). The increased cortico-muscular coherence could be driven by compromised connectivity within the sensorimotor cortex and reflect reduced sensory attenuation (or increased gain afforded to bottom-up prediction errors). NIBS studies using transcranial direct current stimulation (tDCS) specifically targeting sensorimotor cortices have shown to be effective in reducing the fatigue severity in MS (Cancelli et al., 2018; Tecchio et al., 2015, 2014). This could be resetting the connectivity within the sensorimotor cortex resulting in gain normalisation.

When taken together, the above support the hypotheses that pathological fatigue, one of the most disabling symptoms in several neurological disorders such as stroke, MS and PD, is a result of higher perceived effort due to poor sensory attenuation. It is important to note that the free energy principle and hence active inference are used as a narrative framework to explain sensory attenuation and altered effort perception in PSF, and there are other theoretical frameworks of motor control, not necessarily tied to free energy, that may also lead to similar predictions.

1.7 Aims of this thesis

There is currently no direct experimental evidence that perceived effort and sensory attenuation are altered in PSF. The aim of this thesis is to test the hypothesis that PSF is associated with altered effort perception because of reduced sensory attenuation. Firstly, I will explore the association between PSF and effort perception in a simple motor task (Chapter 3). Secondly, I will explore the relationship between PSF and sensory attenuation using a behavioural task that has previously been used to quantify sensory

attenuation, namely a force matching task (Chapter 4). Thirdly, I will explore neurophysiological changes during movement preparation and immediately prior to movement execution using TMS in stroke survivors with varying severity of fatigue (Chapter 5). If PSF is a result of sensory attenuation of voluntary movements and sensory attenuation is inextricably associated to cortical excitability, stroke survivors with PSF would exhibit different neural activity patterns prior to movement depicted by a different excitability time course when compared to stroke survivors without PSF. I will then explore the feasibility of using tDCS as a method to increase corticospinal excitability and explore its use as potential therapeutic intervention for PSF (Chapter 6). Along with measures of fatigue severity, measures of neurophysiology and behaviour in this longitudinal study will allow for assumptions as to what might drive the change in fatigue severity. In Chapter 7, I will further explore the association between corticospinal excitability, fatigue severity and hemisphere affected by the stroke to identify specific circuits and network level dysfunctions that might be implicated in PSF. Finally, the results presented will be discussed with the aim of providing a mechanism on which to build our understanding of chronic pathological fatigue along with future directions in Chapter 8.

Chapter 2: Studying Post-Stroke Fatigue

One of the most common challenges in conducting research studies in clinical populations is related to problems with recruitment. Insufficient recruitment can have serious consequences such as having to extend the length of the study leading to higher resource demand and increased cost or resulting in statistically underpowered studies with unpublishable results. Patient recruitment becomes even more important when studying a complex symptom such as chronic pathological fatigue. Fatigue is a multidimensional experience with physical, cognitive, and emotional components. As previously mentioned, PSF has considerable overlap with other common affective symptoms after stroke. It is therefore important to consider these factors when recruiting stroke survivors for the purpose of carrying out studies on PSF. In very simple terms, one can assume that by controlling for factors that have previously been shown to exacerbate fatigue, such as depression, any experimental findings are a result of ‘pure fatigue’ and not due to other underlying symptoms. Several other factors may influence experimental findings, but this is an important step that must be considered when designing experiments with the aim of developing a mechanistic understanding of PSF. This makes recruitment even more difficult as the pool of available patients who meet the inclusion criteria is greatly reduced. Developing a streamlined process in which patients can be identified, screened and enrolled into research studies is essential for the successful completion of such studies (figure 2.1).

2.1 Initial recruitment process

Stroke survivors treated at University College London Hospital (UCLH) are approached while in the hyperacute stroke unit (HASU) by members of the clinical research (CRN) and are asked whether they would consider taking part in research studies. Patients that

give permission to be contacted by means of written informed consent are then added to a database by the CRN. The database contains various demographic data such as name, date of birth, date of stroke, hospital number, contact information as well as some stroke related data such as extent of physical disability at the time of consent and whether this was the patient's first stroke. The database was securely sent to Queen Square every six months from which potentially eligible stroke survivors were identified.

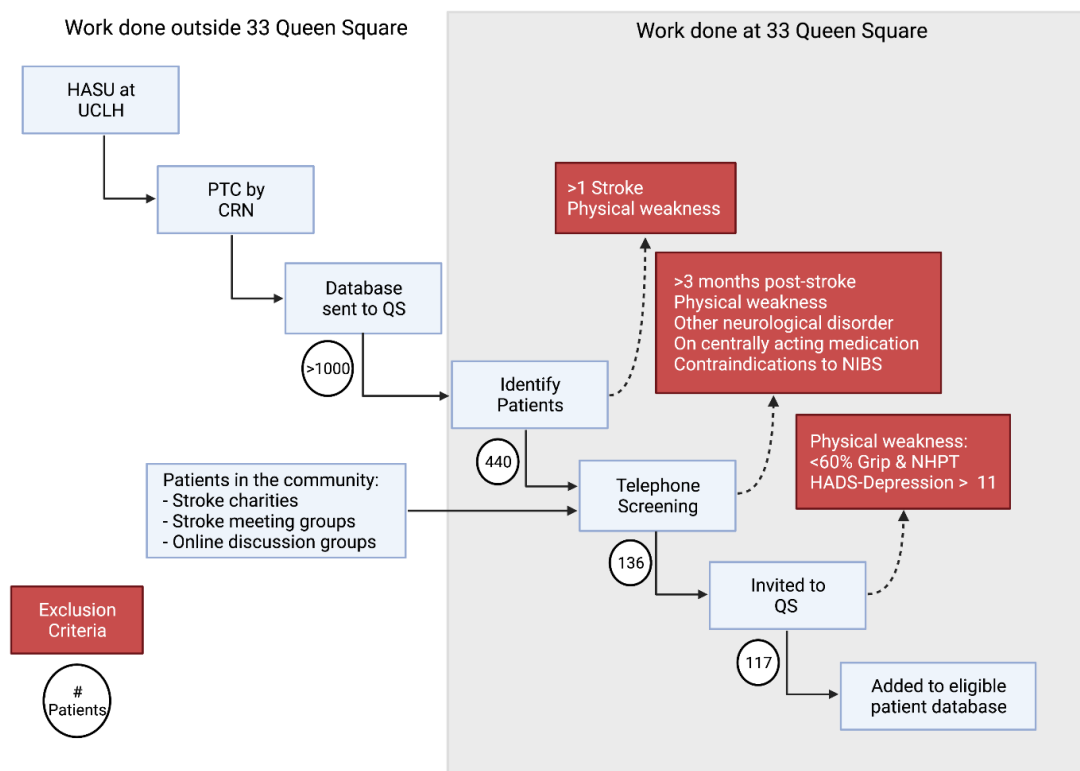


Figure 2.1 – Recruitment pipeline from UCLH: Process of how stroke survivors were recruited from UCLH and from the community into the various research studies. The boxes on the left (white section) highlight the work that was done by others and the boxes on the right (grey section) highlight the work that was done by me. Blue boxes indicate the process of identifying and recruiting stroke survivors, red boxes indicate the reason for exclusion from the study and the numbers in the circle indicate the number of stroke survivors at each stage.

2.2 Identifying Stroke Survivors

For the reasons stated above, patient recruitment that took place between February 2017 and March 2020 for all studies carried out as part of this thesis included strict inclusion and exclusion criteria. Stroke survivors that suffered their first stroke and had minimal

physical disability at the time of consent were initially identified from the database and later screened. Stroke survivors were also recruited from the community through various stroke charities, stroke meeting groups, online discussion groups and through various social media platforms. In total 440 stroke survivors were identified.

2.3 First level screening

The screening procedure was carried out in two steps. As mentioned previously, there are a number of factors that can result in fatigue in the acute stages of stroke recovery. The scope of the studies included in this thesis was to study chronic pathological fatigue and therefore stroke survivors were contacted via telephone to carry out the first level of screening at least three months after their stroke. On first level screening, patients were screened on the following criteria: a) clinical diagnosis of any other neurological disorder; b) prescribed medication; c) contraindications to NIBS; d) extent of physical disability, specifically of the upper limb.

The proposed sensory attenuation model of fatigue is a disease independent mechanism that might underlie the symptom of fatigue in various neurological disorders. However, how the presence of multiple neurological disorders subsequently impact fatigue is not clear (e.g. the impact on fatigue of a stroke on someone suffering from MS). This complex picture makes identifying the mechanisms that underlie fatigue even more difficult. To make the interpretation of the results more straightforward, stroke survivors that had a clinical diagnosis of any other neurological disorder were excluded from the study.

Stroke survivors are often prescribed a number of medications after their stroke which is highly dependent on the underlying cause of the stroke. Given that the majority of strokes are ischaemic strokes, most stroke survivors are prescribed one or a combination of antiplatelet medication, anticoagulants, blood pressure medication and/or statins. These medicines primarily target the vasculature with the aim of preventing future strokes and

form an essential part of routine stroke treatment. In some instances, stroke survivors are also prescribed medication to help with the management of some of the consequences of stroke, such as chronic affective symptoms. These medicines include antidepressants such as fluoxetine and citalopram, as well as wake-promoting agents such as modafinil, to assist with sleep disturbances. Most of the medication aimed at treating chronic affective symptoms target various neurotransmitter pathways within the central nervous system which influence neurophysiology and subsequent behaviour and perception. To ensure that the results of the studies were not influenced by external factors such as medication, stroke survivors that were taking any centrally acting medication (medication with a known effect on the central nervous system) were also excluded from the study.

NIBS techniques such as TMS are becoming increasingly popular in both research studies and clinical applications. Although TMS is a generally safe and painless technique with minimal side effects, there are safety issues that need to be considered to minimize its risk. The majority of TMS guidelines are with respect to the stimulation parameters used in various TMS protocols. There are, however, some additional factors that should be considered when selecting participants in TMS studies. The most recent safety guidelines for the application of TMS advise on using a standard screening questionnaire (Rossi et al., 2009). Positive responses to one or more of the first thirteen questions on the questionnaire does not represent absolute contraindications to TMS, but the risk/benefit ratio should be carefully considered. Stroke survivors that were deemed unsuitable for TMS based on their responses on the TMS screening questionnaire were excluded from the study.

Physical disability and PSF are closely associated as has been previously described. For the purpose of these studies, only stroke survivors that had minimal physical impairment were eligible to participate. Stroke survivors were therefore asked the following questions:

"Can you squeeze a ball with both you're affected and unaffected hand"

"Do you think you have more than 50% grip strength on your affected hand when compared to your unaffected hand?"

Stroke survivors that responded positively to both the above questions and met all other eligibility criteria mentioned above (30% of stroke survivors contacted) were invited into the lab at Queen Square to complete the second level of screening.

2.4 Second level screening

The second level screening procedure took place in the lab at 33 Queen Square and involved a range of clinical tests used to assess upper limb function followed by a range of questionnaires. To ensure minimal physical impairment of the upper limb, all stroke survivors were asked to complete a grip strength test, the Nine Hole Peg Test (NHPT) and the Action Research Arm Test (ARAT), testing grip strength, manual dexterity, and gross upper limb function respectively. The grip strength test involved stroke survivors squeezing a digital handheld dynamometer (Jamar) as hard as they could. The stroke survivors were encouraged to squeeze the device as long and as tightly as possible for the best result until the digital reading stopped rising. This procedure was repeated three times for each hand, alternating side each time. To calculate the % of grip strength on the affected side compared to the unaffected side, the average of the three attempts on the affected side was divided by the average of the three attempts on the unaffected side and then multiplied by 100. A score of less than 100% indicates weaker grip strength on the affected side compared to the unaffected side whereas a score greater than 100% indicates stronger grip strength on the affected side compared to the unaffected side. The NHPT is easy and quick to administer and is widely considered a gold standard metric for manual dexterity and was originally introduced in 1971 (Kellor et al., 1971). The NHPT requires participants to repeatedly place nine pegs into nine holes, one at a time, as quickly as

possible. The time needed to complete the NHPT in seconds is measured using a stopwatch and is started when participants touch the first peg and stopped when participants place the final peg into the hole. This procedure was repeated three times for each hand, alternating side each time. To calculate the % of manual dexterity on the affected side compared to the unaffected side, the best of the three attempts on the affected side was divided by the best of the three attempts on the unaffected side and then multiplied by 100. A score of less than 100% indicates less manual dexterity on the affected side relative to the unaffected side whereas a score greater than 100% indicates greater manual dexterity on the affected side relative to the unaffected side. Finally, ARAT is a commonly used standardized and reliable measure of upper limb function after stroke (Nijland et al., 2010). The ARAT consists of 19 items that are grouped into four subtests (grasp, grip, pinch and gross movement). All items are rated on a 4-point ordinal scale ranging from zero (no movement possible) to three (normal performance of the task). The subtest scores vary according to the number of items performed in each subtest, with a maximum score of 57 points. The ARAT was repeated with both the affected and unaffected hand and the asymmetry between the two sides was calculated as previously for NHPT. These clinical tests assessing upper limb function can also be affected by handedness. It has previously been suggested that the dominant hand is approximately 10% stronger regarding grip strength and more dexterous than the non-dominant hand (Incel et al., 2002). Hand dominance was assessed by simply asking the stroke survivors what they believed to be their dominant hand. Although, using a formal handedness assessment such as the Edinburgh handedness inventory would have been more precise, for the purpose of this project and the time constraints available using a simple question was deemed appropriate (Veale, 2014). When taking into consideration the differences in upper limb function between the dominant and non-dominant hand, minimal physical impairment was therefore defined as a score greater or equal to 60% on the affected side

compared to the unaffected side on any of the three upper limb clinical tests. Stroke survivors that scored less than 60% were considered ineligible and were excluded from the study.

Stroke survivors were also screened for depressive tendencies. As previously mentioned, there is significant overlap between PSF and PSD and until recently PSF was considered to be a secondary symptom to PSD. Despite evidence in support of fatigue being independent of depression, the presence of depression or depressive tendencies could further exacerbate the severity of fatigue. Therefore, depression and anxiety scores were assessed using the Hospital Anxiety and Depression Scale (HADS) and were included as covariates in subsequent analyses of the studies included in this thesis. The HADS is a 14-item questionnaire with a depression and anxiety subscale. The first seven items of the questionnaire (1-7) are targeted towards gauging anxiety levels while the last seven items of the questionnaire (8-14) are targeted towards gauging depressive tendencies. Participants are asked to rate the degree to which they agree with a statement ranging from 0 (strongly disagree) to 3 (strongly agree) based on how they have been feeling over the preceding week from the day of administration. The total score for each subscale is calculated by adding up the score across the 7 items. There are both positive and negative statements within the HADS questionnaire. The negative statements are scored based on the true response while the inverse is used to score the positive statements within the questionnaire (3 minus the score for the specific item). A score of 0 to 7 for either subscale could be regarded as being in the normal range, with a score of 11 or higher indicating probable presence of the mood disorder (Snaith, 2003). With that in mind, stroke survivors that scored greater than 11 on the depression subscale of the HADS were excluded from the study as despite not having a clinical diagnosis of depression, there was a high probability that they suffered from depression.

Cognitive disability was not part of the exclusion criteria of the studies included in this thesis, however, all stroke survivors completed the symbol digits modalities test (SDMT) at the time of screening. SDMT is the most commonly used neuropsychological test of information processing speed and is highly correlated with activities of daily living (Costa et al., 2017). In the coding section of the test, participants are presented with a page headed by a key that pairs nine symbols with numbers 1-9. The rows below contain only numbers and the subject's task is to write the correct symbol to the corresponding number. The first 10 trials are practice trials in which the participant can familiarise themselves with the task. The subject is then timed to determine how many correct responses can be made in 90 seconds. To eliminate the sensorimotor impact of writing, participants are then asked to complete the copying section of the test. Participants are asked to simply copy the symbol they are shown and are timed to determine how many correct responses can be made in 60 seconds. The number of correct responses per second is calculated for both the coding and copying section of the test, with the measure of information processing speed calculated by dividing the rate of correct responses in the coding section by the rate of correct responses in the copying section. This measure of cognitive function was subsequently correlated with fatigue scores and used as an additional covariate in later analyses.

Of the 136 stroke survivors that completed the first level screening, a total of 117 stroke survivors were eligible to take part in the various studies and were added to an internal database. Stroke survivors from that database were then invited to complete the studies included in this thesis.

2.5 Fatigue Questionnaires

At the time of second level screening and for all studies included in this thesis, two measures of fatigue were used. The FSS-7, previously described in Chapter 1, was used

as a measure of trait fatigue to capture the experience and impact of fatigue on day to day living for a pre-determined time period leading up to the day of testing (Johansson et al., 2014). The FSS-7 questionnaire was scored using the standard procedures where the average of each of the seven statement scores was considered as the participant's overall fatigue score with an average score of one indicating no fatigue and an average score of seven indicating very severe fatigue. A measure of state fatigue was also captured characterizing the momentary state of fatigue at a given moment in time. State fatigue was captured with a VAS ranging from zero to ten, in which patients were asked 'How fatigued are you at this moment in time?'. A score of zero indicates no fatigue and a score of ten indicates very severe fatigue.

Measuring both trait and state fatigue allows one to distinguish between pathological and physiological fatigue across the different studies included in this thesis. A high score on the trait fatigue measure is indicative of pathological fatigue, whereas a high score on the state fatigue measure can be a result of both pathological and physiological fatigue. Using both these scores in subsequent analyses, allows one to distinguish between pathological and physiological fatigue.

2.6 Stroke survivor demographics

The stroke survivors included in the internal database were tightly controlled based on the abovementioned screening criteria. Demographics of the 117 eligible stroke survivors included in the database can be found in table 2.1. Fisher's exact test were used to compare the FSS-7 scores across the different categorical variables such as Sex, Affected Hand, and Dominant Hand while spearman correlations were used to examine the association between FSS-7 and the various continuous variables such as Age, Grip Strength, NHPT, ARAT, Processing Speed, HADS-Anxiety and HADS-Depression.

The stroke survivors included in the database had a wide range of FSS-7 scores, ranging from no fatigue (FSS-7 = 1) to very severe fatigue (FSS-7 = 7) and anywhere in between. Females had significantly higher levels of fatigue when compared to males in the cohort of stroke survivors.

Characteristic	N = 117 ¹	p-value ²
FSS-7	4.14 (2.00,5.43)	
Sex		0.0014
Female	39 (33%)	
Male	78 (67%)	
Affected Hand		0.2702
Left	54 (47%)	
Right	62 (53%)	
Dominant Hand		0.1308
Left	12 (10%)	
Right	105 (90%)	
Age	58 (47,67)	0.0026
Grip (% unaffected hand)	104 (88,120)	0.518
NHPT (% unaffected hand)	103 (86,119)	0.575
ARAT (% unaffected hand)	100 (100,100)	0.121
Processing Speed	1.11 (0.90,1.42)	0.737
Anxiety	4.0 (2.0,8.0)	< 0.001
Depression	4.0 (3.0,7.0)	< 0.001

¹Median (25%,75%); n (%)

²Spearman correlation; Fisher's exact test

Table 2.1 – Demographics of all eligible stroke survivors. Fisher's exact test were used to compare the FSS-7 scores across the different categorical variables such as Sex, Affected Hand and Dominant Hand. Spearman correlations were used to examine the association between FSS-7 and the various continuous variables such as Age, Grip Strength, NHPT, ARAT, Processing Speed, HADS-Anxiety and HADS-Depression. P-values indicate the significance of the association between FSS-7 and each categorical or continuous variable.

The finding of greater fatigue in females than males has previously been reported in the stroke population (Mead et al., 2011; Schepers et al., 2006). Whether the imbalance is reflective of report bias with men considering less acceptable to report fatigue related symptoms or a difference in physiology remains unknown. It is important to consider that in the current cohort of stroke survivors there were twice as many males than

females. The difference in fatigue between males and females observed in this study may therefore be a sampling issue. It is evident that hemisphere affected, and dominant hand have no effect on fatigue severity and is in line with what has previously been reported in the literature. There is however a significant negative correlation between fatigue severity and age, in that younger stroke survivors reported higher levels of fatigue. As previously highlighted, it is possible that younger stroke survivors have a higher expectation of returning to work and returning to their pre-stroke mental and physical state that may result in higher reports of fatigue as they are pushing themselves (Naess and Nyland, 2013). All eligible stroke survivors had minimal physical impairment in the upper limb contralateral to the hemisphere affected by the stroke, evident from the high Grip strength, NHPT and ARAT scores. As previously described in the introduction of this thesis, there was no correlation between physical impairment and fatigue severity. The same holds true with regards to cognitive impairment; all stroke survivors had minimal cognitive impairment evident by high processing speed scores and a lack of association between cognitive impairment and fatigue severity. Despite all stroke survivors scoring within the normal range for both the anxiety and depression subscale of HADS, there was a significant positive correlation between fatigue severity and both anxiety and depression scales. This highlights the overlap between various affective symptoms post-stroke and the importance of controlling and accounting for these factors when attempting to make meaningful interpretations with regards to fatigue.

Chapter 3: Why is everything so effortful? Perceived effort in post-stroke fatigue

3.1 Introduction

Fatigue after stroke, sometimes years after the stroke, is highly prevalent, yet little is known about its underlying mechanisms as highlighted previously. A recently proposed model that may shed some light on the mechanisms that underlie PSF is the sensory attenuation model of fatigue (Kuppuswamy, 2017). Within this model, poor sensory attenuation leads to heightened perception of effort and subsequently high fatigue. Altered effort perception in physical tasks is seen in stroke survivors and is not driven by actual energy expenditure or force output (Yen and Li, 2015). Aside from some qualitative evidence, there is little direct evidence to link altered perceived effort to PSF. In this study, I aim to explore the link between perceived effort and PSF.

Reports of perception are notoriously subject to response bias with bias arising from a number of sources, including those internal and external to the participant (Jones et al., 2015; Moore and Picou, 2018). Perceived exertion has mostly been tested in post-exercise paradigms where measures such as visual analogue scales (VAS) and Borg Scales have been validated against physiological measures of exertion such as heart rate and maximal aerobic capacity (Smith et al., 2016; Van Cutsem et al., 2017). They conclude PE is less subject to bias in some populations. However, in the current study PE is measured in a non-exercise paradigm and in a disease population with a condition that is highly stigmatised and under recognised (Crosby et al., 2012; Walsh et al., 2015). Hence, a response bias in PE was expected. Therefore, in addition to a VAS, an explicit measure of PE, a novel implicit measure of perceived effort based on line length perception was also introduced. It is difficult to distinguish between perceptual and non-perceptual effects as there is no direct way to measure perception, however using behavioural

responses to measure and infer a perceiver's experience is one way to overcome this problem. The perceptual experience of spatial properties such as distance, gradient and size has previously been shown to be modulated by the amount of energy expended (Bhalla and Proffitt, 1999). There are several experimental findings in support of this action-specific account of perception which is influenced by both chronic and temporary physical manipulations. Patients with chronic pain or overweight subjects perceive distances to be further when compared to control subjects and carrying a heavy backpack or wearing ankle weights also influences distance perception (Lessard et al., 2009; Proffitt et al., 2003; Sugovic et al., 2016; Witt et al., 2009). This action-specific account of perception takes advantage of the susceptibility of visual perception to physical effort where high effort unfavourably biases distance estimation. Most of these paradigms require egocentric estimation of distances, with respect to self. These perceptual effects however also hold true for allocentric distance estimation and are influenced by cross-modal interactions between internally and externally driven processes (Fini et al., 2015; Pooresmaeli et al., 2014; Tenhundfeld and Witt, 2017). On similar lines, a line length estimation task was developed and shown to be biased by prior exertion, which I use as a measure of implicit PE (Clark et al., 2016).

Fatigue and fatigability are two independent constructs that do not necessarily influence each other in conditions of pathological fatigue such as in post-stroke fatigue (Kluger et al., 2013). Here the aim is to investigate fatigue as opposed to fatigability using validated questionnaires. Trait fatigue is a relatively stable measure with state fatigue varying considerably across time. Measuring both state and trait fatigue in this study will allow to potentially draw inferences about direction of causality. State fatigue, the more immediate state in relation to task performance is likely to causally influence PE whilst trait fatigue less likely so.

To summarise, the primary aim of this investigation is to definitively establish the relationship between post-stroke fatigue and PE. With multiple measures of fatigue (trait and state), PE (explicit and implicit) and motor output (target overshoot, hold time and force variability) I aim to draw further conclusions about the origins of altered PE and direction of causality between fatigue and PE.

3.2 Methods

3.2.1 Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by London Bromley Research Ethics Committee (REC reference number: 16/LO/0714). Written informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

3.2.2 Participants

Stroke patients were recruited from the database of eligible stroke survivors described in Chapter 2 of this thesis. Based on a previous study using the same experimental paradigm in healthy participants, to obtain a medium sized effect ($f^2 = 0.15$) with statistical power of 0.8 at an alpha level of 0.05 using a single predictor in a linear regression model, fifty-four datasets were deemed necessary (Clark et al., 2016). Fifty-eight stroke patients took part in the experiment between January 2018 and June 2019. More patients were recruited than necessary in order have at least fifty-four datasets that were eligible for final analysis.

3.2.3 Procedure

In this single session cross-sectional study, patients performed a perceived effort (PE) task on a desktop computer running Psychtoolbox (psychtoolbox.org) implemented within MATLAB (2016b, MathWorks). Trait and state measures of fatigue were captured using the FSS-7 and VAS respectively, as has been previously described in Chapter 2. PE was measured using a VAS and line length estimation, an explicit and implicit measure of

PE respectively. Written instructions were given to each patient prior to the start of the experiment.

	<i>Patients (N = 58)</i>	<i>P-value</i>
Gender		<i>P = 0.3207</i>
Females Males	18 40	
Hemisphere Affected		<i>P = 0.9681</i>
Left Right	30 28	
Dominant Hand		<i>P = 0.2366</i>
Right Left	55 3	
Age (years)		
Mean (SD)	59.93 (12.44)	<i>P = 0.0511</i>
Time Since Stroke (years)		
Mean (SD)	4.23 (4.69)	<i>P = 0.3458</i>
Grip (% unaffected hand)		
Mean (SD)	91.03 (22.87)	<i>P = 0.1815</i>
NHPT (% unaffected hand)		
Mean (SD)	87.90 (23.21)	<i>P = 0.2976</i>
ARAT (% unaffected hand)		
Mean (SD)	99.21 (3.42)	<i>P = 0.1361</i>
SDMT		
Mean (SD)	1.12 (0.48)	<i>P = 0.9160</i>
Depression - HADS		
Mean (SD)	5.66 (3.30)	<i>P = 0.0125</i>
Anxiety - HADS		
Mean (SD)	6.24 (3.75)	<i>P = 0.1621</i>
State Fatigue		
Mean (SD)	3.84 (2.28)	<i>P < 0.0001</i>
FSS-7		
Mean (SD)	4.15 (1.82)	

Table 3.1 - Demographics of stroke survivors for PE task: Demographics of all stroke survivors that took part in the study. Fisher’s exact test were used to compare the FSS-7 scores across the different categorical variables while Spearman correlations were used to examine the association between FSS-7 and the various continuous variables. Significance values for the association between FSS-7 are reported for continuous and categorical data.

3.2.4 Line length familiarisation

Before the main experiment, patients completed a line length familiarisation task. Patients were shown six lines: three belonged to the 'short' category (1, 2, and 3 cm) and three belonged to the 'long' category (10, 11, and 12 cm). Following presentation of the six lines, patients were shown each of the learned lines without information about the category it belonged to and were asked to judge the length of line. Patients responded using the keyboard, left arrow key for 'short' and right arrow key for 'long'. They were then asked to rate their confidence in their response using a VAS. If patients' response was less than 100% correct, the procedure was repeated from start until they were able to distinguish between the 'short' and 'long' lines.

3.2.5 Perceived effort paradigm

Patients sat facing a monitor (DELL 1909W, 19" LCD Display) and held a handgrip dynamometer (Biometrics Ltd) with their dominant hand and performed an isometric handgrip task, while the keyboard was placed in front of their non-dominant hand. Force data from the dynamometer was acquired at 500 Hz via a data acquisition interface (Power1401, CED) and recorded in MATLAB (2016b, MathWorks). Each trial was 5 seconds long in which patients were required to sustain a grip force for 3-seconds at three different levels: 20%, 40% or 60% of their maximum voluntary force (MVF). Immediate force feedback was shown on the monitor as filling of a red bar, which turned green once the minimal required target force was reached. The minimal target force for each trial was indicated by a cross on the screen. The grip force-visual feedback relationship was individually adjusted for every patient to eliminate potential influence on PE. Before the experiment, patients practiced each force level with their dominant hand to familiarize themselves with the effort required. After each grip, participants performed a line length estimation. The line presented could have a length of 3.5 cm to 8.5cm with a total of 24

different line lengths, 12 short and 12 long. Twenty-four lines presented under the three force conditions resulted in a total of 72 trials. The order of forces and line lengths was randomised with equal numbers of the three different force levels in each block. The experiment consisted of three blocks of 24 trials. Participants reported if the presented line was 'short' or 'long' using the left and right arrow key of the keyboard respectively. They were instructed to base their estimation on the length of lines presented during the familiarisation phase. If they determined the presented line to be shorter than half the length of the longest line presented during the familiarisation (12 cm), they reported 'short', otherwise reported 'long'. There was no time limit to their response. The inter-trial interval was 1.5 seconds. The implicit PE task is shown in figure 3.1A.

After three blocks, participants performed a final block of 9 trials. This block was used as an explicit measure of PE (figure 3.1B). Each trial consisted of a 5-second grip with visual feedback at the three different force levels, 20%, 40% or 60% of MVF, with three trials for each force level. This was followed by the question: 'How Effortful was the Squeeze?'. Patients had to respond using a VAS ranging from 'Not at all' to 'Very Hard'.

3.2.6 Analysis

Data was extracted from MATLAB into SigmaPlot (SigmaPlot Version 13.0) for statistical analysis.

3.2.7 Fatigue questionnaires

FSS-7 was scored using the standard procedure where the average of each of the seven statement scores was considered as the participant's overall fatigue score. The effect of FSS-7 on the patient demographics was examined using a Fisher's exact test for categorical data and a Spearman correlation for continuous data.

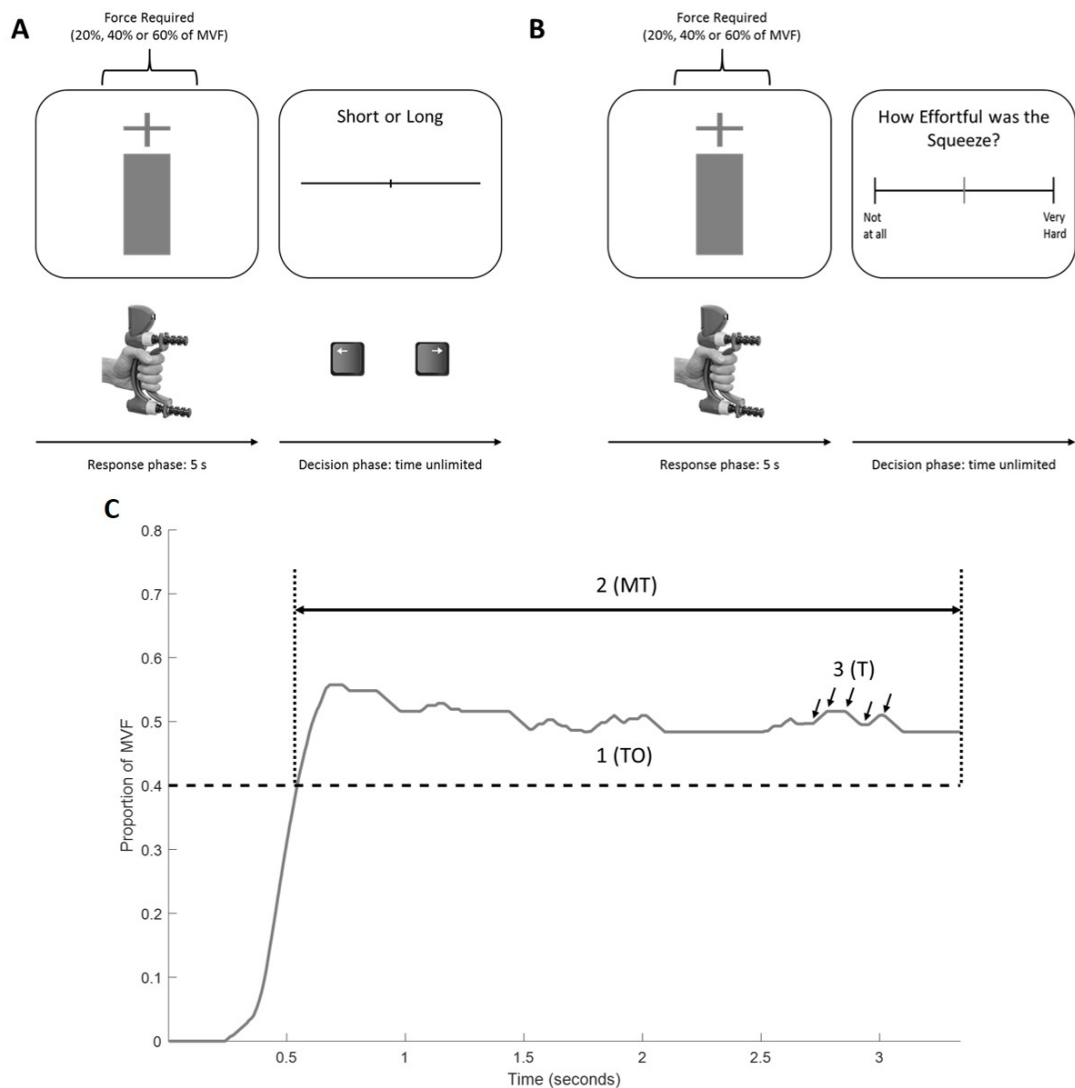


Figure 3.1 – Perceived Effort task: Task design for Implicit PE task (A) and Explicit PE task (B). Each trial starts with a cross showing the target force level (20%, 40% or 60% maximum voluntary contraction - MVF). Patients performed an isometric handgrip task using a hand held dynamometer and were instructed to get the bar to the target force level. An example force trace with the three measures of motor performance (TO (1) – target overshoot, MT (2) – length of hold, T (3) – force variability across the entire length of the hold) is shown in panel (C). After 5 seconds, patients performed a line length estimation in the Implicit PE trials, or explicitly reported how effortful the trial was in the Explicit PE trials.

3.2.8 Perceived effort – explicit

VAS scores were averaged across the three trials in each force level (20%, 40% and 60% MVF) for individual participants and were named VAS_{20} , VAS_{40} , and VAS_{60} respectively.

3.2.9 Perceived effort – implicit

Two types of measures were extracted from the implicit PE trials. (1) A sum of the number of lines reported as long (SL) for each individual in each force level (SL₂₀, SL₄₀, SL₆₀ refer to number of lines in the 20%, 40% and 60% MVF conditions). The total number of lines presented were 24 at each force level. Participants who reported all 72 lines to be long/short were excluded as this was taken as a failure to understand task instructions. Three participants were excluded based on this criterion. (2) The number of long responses for each line length presented was calculated separately for each force condition in each participant. This measure allowed us to fit a psychometric curve for each participant in each force condition (the 20%, 40% and 60% MVF) determining their sensitivity and bias in line length discrimination. From this fit, the sensory threshold (i.e. the point of equal proportion of response for each response option) and the sensory slope (defined as the inverse of the difference in line length observed between the point of 25% and 75% proportions of “long line” responses) was extracted. These measures were then compared across force conditions using paired t-test (two tailed) and correlated to fatigue score (FSS-7).

3.2.10 Motor performance and motor control

Three measures of motor performance were extracted from the isometric handgrip task for each MVF condition (20%, 40% and 60%). (1) Length of hold (MT) – The maximal time, in seconds, spent above target in each trial, averaged across trials in each condition (MT₂₀, MT₄₀, MT₆₀). (2) Target overshoot (TO) – the mean force exerted in each individual trial for the length of hold, expressed as a percentage of maximal force and averaged across trials in each condition (TO₂₀, TO₄₀, TO₆₀). (3) Force variability (I) – The number of transitions in the force trace during the time above target was counted and taken as the measure of force variability in each condition (I₂₀, I₄₀, I₆₀). TO and MT were

taken as motor performance parameters and T as motor control parameter. A sample force trace of a single trial with the three measures of motor performance extracted is shown in figure 3.1C.

3.3 Results

Fifty-eight stroke patients (18 females; mean (SD) age = 59.93 (12.44); mean (SD) time post-stroke = 4.23 (4.69) years) with mild physical impairment (mean (SD) grip = 91.03 (22.87); mean (SD) NHPT = 87.9 (23.21); mean (SD) ARAT = 99.21 (3.42)) completed the study. FSS-7 and state fatigue scores ranged from 1 to 7 (total scale range 1-7) and 0 to 8 (total scale range 0-10) respectively. Patient demographics can be found in table 3.1. There was no significant difference in FSS-7 score based on gender, hemisphere affected or dominant hand and no significant correlation between FSS-7 and age, time since stroke, grip, NHPT, ARAT, SDMT and anxiety score. There was a significant correlation between FSS-7 and depression score and state fatigue (table 3.1).

Measures	Correlation Coefficients (CC)	Significance value (P-value)
TO20 and TO40	0.819	<0.0001
TO40 and TO60	0.884	<0.0001
TO20 and TO60	0.654	<0.0001
MT20 and MT40	0.839	<0.0001
MT40 and MT60	0.880	<0.0001
MT20 and MT60	0.720	<0.0001
T20 and T40	0.760	<0.0001
T40 and T60	0.926	<0.0001
T20 and T60	0.713	<0.0001

Table 3.2 - Motor performance correlations: Shown are the correlation coefficients and significance values (p values) of the 3 measures of motor performance across the different force conditions (MT = length of hold; T = force variability; TO = target overshoot).

3.3.1 Collinearity analysis for perceived effort and motor measures

A Pearson Product Moment correlation analysis was performed between the explicit measures of perceived effort (VAS_{20} , VAS_{40} , VAS_{60}) and implicit measures of perceived effort (SL_{20} , SL_{40} , SL_{60}) in the 3 force conditions of 20%, 40% and 60% maximal voluntary force. There were significant correlations between VAS_{20} and VAS_{40} ($r(56) = 0.288$, $p = 0.03$, CI [-0.27, 3.44]), between VAS_{40} and VAS_{60} ($r(56) = 0.397$, $p = 0.002$, CI [1.74, 7.41]), but no significant correlation between VAS_{20} and VAS_{60} . When considering the implicit measures of perceived effort, a strong and significant correlation was observed between SL_{20} and SL_{40} ($r(53) = 0.869$, $p < 0.0001$, CI [3.77, 22.21]), between SL_{40} and SL_{60} ($r(53) = 0.868$, $p < 0.0001$, CI [6.64, 23.78]) and between SL_{20} and SL_{60} ($r(53) = 0.909$, $p < 0.0001$, CI [6.46, 24.03]). As the implicit measure of PE in the different force conditions (SL_{20} , SL_{40} , SL_{60}) were strongly correlated, a combined measure of SL_{sum} was used in the final regression analysis where SL_{sum} was the sum of SL_{20} , SL_{40} and SL_{60} . Despite significant correlations between some of the VAS scores, given the weak correlation coefficients, all three VAS measures were used as independent variables in the regression analyses. A Pearson Product Moment correlation analysis was performed on the measures of target overshoot (TO_{20} , TO_{40} , TO_{60}), length of hold (MT_{20} , MT_{40} , MT_{60}) and force variability (T_{20} , T_{40} , T_{60}). There were strong and significant correlations between the three force levels in each of the measures TO, MT and T. Table 3.2 shows the correlation coefficients and significance values of the pairs of conditions. Given the strong correlations, the three conditions in each motor parameter were averaged into TO_{avg} , MT_{avg} and T_{avg} to be entered into the regression analysis for FSS-7.

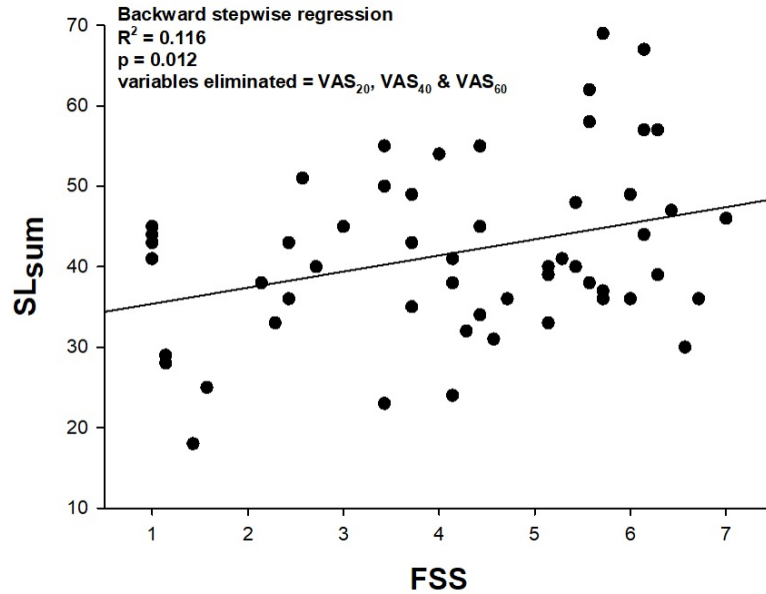


Figure 3.2 – Implicit PE and PSF: The combined measure of implicit PE SLsum (Y-axis) is plotted against FSS (X-axis). A significant correlation is seen between the two variables.

3.3.2 Perceived effort and FSS-7

In order to test the effect of fatigue on perceived effort, a stepwise backward linear regression analysis was performed with FSS-7 as the dependant variable and SL_{sum} , VAS_{20} , VAS_{40} and VAS_{60} entered into the model as independent variables. Of the four measures of PE, SL_{sum} explained 11.6% of the variance in FSS-7 score ($R = 0.34$, $p = 0.012$, CI [1.69, 7.02], Figure 3.2), with the explicit VAS measures not contributing significantly to FSS-7. Figure 3.3A-F plots all six measures of PE (VAS_{20} , VAS_{40} , VAS_{60} and SL_{20} , SL_{40} , SL_{60}) against FSS scores. Figure 3.3G-I shows the implicit PE measure when the cohort of 58 stroke survivors were divided into high ($FSS-7 > 4$) and low ($FSS-7 < 4$) fatigue. Although there was no significant difference in the estimated midpoint of the line length between the high and low fatigue groups, there was a consistent 0.5cm leftward shift in all three force levels in the high fatigue group when compared to the low fatigue group.

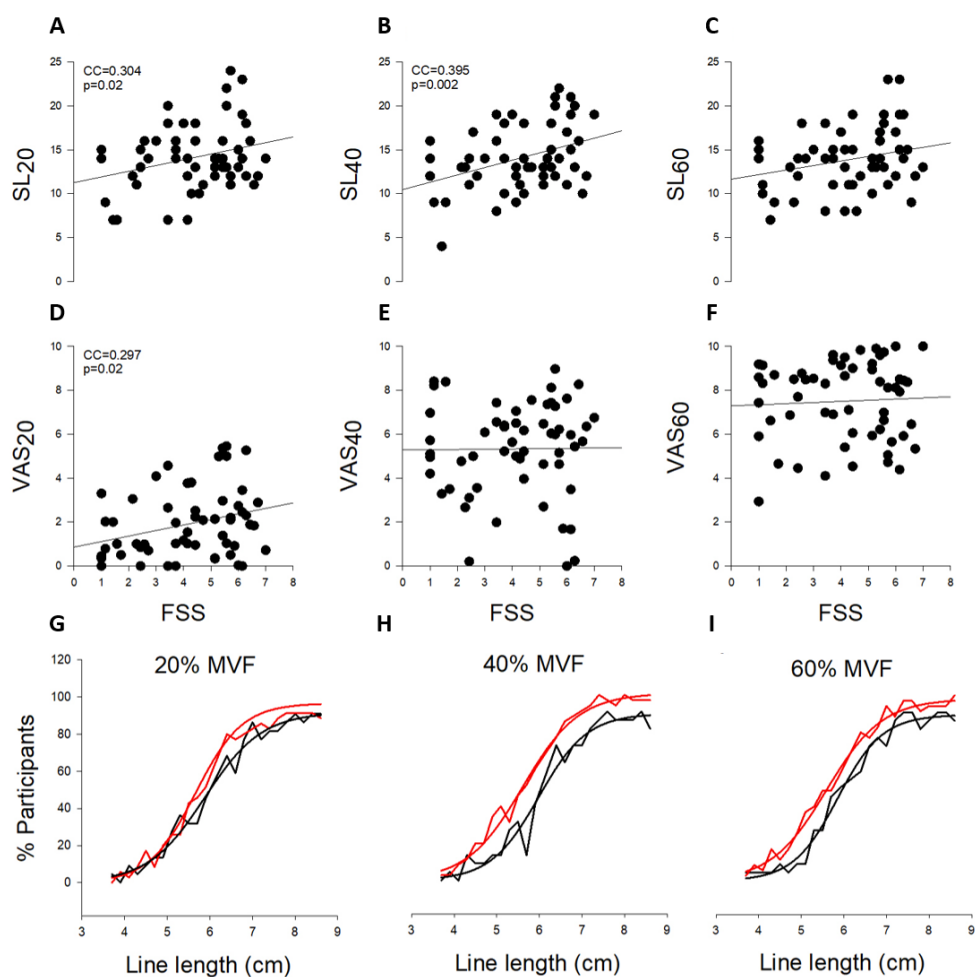


Figure 3.3 – PE and PSF: Measures of Implicit PE (A, B & C) and Explicit PE (D, E & F) are plotted against Fatigue Severity Scale scores (X-axis). There is a significant positive correlation between SL20, SL40 and SL60 and FSS, with SL20, and SL40 reaching statistical significance. There is also a statistically significant correlation between VAS20 and FSS but not in the higher force conditions. In this figure the % of participants (Y-Axis) who reported a given line length to be long is plotted against each line length (X-Axis) presented during the Implicit PE task (G-I) in the 3 different force conditions (20%, 40% and 60% MVF). The red line represents the fatigue group with score > 4 (n=32) and black line represents the fatigue group with score < 4 (n=22). The estimated mid-point of a 12cm line is shifted to the left by 0.5cm in all three force levels in the high fatigue group (red line) when compared to low fatigue group (black line).

Figure 3.4A shows the average curve fits for each line length presented and each force condition for the proportion of “long” response. For each participant, the fitted slope and sensory threshold was extracted and compared across conditions. Sensory threshold was significantly lower than 6 (mid-point) for force conditions above 40% MVF, when

considering proportion of response (40% MVF: $t(54) = -2.2$ $p = 0.032$, CI [5.45 , 5.97] ; 60% MVF: $t(52) = -2.34$ $p = 0.023$, CI [5.47 , 5.95]), suggesting that participants were biased towards perceiving the line as longer than its actual length. However, sensory thresholds were not significantly different between force conditions when estimating it based on the proportion of response (all p s > 0.92). Similarly, no significant difference was found between force conditions when estimating the sensory slope based on proportion of response (all p s > 0.15). The psychometric curve parameters were then correlated with the individual fatigue scores, separately for each force condition and when pooling all conditions together. No significant correlation was found between the sensory slope and fatigue scores for any of the conditions or when pooling all conditions together, when considering the proportion of response (all p s > 0.14), suggesting that perceptual sensitivity was not affected by fatigue. A significant negative correlation was found however between fatigue and sensory threshold for the intermediate force condition 40% MVF when considering response proportion ($r^2 = 0.11$, $F = 6.61$, $p = 0.01$, CI [-0.32, -0.03]). A similar trend was observed when considering the proportion of response and pooling all conditions together ($r^2 = 0.05$, $F = 3.17$, $p = 0.08$, CI [-0.25, 0.01]). This suggests that higher fatigue scores were associated with a stronger bias towards perceiving the lines as longer than they are.

3.3.3 Motor performance, control, and FSS-7

To test how fatigue impacted motor performance and motor control, a stepwise backward linear regression analysis was performed with FSS as the dependant variable and TO_{avg} , MT_{avg} and T_{avg} entered into the model as independent variables. Of the three measures, MT_{avg} explained 17.8% of the variance in FSS-7 ($R = 0.421$, $p < 0.001$, CI [1.4, 7.25], Figure 3.5A), with measures of TO and T not significantly adding to the explanatory power of the variables. Figure 3.5b & 5c plots TO_{20} , TO_{40} , TO_{60} , and MT_{20} , MT_{40} , MT_{60}

against FSS-7, all of which significantly correlated with FSS-7 individually. The measure of T_{20} but not T_{40} and T_{60} correlated with FSS-7.

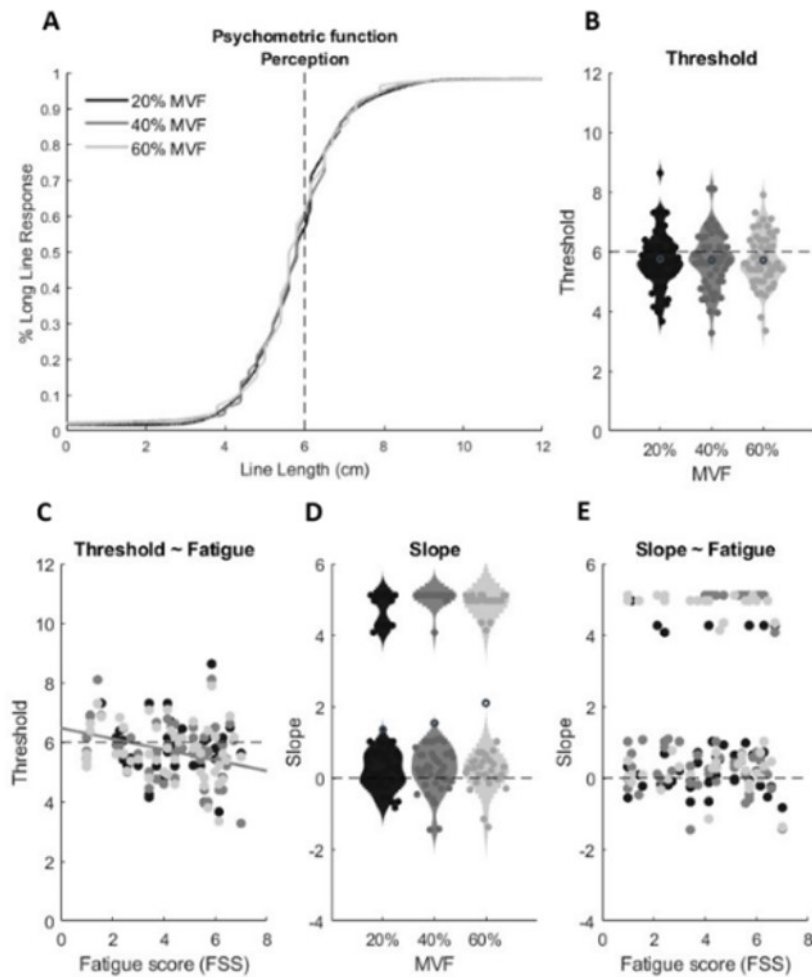


Figure 3.4 – Psychometric curve parameters and PSF: Fitting of the psychometric curve for the line length discrimination task based on response choice (A-E) in each effort condition (dark grey = 20% MVF; medium grey = 40% MVF; light grey = 60% MVF). (A): Average fitted psychometric curve between presented line length and proportion of “long” responses across participants. Each fit was performed separately for each force condition and each participant. (B, D) Violin plot of the obtained fit parameters corresponding to the sensory threshold (B) and sensory slope (D) based on proportion of response for each condition. Black circle represents the population mean. (C, E) Correlation results between Fatigue Scores (FSS) and psychometric curve parameters based on response choice for each effort condition. Significant correlations are indicated by a plain line.

3.3.4 Motor performance, control and perceived effort

Implicit perceived effort (SI_{sum}) was not explained by any of the motor performance and motor control measures. A stepwise backward linear regression analysis with explicit perceived effort in the 20% force condition (VAS_{20}) as the dependant variable and TO_{avg} , MT_{avg} and T_{avg} as independent variables showed a small but significant contribution of MT_{avg} to VAS_{20} ($R = 0.306$, $p = 0.021$, CI [-0.11, 4.15]) explaining 9.4% of the variance (Figure 3.5D). Similarly, 15.9% of the variance in VAS_{40} was explained by a combined measure of MT_{avg} and TO_{avg} ($R = 0.399$, $p = 0.014$ & 0.004 , CI [-0.34, 8.24], Figure 3.5E) and T_{avg} explained 9.9% of the variance in VAS_{60} ($R = 0.315$, $p = 0.017$, CI [5.77, 11.61], Figure 3.5F).

3.3.5 State fatigue, motor performance, motor control and perceived effort

All the above tests were performed with state fatigue as the dependant variable and none of the measures of perceived effort and motor measures explained the variance in state fatigue.

3.4 Discussion

In this cross-sectional, observational study of 58 chronic, first time, non-depressed, mildly impaired stroke survivors, I show for the first time, a significant relationship between fatigue and perceived effort (PE). In the absence of prior exertion, higher self-reported trait fatigue can be explained by a higher level of implicit PE observed during a physical task. I also show that explicit measure of PE fails to explain trait fatigue. Behaviourally, prolonged motor output indexed by longer sustained target forces was associated with high fatigue levels. Prolonged time above target and greater force than required, was related to higher explicit PE in the low and medium force conditions. In the high force condition, greater PE was associated with higher force variability during the task. The

measure of state fatigue was neither explained by altered PE nor altered motor control and performance.

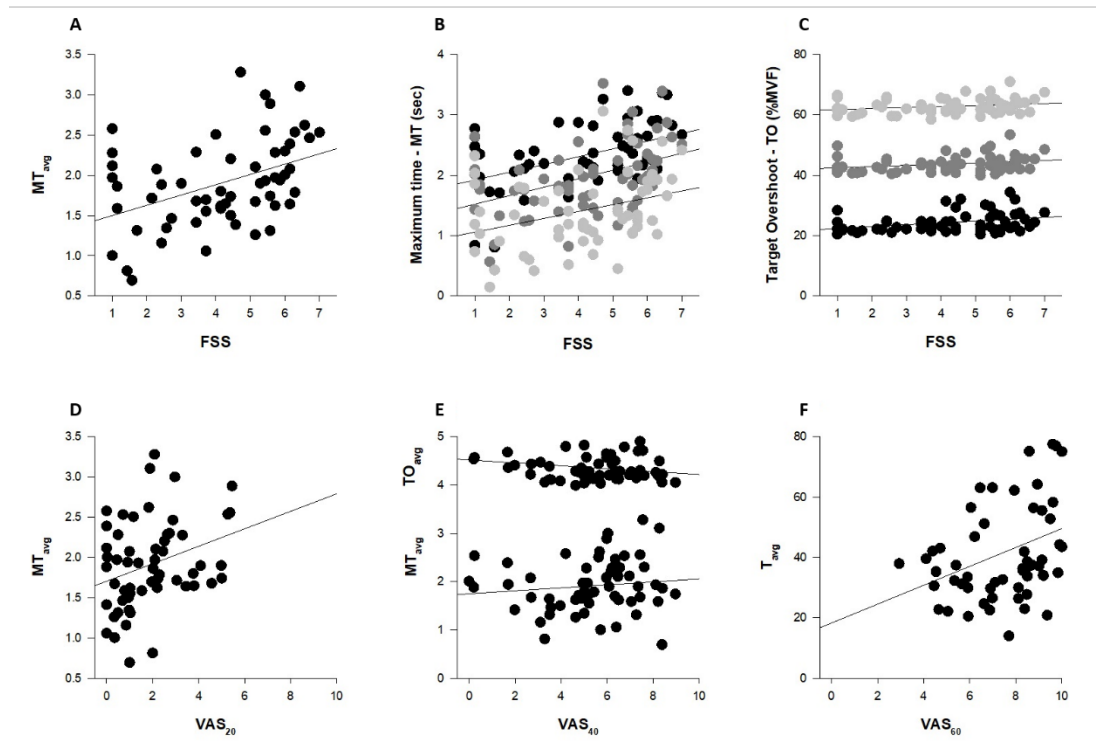


Figure 3.5 – Motor control and PSF: The combined measure of time (sec) above target MT_{avg} (Y-axis) is plotted against FSS (X-axis). A small but significant correlation is seen between the two variables. In this figure we plot TO_{20} , TO_{40} , TO_{60} , and MT_{20} , MT_{40} , MT_{60} in the isometric hold task. Maximum time in seconds (left graph) and target overshoot as % MVF (right graph) are plotted against fatigue scores (X-Axis). There is a statistically significant positive correlation between fatigue and both parameters of motor performance in all three force conditions. The relationship between explicit PE (VAS_{20} , VAS_{40} and VAS_{60}) is plotted against parameters of motor performance (MT_{avg} and TO_{avg}) and motor control (T_{avg}). VAS_{20} and VAS_{40} are partially explained by regressors of motor performance – time above target (MT_{avg}) and target overshoot (TO_{avg}) whilst VAS_{60} is partially explained by measure of motor control – force variability (T_{avg}).

3.4.1 Implicit and Explicit Effort in PSF

Fatigue in the chronic phase after stroke, is related to lower motor cortex excitability and poor attention, and is independent of motor weakness, lesion location or biological markers of fatigue such as inflammation (De Doncker et al., 2018; Annapoorna Kuppaswamy et al., 2015; Radman et al., 2012). Based on these wide range of findings in

post-stroke fatigue, a recently proposed a framework wherein sensory information is incorrectly gated, possibly due to poor sensory predictions, leads to altered perception. Altered perception, specifically altered perception of effort in the context of motor actions, underpins post-stroke fatigue (Kuppuswamy, 2017). Here, I show that the greater the fatigue in stroke survivors, the higher the effort in a motor task despite individual calibration of task related force. This suggests, for the same proportional afferent input from the contracting muscle, there is a greater precision afforded to the bottom-up sensory prediction error, giving rise to higher sense of effort in the high fatigue individuals. Sensory predictions and their associated precision along with PE has been extensively studied in schizophrenia where a lack of effort in relation to movement, leads patients to attribute movement to external control (Lafargue and Franck, 2009). The almost complete lack of precision-weighted predictions in schizophrenia has been shown to drive this sense of external control, by near abolition of PE (Frith and Done, 1989; Lafargue et al., 2006). A similar fundamental framework of PE and sensory predictions can explain the result of higher PE. I propose that higher PE is driven by decreased gain (less precise) of sensory prediction errors as opposed to a lack of predictions seen in schizophrenia. Both explicit and implicit measures of PE correlated with trait fatigue in the lowest force level, however, in higher force levels only implicit PE correlated with trait fatigue. A possible explanation is that explicit PE is not subject to response bias when the task is relatively easy, but with greater difficulty, response bias invalidates the measure of explicit PE. A second possible explanation is the inability to consciously access accurate interoceptive information during high effort activity in itself may drive the feeling of fatigue.

3.4.2 Motor control and PSF

An interesting, yet counter-intuitive finding in this study is the significantly higher force levels and hold times exerted by those with high fatigue during the task. It is unclear why one must exert higher force when reporting high levels of fatigue. A possible explanation could be that those with higher fatigue have less precise sensory predictions and hence to ensure successful task completion, they exert greater than required force. Exerting greater force, and for longer, results in higher PE as shown here in the low and medium force conditions. A recent study investigating the relationship between force and PE demonstrate that PE is not simply a function of metabolic cost. PE is a reflection of several movement related cost parameters, of which time is a major driver i.e. longer the motor performance, higher the perceived effort (Cos, 2017; Morel et al., 2017). Therefore, greater PE seen in this study could result from prolonged grip that is driven by imprecise sensory predictions. Such altered motor performance in fatigue has been previously reported in cancer fatigue patients (Lacourt et al., 2018). Cancer survivors with high fatigue, not under medication, tended to opt for more high effort trials in an effort based choice task. These results taken together with the current study, points to a disease independent motor behaviour trait in high fatigue.

The corticospinal tract (CST) can be directly affected by stroke and a question that arises is, if changes in output pathways may directly affect perceived effort. First, in this study stroke survivors with moderate to severe muscle weakness were excluded, thereby ensuring minimal changes in CST and any differences were similar across high and low fatigue. Despite this exclusion criteria, there is still a possibility of alterations in CST playing a role in driving greater force and longer holds in the grip task. Force variability is a measure of motor control and is consistently altered in those with stroke (Kang and Cauraugh, 2015). In the current study, force variability does not explain the difference in

perceived effort both in the low and mid force conditions suggesting that PE cannot be directly attributed to changes in efferent output pathways. However, in the high force condition, greater force variability explains higher fatigue. This suggests that perception of effort is possibly informed by different movement parameters in the low force conditions when compared to the high force conditions.

3.4.3 State versus Trait fatigue

The results of the current study do not allow for further elaboration, however it would suffice to say that future studies into perception and post-stroke fatigue must carefully differentiate between high and low effort tasks. Establishing direction of causality between PE and fatigue is paramount if meaningful treatments are to be developed. Like with many chronic symptoms, it is very difficult to establish the order of appearance of the various changes seen in performance and perception related to fatigue. A pertinent question that arises is whether fatigue can result in higher PE. The answer is invariably yes. However, the methodology used to capture fatigue may give us some room for nuanced interpretation of the current results. Trait and state measures of fatigue capture two very different phenomena. As with all affective measures, trait measures capture a more stable state of being whilst state measures capture the momentary state of being. Trait measures may be influenced by state measures and vice-versa, however, in this study all performance and perceptual measures were performed at a single point in time leading to state fatigue not always reflecting the trait measure. What this means is, in some patients, despite experiencing high levels of fatigue over a certain period of time past, the momentary state during performance of the laboratory tests was different. Here it is a reasonable assumption that immediate perception and performance is likely to be influenced by the state of the being at that moment, i.e. by the state measure of fatigue and not the trait measure. The lack of a significant relationship between state fatigue and

measures of perception and performance suggests that fatigue may not be driving perception and performance. However, to definitively establish that altered perception may drive fatigue, one must alter perception to see if a change in fatigue is observed. Future intervention paradigms must track perception to identify if any change seen in fatigue is driven by altered perception.

3.4.4 Limitations

Despite providing several insights into the association between PSF and PE, this study is not without its limitations. The relationship between post-stroke fatigue and perceived effort has been studied in a well-defined group, which limits its generalisability. However, this may also be considered a strength of the study too, as it gives us a clearer picture of primary fatigue and its mechanisms. Future studies must include both depressed and non-depressed patients. The number of trials in each ‘force-line length’ condition could be viewed as a limitation. Despite having 24 different line lengths, the ‘estimated line length’ measure required participants to divide them into 2 categories – ‘short’ or ‘long’. Therefore, there were 12 trials in the short category and 12 in the long category. As the response required was one of two and not twelve, for the ‘estimated line length’ measure, effectively there were 12 repetitions in each ‘force-line length’ combination. We chose not to have the exact line length for 12 repetitions, as this could have resulted in a learning effect. Having any more than 12 in each condition would have considerably lengthened the protocol resulting in fatigability playing a role in the results. The hand grip task was relatively simple with very little performance variability; hence 12 trials were deemed sufficient for a representative average for each condition.

3.5 Conclusions

To conclude, I show that high implicit PE explains high post-stroke fatigue, possibly mediated by changes in motor performance. These results add strength to the idea that

fatigue is predominantly driven by perceptual changes underpinned by sensory disturbances and that treatments must focus on modifying sensory processing and perception.

Chapter 4: Sensory Attenuation and Post-Stroke Fatigue: a force matching paradigm

4.1 Introduction

Stroke survivors suffering from chronic persistent fatigue often report simple day-to-day activities as more effortful when compared to prior to their stroke. In chapter 3, I have demonstrated that the perception of effort in stroke survivors who report high levels of fatigue is altered (Doncker et al., 2020). Those with high severity of fatigue perceive low effort tasks as more effortful compared to those with low severity of fatigue. The majority of day-to-day activities such as brushing your teeth or making a cup of coffee are low effort activities that, under normal circumstances, are perceived as effortless. If these simple tasks are constantly perceived as more effortful, this might give rise to the experience of persistent fatigue, as is the case in PSF. The sensory attenuation model of fatigue, as described in the introduction of this thesis, proposes a mechanism in which reduced sensory attenuation may underlie the perception of high effort for low effort activities.

Sensory attenuation is a key principle of sensory processing and motor control in which self-generated sensations are perceived as less intense than externally generated sensations and has previously been reported across different sensory modalities (Cardoso-Leite et al., 2010; Niziolek et al., 2013; Shergill et al., 2003). It allows for the processing of salient and unexpected stimuli and hence allows one to distinguish between self and externally generated sensory input. This is a key feature in biological systems which are constantly bombarded with sensory information. Sensory attenuation is classically used to describe the inability to tickle oneself (Blakemore et al., 2000). Although having participants be tickled as well as tickle themselves and have them rate the degree of ticklishness is an

attractive proposition, for the purpose of quantification it is not meaningful. Instead, a classical method often used to quantify sensory attenuation is a force matching paradigm. In such paradigms, participants are asked to match externally generated target forces either by pressing directly on themselves or by using an external device (often using a joystick) to manipulate the force applied, resulting in two conditions, a self-generated condition and an externally generated condition respectively. It has previously been reported that participants significantly overestimate a target force when the matched force is self-generated but are fairly accurate when the matched force is externally generated (Pareés et al., 2014; Shergill et al., 2005, 2003; Wolpe et al., 2016). In fact this overestimation effect is quite robust with 98% of adults showing sensory attenuation in the self-generated condition (Wolpe et al., 2016).

Different theoretical frameworks have been used to explain the perceptual phenomenon seen when performing such a paradigm. The central cancellation theory suggests that during a self-generated movement, an efference copy of the motor command is produced which is used to predict the sensory consequences of the upcoming movement. The predicted and actual sensory input are then compared to generate a prediction error. In the self-condition, there is no difference between the predicted and actual sensory input and any reafferent input is cancelled out or attenuated leaving only externally produced afferent information (Franklin and Wolpert, 2011). This explains the overestimation effect and allows an individual to distinguish between self and externally generated sensations. This perceptual phenomenon can also be explained using active inference (Brown et al., 2013). According to the active inference framework, during self-generated movements, the precision afforded to predicted reafferent activity is reduced (increased sensory attenuation). This means that the post-synaptic gain of pyramidal cells within the cortex that receive the input is reduced and a more intense stimulus is necessary to achieve the same neuronal response. This explains the overestimation of target forces during self-

generated movements. However, when the movement is externally generated, the post-synaptic gain of pyramidal cells within the cortex that receive the input is increased (reduced sensory attenuation) as there is no prior information to guide the perception of the bottom-up afferent input, resulting in more veridical force matching. Irrespective of the theoretical framework, the perceptual phenomenon of force overestimation in force matching paradigms is believed to be a result of sensory attenuation afforded to self-generated actions.

Changes in the precision of sensory information relative to predicted sensory input and therefore changes in sensory attenuation can therefore have a widespread impact on sensorimotor control and perception (Edwards et al., 2012). The force matching paradigm has been used to quantify sensory attenuation and subsequently describe a range of motor and perceptual deficits seen in many neurological and psychiatric disorders such as PD, schizophrenia, functional movement disorders as well as in ageing (Pareés et al., 2014; Shergill et al., 2005; Wolpe et al., 2018, 2016). Abnormalities in sensory attenuation at different levels of the cortical hierarchy will determine the type of symptom developed, be it motoric or perceptual. Patients with PD, schizophrenia or functional movement disorders are more accurate at matching a target force with a self-generated matched force and hence show reduced sensory attenuation (Pareés et al., 2014; Shergill et al., 2005). This implies a greater precision afforded to bottom-up prediction errors. From a motor control perspective, this can explain the akinetic symptoms seen in PD as a reduction in sensory attenuation does not allow the expression of proprioceptive predictions that initiate a movement (Wolpe *et al.*, 2018). Reduced sensory attenuation in patients with schizophrenia and functional movement disorders has been used to explain alterations in sense of agency, where patients attribute the sensory input from the resulting movement to an external agent (Pareés et al., 2014; Shergill et al., 2005). Reduced sensory attenuation has also been reported in the general population in individuals with delusional beliefs

(Teufel et al., 2010). To experience a sense of control over an action, a sense of agency, one must be able to feel a sense of effort associated to the action with actions that are experienced as more effortful being associated with a higher sense of agency (Demanet et al., 2013). In fact, patients with schizophrenia, the classic case of altered sense of agency, show reduced or complete lack of sense of effort that may be associated with the observed abnormalities in sensory attenuation (Lafargue and Franck, 2009).

I have previously suggested that PSF is a result of higher perceived effort due to poor sensory attenuation. Given the evidence from studies on sensory attenuation in patients with schizophrenia, abolished sensory attenuation results in a complete lack of sense of effort and the sensation of alien control over one's own actions, while a reduction in sensory attenuation may result in an increased perception of effort seen in PSF. Given that the force matching task has previously been used to quantify sensory attenuation in a range of clinical conditions, I used the same task to test my hypothesis. If correct, stroke survivors with fatigue will be more accurate in matching a target force using a self-generated force (reduced sensory attenuation) when compared to stroke survivors without fatigue and healthy control subjects.

4.2 Materials and Methods

4.2.1 Participants

The study was approved by London Bromley Research Ethics Committee (REC reference number: 16/LO/0714). Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. Stroke survivors were recruited from the database of eligible stroke survivors described in Chapter 2 of this thesis. Forty-eight stroke patients took part in the experiment between September 2017 and May 2021. Twenty-one healthy volunteers were also recruited through the departmental subject pool and took part in the study.

Additional data for healthy volunteers was provided by the Cambridge Centre for Ageing and Neuroscience (CamCAN), a population-based cohort of healthy adults. CamCAN funding was provided by the UK Biotechnology and Biological Sciences Research Council (grant number BB/H008217/1), together with support from the UK Medical Research Council and University of Cambridge, UK.

4.2.2 Questionnaires

Trait fatigue was quantified at the very start of the experimental session using the Fatigue Severity Scale (FSS-7), a seven-item questionnaire asking for ratings of fatigue ranging from one to seven (strongly disagree to strongly agree) over the preceding week from the day of administration. An average score of seven being the highest fatigue and a score of one being no fatigue (Johansson et al., 2014). Stroke survivors also completed the HADS, a 14-item questionnaire with a depression and anxiety subscale, prior to the study. A score of 0 to 7 for either subscale could be regarded as being in the normal range, with a score of 11 or higher indicating probable presence of the mood disorder (Snaith, 2003).

4.2.3 Materials

The robotic device used in force matching paradigms requires participants to maintain the hand feeling the force in a supine position. This position when held for extended periods of time can be uncomfortable, especially in stroke survivors. Therefore, the force matching task was performed using a custom-made device in which the hand feeling the force rested on a pillow in a natural position defined as halfway between pronation and supination. The device acted both as a force transducer and as a force sensor. The force transducer was controlled using air flowing in and out of the device using a pulse code modulation approach, with the pressure of air flowing through the system determining the level of force transmitted. The different levels of force produced by the force transducer were controlled using the digital and analogue outputs of a programmable

output system (Power1401, CED) using Signal (version 6.04, CED). Force data from the force sensor was acquired at 2,500 Hz via the digital input channels of the data acquisition interface (Power1401, CED) and visualised via Signal. The device was calibrated to identify how much voltage output was translated into force and the subsequent effect on the reading from the force sensor. A 0.25V output was equivalent to a 1 N force, which was equivalent to a 0.0197V reading by the force sensor.

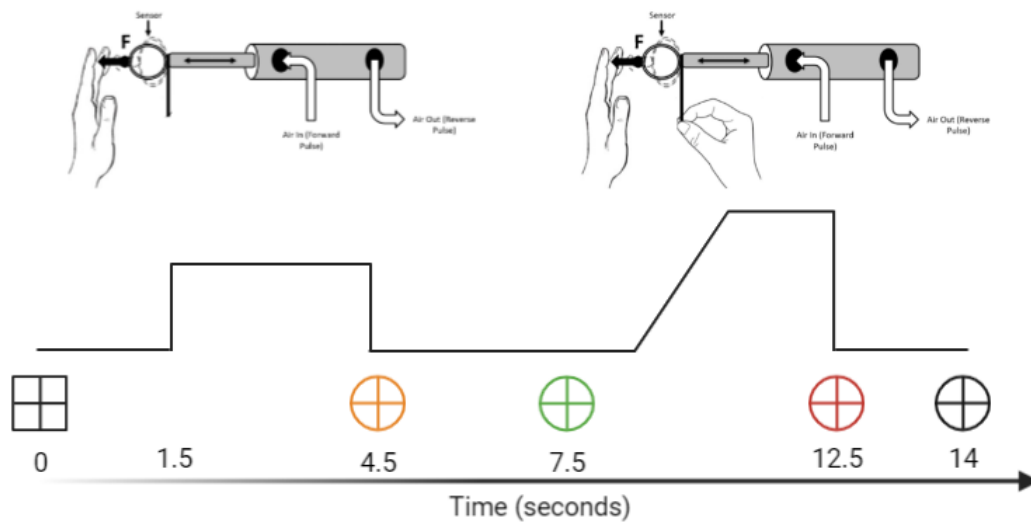


Figure 4.1 – Force Matching paradigm: The force matching paradigm used to quantify sensory attenuation. An illustration of the force trace produced and the stimuli presented on each trial is displayed.

4.2.4 Procedure

Participants, both healthy volunteers and stroke survivors, attended the lab for a single session and performed the force matching task. Participants sat in front of a table and placed the tip of their left index finger in front of the force transducer on a specifically designed finger rest while looking at a computer monitor (DELL 1909W, 19” LCD Display). Each trial begun with the presentation of a black box with a fixation cross and 1.5 seconds later the force transducer applied the determined level of target force to the left index finger. The target force was chosen from a four pre-determined force levels: 1, 2, 3 and 20 Newtons (N). The target forces were presented in a pseudo-random order

with each target force presented once within a cycle of four trials. The target force was presented for 3 seconds. At the end of the presentation period, the target force was removed and an orange circle with a fixation cross was presented on the screen. Participants were instructed to simply remember the level of force they just experienced on the tip of their finger and do nothing else for a further 3 seconds. Participants were then presented with a green circle with a fixation cross, which was the cue to match the intensity of the force they just experienced by mechanically manipulating a lever located on the force transducer with their right hand. Participants were given 5 seconds to match the level of force previously experienced and were instructed to hold that level of force until they were presented with the stop cue, a red circle with a fixation cross. At the presentation of the stop cue, participants were instructed to release the lever and the force transducer returned to its original position automatically. The cue then changed to a black circle with a fixation cross that was indicative of the inter trial interval, which was set at 1.5 seconds. An illustration of the stimuli presented, and the force trace produced across each trial can be seen in figure 4.1. The force sensor located at the end of the transducer measured both the target and matched forces applied to the left index finger. All participants completed an initial familiarisation phase of 12 trials (three cycles of the four target forces) before the start of the main experiment. The main experiment consisted of a total of eight blocks of 20 trials each (160 trials in total), with five trials for each target force presented per block to ensure the same total force was experienced in each block. Subjects were given a two-minute break between blocks. None of the applied forces was experienced as painful by any of the participants. Stimulus presentation was carried out on a desktop computer using a custom-built script in Signal (version 6.04, CED) software. Participants from the Cam-CAN database performed the force matching paradigm as described in Wolpe et al (Wolpe et al., 2016). A lever attached to a torque motor applied a pre-determined target force (1.0, 1.5, 2.0 and 2.5 Newtons) for 2.5 s to the left index

finger positioned under the lever. At the end of the target force presentation period, participants used their right index finger to match the force they had just felt on their left index finger by pressing directly on top of the lever, mechanically transmitting the force to the left index finger. The matched force was calculated as the mean force measured between 2 and 2.5 s after the start of the matching period. A force sensor at the end of the lever measured both the target and matched force.

4.2.6 Analysis

4.2.6.1 Fatigue questionnaires

FSS-7 was scored using the standard procedure where the average of each of the seven statement scores was considered as the participant's overall fatigue score. Stroke survivors were subsequently divided into two groups, high and low fatigue groups, based on their FSS-7 scores. Stroke survivors with an FSS-7 score greater or equal to five were classified as high fatigue and those with an FSS-7 score less than five were classified as low fatigue.

4.2.6.2 Sensory attenuation and behaviour

The data files were extracted from Signal into MatLab and were analysed offline using custom-written routines in MatLab (2018a, Mathworks). Average force data was measured at the start of the experiment (prior to target force onset) and during the waiting phase (prior to cue onset to start matching). Any force activity during the waiting phase was indicative of premature responses and these trials were discarded. Participants in which more than 20% of trials were rejected, were excluded from the final analysis. On average, 7% of trials were discarded for the stroke survivor dataset and 4% of trials were discarded for the healthy volunteer dataset. The amplitude of the target force was taken as the mean activity of the force trace in the last two seconds of the target phase minus the baseline activity. As seen in Chapter 3 of this thesis, stroke survivors with fatigue have

altered force output. Therefore, using a fixed time window to measure matched force across all participants was not the most accurate method. Instead, to measure the amplitude of the match force, a sliding window was used to identify the 500 ms interval during the matching phase that had the minimum force variability. Force variability was quantified by calculating the coefficient of variation (SD/mean) over the entire duration of the matching phase. The mean force within that 500 ms time window was calculated on a trial-by-trial basis and used as the matched force. Trials in which the force level during the matching phase was not greater than that of the waiting phase for at least two of the five seconds were indicative that subjects did not respond to the cue correctly and forgot to respond and were discarded from further analysis. The degree of sensory attenuation was then quantified by subtracting the target force from the matched force.

$$\textit{Sensory Attenuation} = \textit{Matched Force} - \textit{Target Force}$$

A value greater than zero indicates that subjects applied more force than what they previously felt, a value equal to zero indicates that subjects applied exactly the same amount of force as what they previously felt and a value less than zero indicates that subjects applied less force than what they previously felt. This was carried out for each of the four force conditions. There was large amount of within and across subject variability in the measured target force for the 20 N condition, so this condition was excluded from all subsequent analysis. The degree of sensory attenuation in the Cam-CAN database was quantified using the same approach described above and was averaged across all trials and target force levels.

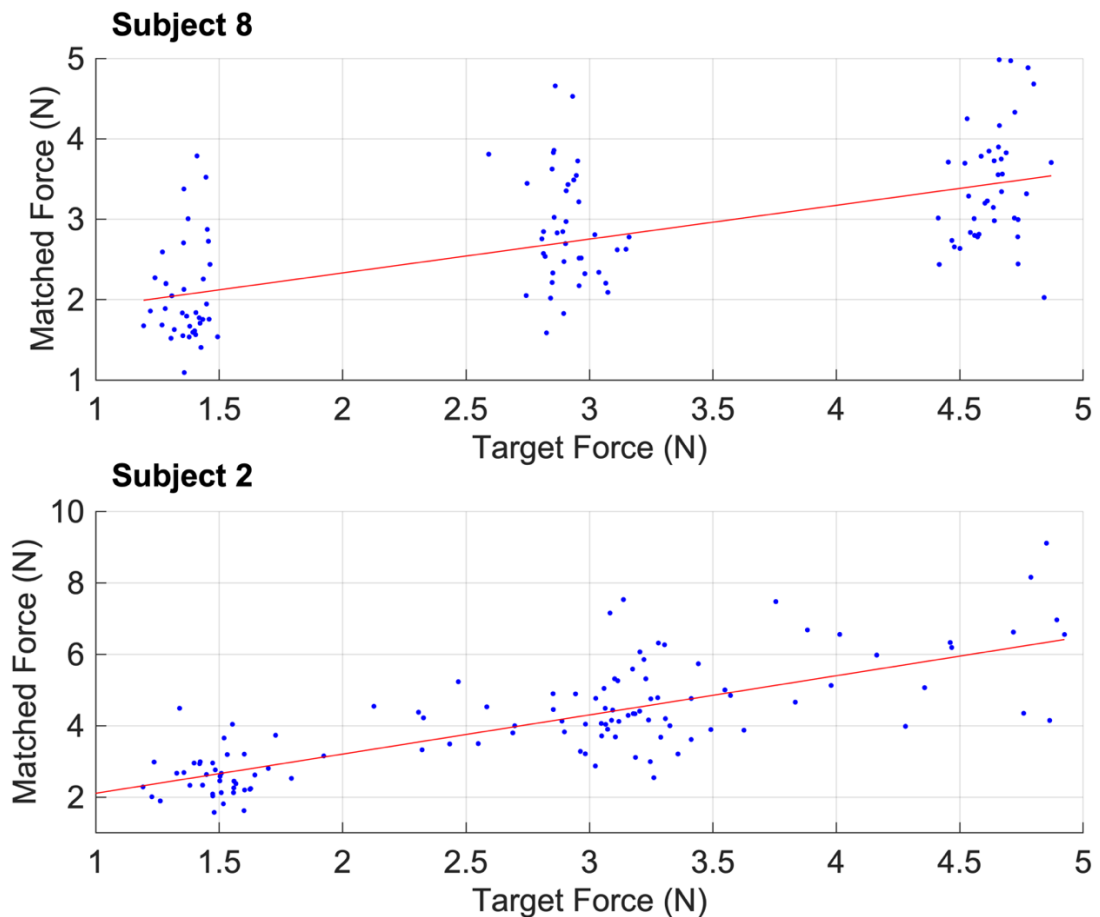


Figure 4.2 – Target vs Matched Force: The association between target force and matched force in two subjects. The blue dots represent each trial, and the red line is the first order polynomial fitted to the data. The top panel (subject 8) indicates that the subject felt three distinct target force levels that did not vary across conditions. The bottom panel (subject 2) indicates that the target force was not fixed across conditions and varied throughout the experiment.

A classical method used to analyse data obtained from force matching paradigms is to compare the amount of sensory attenuation as defined above for each of the different levels of target force. However, post-hoc analysis of the force traces revealed that the amount of force that subjects experienced during the target phase was not fixed across the different conditions (figure 4.2). It appeared to be influenced by the positioning of the subject's finger. An additional analysis was therefore carried out on the healthy volunteer and stroke survivor datasets treating the target force as a continuous scale rather than four categorical values. This was done for the three low force conditions (1N, 2N and 3N) in which a linear relationship between target force and matched force is expected.

A first order polynomial was fitted as a function of target force and matched force. A robust linear least-squares fitting method, namely the bisquare weights method, was incorporated into the first order polynomial. The bisquare weights method simultaneously seeks to find a curve that fits the bulk of the data using the least-squares approach while minimizing the effect of outliers. This method minimizes the weight sum of squares, where the weight given to each data point depends on how far the point is from the fitted line. Points near the line get full weight, while points farther from the fitted line get a reduced weight. Points that are further from the line than would be expected by random chance get a zero weight. The resulting coefficients of the fitted line were used for later statistical analysis. The gradient of the first order polynomial indicates how sensory attenuation changes as a function of target force while the y-intercept of the first order polynomial indicates the initial degree of sensory attenuation. As well as the coefficients of the first order polynomial, the goodness of fit (adjusted R^2 value) was also recorded for each participant and used for later analysis.

Additional behavioural measures were extracted from the force traces across all subjects to identify whether fatigue influenced task performance. A total of seven variables were extracted that reflected behaviour. These included: 1. The duration of the matching phase taken as the time from force onset to the time of force offset from the cue to start matching; 2. The time spent above the target force during the matching phase; 3. The coefficient of variation of the force trace during the matching phase calculated by dividing the standard deviation of the matched force by the mean of the matched force; 4. The force overshoot taken as the difference between the maximum force reached during the matching phase and the mean force during the matching phase; 5. The time after the cue to start matching that the force overshoot occurred; 6. The total amount of force exerted during the matching phase taken as the area under the force trace; 7. The initiation time of force matching.

4.2.6.3 Statistical analysis

Statistical analyses of the behavioural and motor control data were performed using non-parametric tests, unless stated otherwise, and implemented in R (Version 4.0.5).

4.2.6.3.1 Paradigm

To examine whether the data obtained from the novel force-matching device was similar to that obtained from the setup used previously, data from healthy volunteers from the novel setup was compared to data from the Cam-CAN database. Given the unequal sample size, non-parametric Mann-Whitney test was used to compare the degree of sensory attenuation as well as the within subject variability in sensory attenuation between paradigms.

4.2.6.3.2 Sensory attenuation

Wilcoxon signed-rank test was used to test if the degree of sensory attenuation across all participants in the novel paradigm was significantly different from zero. To examine the effect of fatigue on the degree of sensory attenuation, sensory attenuation was averaged across trials and force conditions for the low target force levels (1, 2 and 3 N). A Kruskal-Wallis test was used to compare the degree of sensory attenuation between the three fatigue groups (Healthy Controls, HC; Low Fatigue Stroke Survivors, LF; High Fatigue Stroke Survivors, HF). Bonferroni corrected pairwise comparisons were subsequently performed using the Dunn test. In addition to the degree of sensory attenuation, the coefficients of the first order polynomial (y-intercept and gradient) were also compared across fatigue groups to examine differences in task performance. Once again, Kruskal-Wallis test was used to compare the coefficients (y-intercept and gradient) across the three fatigue groups (HC, LF, HF).

Characteristic	HC, N = 21 ¹	LF, N = 31 ¹	HF, N = 15 ¹	p-value ²
Sex				0.031
Male	11 (52%)	25 (81%)	7 (47%)	
Female	10 (48%)	6 (19%)	8 (53%)	
Affected Hemisphere				>0.9
Right Hemisphere	0 (NA%)	15 (48%)	7 (47%)	
Left Hemisphere	0 (NA%)	16 (52%)	8 (53%)	
Dominant Hand				0.2
Left Hand	0 (0%)	4 (13%)	2 (13%)	
Right Hand	21 (100%)	27 (87%)	13 (87%)	
Age	52 (25, 63)	64 (58, 72)	56 (48, 67)	0.010
Time	NA (NA, NA)	4.0 (2.5, 6.6)	4.6 (2.1, 5.6)	0.7
Grip	NA (NA, NA)	94 (79, 107)	95 (90, 105)	0.7
NHPT	NA (NA, NA)	92 (75, 104)	98 (90, 114)	0.2
SDMT	NA (NA, NA)	1.15 (0.92, 1.32)	1.01 (0.87, 1.16)	0.4
HADS-Anxiety	NA (NA, NA)	4.0 (2.0, 6.0)	4.0 (4.0, 8.5)	0.4
HADS-Depression	NA (NA, NA)	3.00 (2.00, 6.00)	7.00 (5.00, 9.00)	0.012

¹n (%); Median (IQR)

²Pearson's Chi-squared test; Fisher's exact test; Kruskal-Wallis rank sum test

Table 4.1 – Demographics of stroke survivors and healthy volunteers for force matching paradigm: Demographics of all healthy volunteers and low and high fatigue stroke survivors (HC, LF and HF respectively) that took part in the study. P-values indicate the statistical significance between the three groups. Significance values for the association between FSS-7 are reported for continuous and categorical data. (NHPT = Nine Hole Peg Test; SDMT = Symbol Digit Modalities test; HADS = Hospital Anxiety and Depression Scale).

To examine the relationship between sensory attenuation and PSF further, a linear multiple regression analysis was conducted in the stroke survivor dataset only with sensory attenuation as the dependent variable. Rather than dividing the stroke survivors into high and low fatigue based on their FSS-7 score, fatigue was treated as a continuous

variable and was included in the multiple linear regression. Additional independent variables included the hemisphere affected by the stroke and the age of the stroke survivor. Additional predictors were included to account for differences in sensory processing and motor control and these included the gradient of the first order polynomial (the perceptual sensitivity to increasing force levels), the mean within-trial force variability within each participant and the unexplained variance (adjusted R^2) of the first order polynomial of matched versus target force across each participant. All variables were Z-scaled before entering the model. Assumptions of normality and homoscedasticity of the residuals for each linear regression model were assessed visually using quantile-quantile normal plots and fitted- versus residual-value plots.

4.2.6.3.3 Effect of fatigue on motor control

A Kruskal-Wallis test was used to examine the effect of fatigue (Healthy Controls, HC; Low Fatigue Stroke Survivors, LF; High Fatigue Stroke Survivors, HF) on the various motor control parameters extracted (match duration, time over target force, force overshoot, the time of force overshoot, total force exerted and the initiation time of force matching). Bonferroni corrected pairwise comparisons were subsequently performed using the Dunn test.

4.3 Results

4.3.1 Demographics

Of the forty-eight stroke survivors that completed the study, two were excluded from the final analysis due to a large number of rejected trials (50% and 60% of trials). No subjects were rejected from the healthy volunteer dataset. Participant demographics are displayed in table 4.1.

The CamCAN database (<https://camcan-archive.mrc-cbu.cam.ac.uk/dataaccess/>) contains data from 322 healthy volunteers (167 females; Median (IQR) Age = 63 (48, 79)) that performed the force matching paradigm.

4.3.2 Paradigm

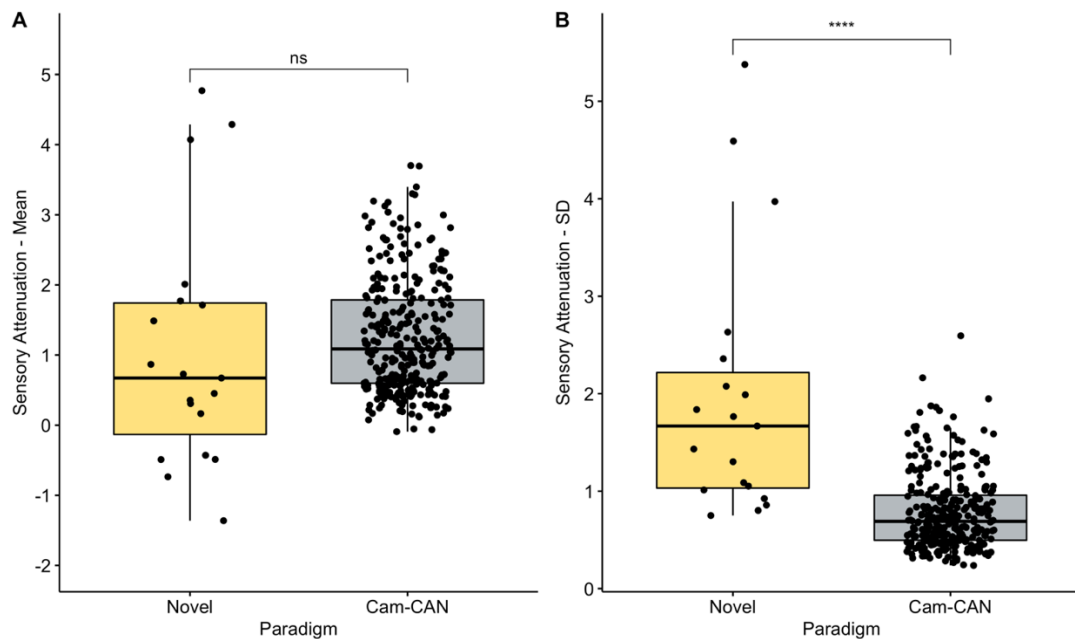


Figure 4.3 – Effect of paradigm on sensory attenuation: The effect of paradigm (Novel and Cam-CAN) on sensory attenuation visualised using boxplots. A. shows the mean sensory attenuation for the healthy volunteers in the novel (yellow) and Cam-CAN (grey) datasets across the different force conditions. B. shows the standard deviation of the mean sensory attenuation for the healthy volunteers in the novel (yellow) and Cam-CAN (grey) datasets. Each dot in the figure indicates a single subject. Significant differences between the two paradigms are indicated by * (n.s = not significant, **** = $p < 0.001$).

Mann-Whitney tests were used to compare the effect of paradigm (Novel and Cam-CAN) on the degree of sensory attenuation in the two healthy volunteer datasets (figure 4.3A). There was no significant difference in the degree of sensory attenuation across the low target force levels between the two paradigms ($W = 2294$, $Z = 0.0901$, $p = 0.1021$). There was however a significant difference in the variability of sensory attenuation within each

participant between the two paradigms ($W = 5225.5$, $Z = 0.310$, $p < 0.001$). This is clear from figure 4.3B, showing the within subject standard deviation of sensory attenuation.

4.3.3 Sensory attenuation

Across all participants in the novel paradigm, mean sensory attenuation across the low force conditions was 1.02 N (s.d. 1.36 N) and was significantly greater than zero (Wilcoxon signed-rank test; $n = 67$, $Z = -4.81$, $p < 0.001$, effect size $r = 0.603$). 47/65 participants showed overall sensory attenuation indicated by a positive mean sensory attenuation. Five healthy volunteers, nine low fatigue stroke survivors and four high fatigue stroke survivors did not show sensory attenuation indicated by a negative mean sensory attenuation.

To examine the effect of fatigue on the degree of sensory attenuation, the average sensory attenuation was compared between the different groups (HC, HF and LF). As there was no difference in the degree of sensory attenuation in our novel paradigm and that used in the Cam-CAN database, the healthy volunteers were pooled together between paradigms. There was no significant difference in sensory attenuation across the different fatigue groups (Kruskal-Wallis rank sum test; $\chi^2(2) = 2.27$, $p = 0.322$, $n = 381$). Pairwise comparisons across the different groups were also non-significant (HC-LF = -0.279, $p = 0.780$; HC-HF = -1.48, $p = 0.135$; LF-HF = -1.10, $p = 0.273$). The same analysis was repeated when stroke survivors and healthy volunteers were matched for age. Once again, there was no significant difference in sensory attenuation different (Kruskal-Wallis rank sum test; $\chi^2(2) = 2.41$, $p = 0.3$, $n = 200$) and pairwise comparisons across the different groups were non-significant (HC-LF = -0.324, $p = 0.746$; HC-HF = -1.55, $p = 0.122$; LF-HF = -1.13, $p = 0.257$).

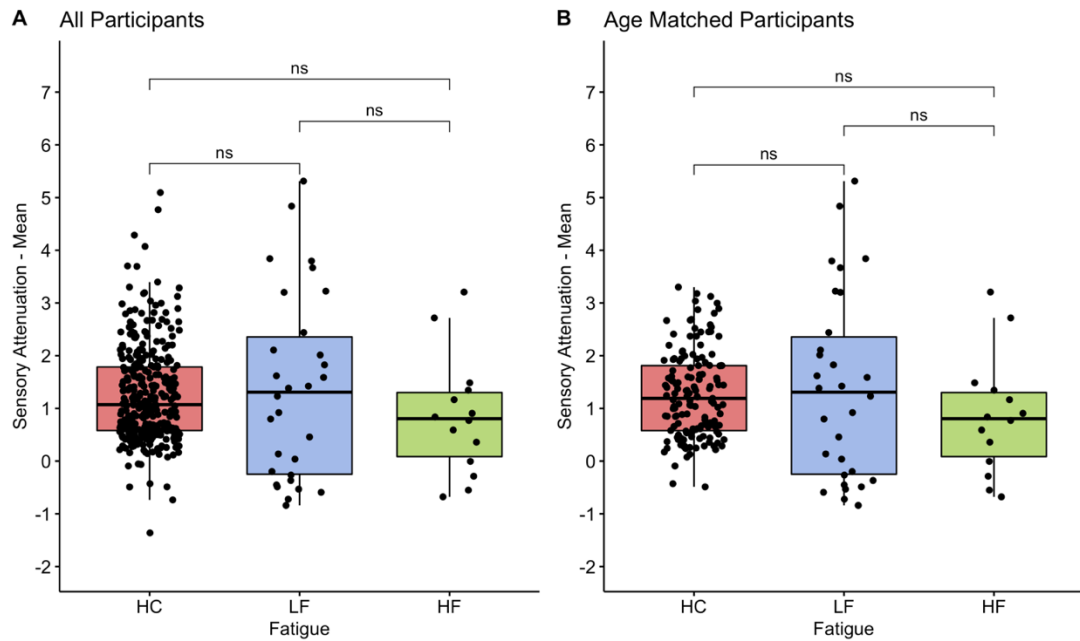


Figure 4.4 – Effect of PSF on sensory attenuation: The effect of fatigue on sensory attenuation. The effect of fatigue on mean sensory attenuation across all target force levels within each participant is represented using boxplots. This is done across all participants (A) as well as when participants in the different groups were matched for age (B). The red boxplots represent the healthy control group (HC), the blue boxplots represent the low fatigue stroke survivor group (LF) and the green boxplots represent the high fatigue stroke survivor group (HF). The black points represent individual participants. Significant differences between the two paradigms are indicated by * (n.s = not significant, **** = $p < 0.001$).

To examine the effect of fatigue on task performance, the coefficients (y-intercept and gradient) of the first order polynomial of target versus matched force were compared across the different groups (HC, LF and HF; figure 4.5). In this instance, the HC group only included data from the ‘Novel’ paradigm as this data was not available from the Cam-CAN database. The y-intercept of the first order polynomial represents the degree of sensory attenuation at “rest” – when target force is equal to zero while the gradient of the first order polynomial represents the relationship between target force and match force with increasing target force level (force sensitivity). There was no significant difference in the y-intercept of the first order polynomial across the different fatigue groups (Kruskal-Wallis rank sum test; $\chi^2(2) = 1.23$, $p = 0.542$, $n = 66$). Pairwise comparisons across the different groups were also non-significant (HC-LF = 1.07, $p =$

0.282; HC-HF = 0.320, $p = 0.749$; LF-HF = -0.625, $p = 0.532$). There was also no significant difference in the gradient of the first order polynomial across the different fatigue groups (Kruskal-Wallis rank sum test; $\chi^2(2) = 0.684$, $p = 0.71$, $n = 66$). Pairwise comparisons across the different groups were also non-significant (HC-LF = 0.783, $p = 0.434$; HC-HF = 0.620, $p = 0.535$; LF-HF = -0.0412, $p = 0.967$).

	Model 1
(Intercept)	1.47 *** [1.03, 1.91]
FSS-7	-0.06 [-0.37, 0.24]
Gradient	1.19 *** [0.89, 1.49]
Unexplained Variance	-0.51 ** [-0.82, -0.21]
Coefficient of Variation	0.10 [-0.19, 0.40]
Affected Hemisphere (Left)	-0.47 [-1.07, 0.13]
Age	0.11 [-0.19, 0.41]
N	44
R ²	0.69

All continuous predictors are mean-centered and scaled by 1 standard deviation. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

Table 4.2 – Multiple linear regression parameters: The results of the multiple linear regression equation showing the beta estimates and their associated 95% confidence intervals for each of the predictors.

To examine the relationship between sensory attenuation and fatigue severity, a multiple linear regression model with mean sensory attenuation across all target force levels as the dependent variable. The independent variables were fatigue severity as assessed using the FSS-7, the affected hemisphere and age of the stroke survivors. To control for basic sensory and motor differences affecting the performance of the force matching experiment, additional predictors were included such as the gradient measuring force sensitivity, force variability and the unexplained variance of the linear fit for each stroke survivor. The multiple linear regression model was statistically significant ($F(6,37) =$

13.88, $p < 0.001$) and explained 64% of the variance in sensory attenuation (adjusted $R^2 = 0.6425$). The standardized beta estimates and their 95% confidence intervals are reported in table 4.2. Despite a significant linear regression model, FSS-7 was not a significant predictor of sensory attenuation (figure 4.6) even when accounting for hemisphere affected, age and basic sensory and motor differences across participants.

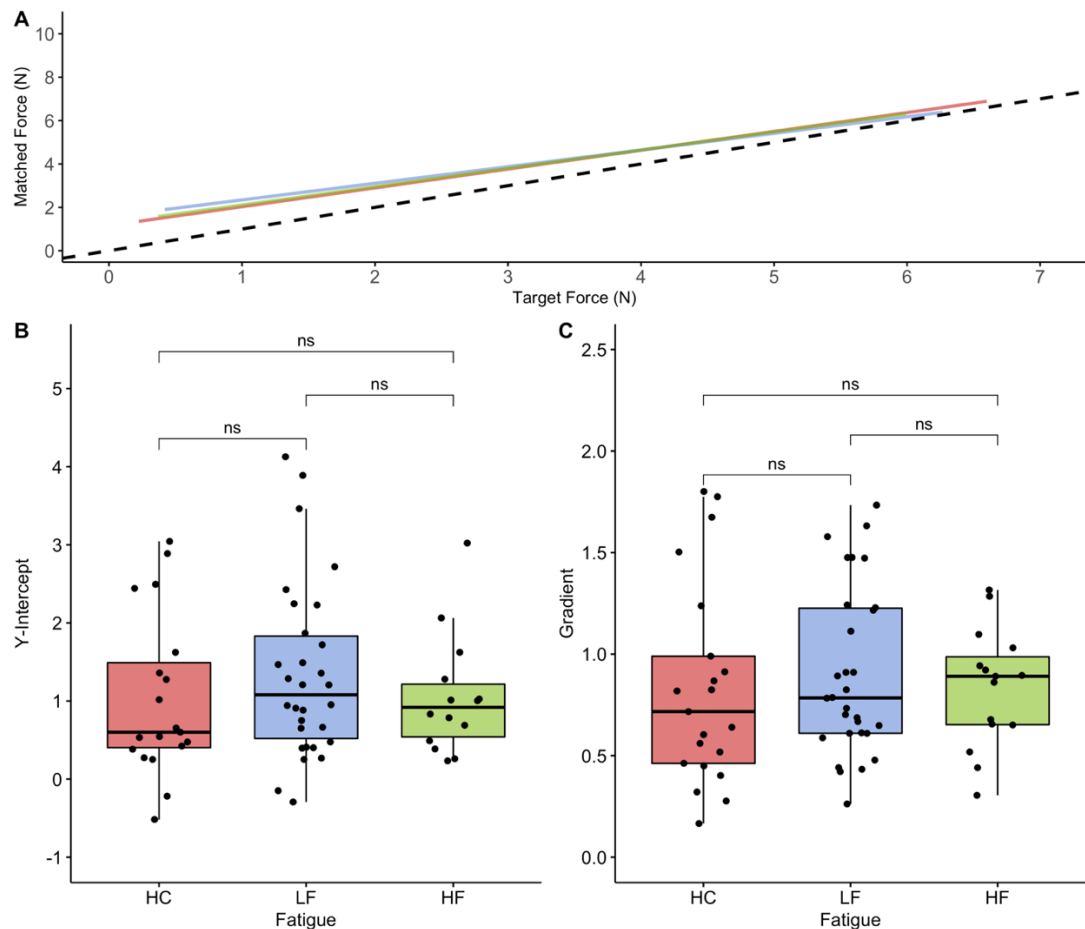


Figure 4.5 – Model parameters and PSF: Differences in sensory attenuation between healthy volunteers and stroke survivors with and without fatigue. A. Mean regression plots of matched versus target force across the different groups. The red line represents the healthy volunteers group, the blue line represents the low fatigue group and the green line represents the high fatigue group. The dashed lined indicates the line of equality. Boxplots representing the y-intercept (B) and gradient (C) of the first order polynomial fitted for each participant. The dots represent individual participants and the colour scheme is the same as in A.

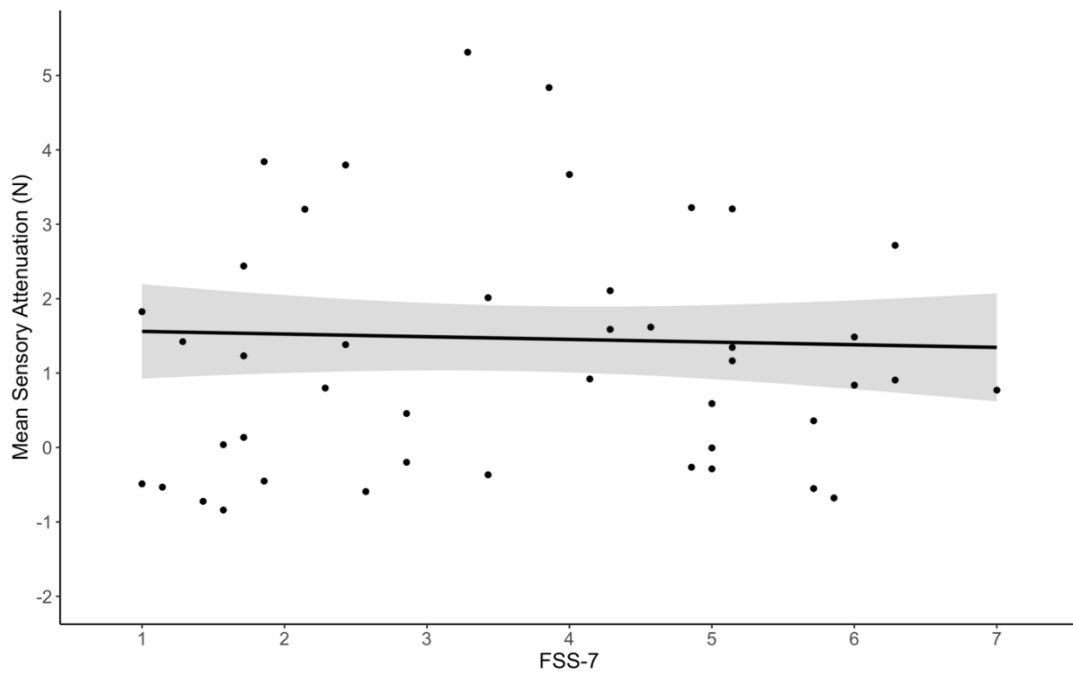


Figure 4.6 – Sensory attenuation and FSS-7. The association between the mean sensory attenuation and fatigue severity (FSS-7). Dots represent individual stroke survivors, the solid dark line represents the result of the multiple linear regression and the shaded area represents the 95% confidence interval.

4.3.4 Motor Control

There was no significant effect of fatigue on the duration of the matching phase (Kruskal-Wallis rank sum test; $\chi^2(2) = 0.8111$, $p = 0.667$, $n = 67$); the time spent above the target force during the matching phase (Kruskal-Wallis rank sum test; $\chi^2(2) = 0.0905$, $p = 0.956$, $n = 67$); the force overshoot during the matching phase (Kruskal-Wallis rank sum test; $\chi^2(2) = 1.48$, $p = 0.477$, $n = 67$); the time of overshoot (Kruskal-Wallis rank sum test; $\chi^2(2) = 4.03$, $p = 0.133$, $n = 67$); the total amount of force exerted during the matching phase (Kruskal-Wallis rank sum test; $\chi^2(2) = 0.997$, $p = 0.607$, $n = 67$); the mean time at which the matching force was stabilised after initiation (Kruskal-Wallis rank sum test; $\chi^2(2) = 0.671$, $p = 0.715$, $n = 67$). All pairwise comparisons across the different groups were non-significant.

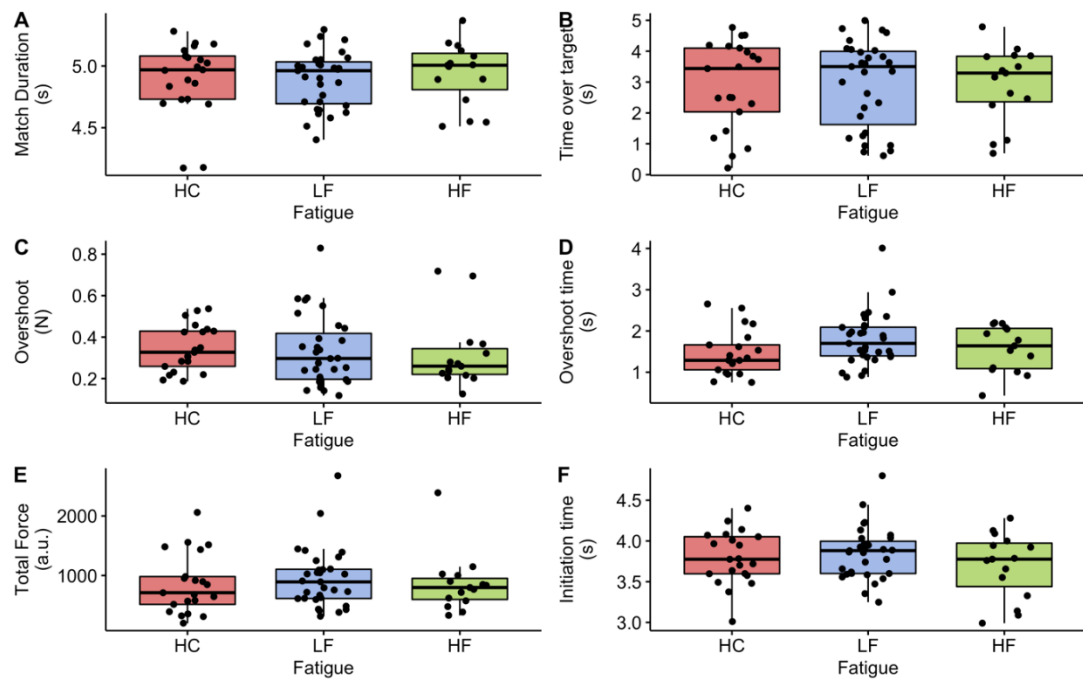


Figure 4.7 – Motor control and PSF: Motor control and task performance (A. Duration of the matching phase; B. The total time spent above the target force; C. The force overshoot; D. The time at which the force overshoot occurred; E. The total force exerted during the matching phase taken as the area under the force trace; F. The time from which the matching phase was taken) during the matching phase across the different fatigue groups. The red boxplots represent the healthy control group (HC), the blue boxplots represent the low fatigue stroke survivor group (LF) and the green boxplots represent the high fatigue stroke survivor group (HF). The black points represent individual participants.

4.4 Discussion

In this study, I aimed to explore the relationship between sensory attenuation, as quantified using the force matching paradigm, and self-reported fatigue. I hypothesised that stroke survivors with high severity of fatigue will show reduced sensory attenuation as indicated by the amount of force overcompensation when asked to match a reference force, while stroke survivors with low severity of fatigue would behave similarly to healthy volunteers. The current results do not provide support to the abovementioned hypothesis. Despite a trend in the hypothesised direction, lower overall sensory attenuation in high fatigue stroke survivors compared to low fatigue stroke survivors and healthy volunteers, this effect was not statistically significant. Following the results from

Chapter 3, in which stroke survivors with high severity of fatigue also exhibited differences in motor control, I explored the association between task performance and fatigue across several different variables. In the current experiment, there was no effect of fatigue severity on any of the measures of motor control and task performance.

4.4.1 Force matching paradigm and sensory attenuation

There are a number of possible explanations for the current results, or lack thereof. The force matching paradigm that has been classically used to quantify sensory attenuation involves subjects placing their index finger, either of the left or right hand, below a lever that is attached to a torque motor while holding their hand in a supine position (Bays et al., 2006; Bays and Wolpert, 2007; Shergill et al., 2003). After feeling a target force on their index finger, subjects are subsequently instructed to match the passively experienced target force with their other index finger by either directly exerting a force onto the lever and pressing onto the index finger below the lever or by controlling the lever indirectly using a sliding linear potentiometer that controlled the torque motor. These two different conditions represent a direct and an indirect condition respectively. In the current study, the setup of the force matching device was modified to increase comfort for stroke survivors. The current setup also involved subjects placing their index finger behind a lever while their hand is at rest in a neutral position, but instead of using their other index finger to directly exert a force onto the lever and subsequently the index finger behind the lever, subjects were asked to manipulate a lever attached to the force transducer with the thumb and index finger of the other hand to match the level of force they had just experienced. In the current setup I did not explore the effect of the indirect condition on sensory attenuation. In the direct condition, the sensory consequences of the movement are predictable and are therefore attenuated. The attenuation of the predicted sensory input is measured as an overcompensation when subjects are asked to match the sensation

of a previously felt force. On the other hand, in the indirect condition, the sensory consequences of the movement are not predictable as the relationship between the action (moving the sliding potentiometer) and its sensory consequences (a force applied to one finger of the other hand) is unusual. In this case, subjects should be able to match the sensation of a previously felt force more accurately as there is no attenuation of the sensory consequences of the movement. In the current study, subjects overestimate a target force less (lower sensory attenuation), albeit not significantly less, than what has previously been demonstrated in a previous study using the classic setup (Wolpe et al., 2016). The average force overcompensation in the direct condition of the Cam-CAN database of 322 healthy participants was 1.198 N and was a robust effect. In total, 98% of participants showed sensory attenuation indicated by a positive mean overcompensation (Wolpe et al., 2016). In the current study, average force overcompensation was 1.02 N and was not as robust as previously reported with only 72% of participants showing sensory attenuation. A major difference between the two experimental paradigms is the within-subject variability in the sensory attenuation. Despite having similar number of trials, 128 trials in the Cam-CAN study and 120 trials in the current setup, and similar target force levels, there was a significantly larger within and across subject variability, indicated by a larger standard deviation, of the average force overcompensation in the current setup. A possible explanation for the increased variability and the lower overall sensory attenuation in the current study is the paradigm used and the fact that subjects had to manipulate a lever to match the target force level rather than directly pressing on themselves. Given the relationship between moving the lever and feeling a force on one finger of the opposite hand is intuitive, this condition could be considered as being something between the direct and indirect condition of the classic paradigm. Although a possibility, given the movement of the lever did not require a plane transformation unlike the indirect condition of the classic study where movement

in the horizontal plane was transformed into movement of the probe in the vertical plane, this is unlikely. The current setup has a closer resemblance to the direct condition than the indirect condition of the classic setup. Given the above, sensory attenuation would therefore be reduced as sensory attenuation is expected in the direct condition while no sensory attenuation is expected in the indirect condition, which is in line with the observed results of overall reduced sensory attenuation across all participants in the current study. Subjects might also be alternating between these two processes throughout the entire task, or different subjects might be using different strategies when performing the task, which might account for the increased variability seen in the current study.

4.4.2 Somatosensory receptors and the force matching paradigm

A key question that one needs to consider is what the force matching experiment measures. The principal idea, as described previously, is that afferent input resulting from self-generated actions is predictable and subsequently attenuated to allow for the processing of salient and unexpected stimuli and hence allows one to distinguish between self and externally generated afferent input (Brown et al., 2013). The force matching experiment is a bimanual task in which one hand is doing the matching while the other hand is the feeling hand. There are therefore two sources of predictable afferent input that are attenuated and contribute to the overestimation effect seen in the direct condition of such paradigms. One source of predictable afferent input is in the form of proprioceptive information originating from somatosensory receptors such as muscle spindles and Golgi tendon organs located within the peripheral musculature of the hand doing the matching (Macefield and Knellwolf, 2018). In the force matching experiment, a lever applies a pre-determined level of force to the tip of the index finger which activates a number of mechanoreceptors embedded within superficial and deep layers of the skin that respond to low energy mechanical stimuli such as light touch, pressure and vibration

(Johnson, 2001). Therefore, the second source of predictable afferent input is in the form of exteroceptive input originating from mechanoreceptors located in the tip of the index finger of the feeling hand. For the two sources of afferent information to be attenuated, they need to be related to each other as evident from the overcompensation effect seen in the direct condition but not in the indirect condition of the force matching experiment. A possible explanation for the results of the current study, a non-significant reduction in sensory attenuation in stroke survivors with high severity of fatigue, is the failure to attenuate one and not both sources of afferent input. This will subsequently result in less overcompensation of a reference force (reduced sensory attenuation) but not as pronounced as when there is a failure to attenuate both sources of afferent input. The question then arises, are stroke survivors with PSF unable to attenuate proprioceptive afferent input or exteroceptive afferent input originating from mechanoreceptors located in the periphery? Stroke survivors with PSF have a sensation of limb heaviness when at rest (Kuppuswamy et al., 2016). When at rest, there is no exteroceptive afferent input to be attenuated so this phenomenon of limb heaviness can be explained as a reduced attenuation of proprioceptive afferent information originating from the resting peripheral muscle tone. Together with the anecdotal evidence from stroke survivors where simple activities of daily living are experienced as more effortful suggests that PSF is more likely a result of reduced sensory attenuation of proprioceptive afferent input and not exteroceptive afferent input originating from mechanoreceptors.

4.5 Conclusion

I cannot draw any conclusions with regards to the effect of fatigue on sensory attenuation, however the results of the current study highlight future questions that should be addressed, namely the relationship between attenuation of proprioceptive afferent input and PSF. A number of methodological issues also arise as a result of the study. Sensory

attenuation has been extensively studied across a number of neurological and psychiatric conditions (Pareés et al., 2014; Shergill et al., 2005; Teufel et al., 2010; Wolpe et al., 2018) using the force matching task which relies on custom-made devices. While these custom-made devices operate under the same principles, consistency in terms of force application and force measurement is essential to allow for meaningful conclusions and having a detailed description of the design, development and functionality of such custom-made devices is invaluable.

Chapter 5: Impact of fatigue on corticospinal excitability during movement preparation

5.1 Introduction

The motor cortex has been primarily thought of as the main output region of the brain, sending efferent projections to the spinal cord that incite movement. However, recent theoretical accounts suggest that the output of the motor cortex is in the form of top-down predictions of the proprioceptive consequences of movement (Feldman and Friston, 2010). The sensory attenuation model of fatigue proposes that fatigue is a result of reduced sensory attenuation and altered effort perception. Attenuation of proprioceptive prediction errors is necessary to initiate movements, as previously described in the introduction, while attenuation of afferent proprioceptive bottom-up input resulting from the movement itself deems the movement effortless.

When preparing for a voluntary movement, there are substantial changes in the activity of neurones within the premotor and primary motor cortex (M1) despite no electromyographic (EMG) activity (Tanji and Evarts, 1976). The state of the motor cortex at a time prior to movement is commonly referred to as the ‘movement preparation’. Notably, corticospinal excitability does not only change during movement initiation but also undergoes distinct modulation during movement preparation (Cisek and Kalaska, 2010). Movement preparation has been extensively studied in humans using TMS over M1 to probe corticospinal excitability changes during cue-driven reaction time (RT) paradigms (Duque and Ivry, 2009; Hannah et al., 2018; Hasbroucq et al., 1997; Ibáñez et al., 2020). Cues for guiding movement are probabilistic in nature and learning the probabilities of upcoming movements enable the motor system to prepare motor output prior to movement initiation. Suppression of corticospinal excitability prior to movement

initiation is seen in muscles that are both involved and uninvolved in an action (Bestmann and Duque, 2016; Duque et al., 2017; Greenhouse et al., 2015). The predicted aspects of sensory information (target cues in RT paradigms) are represented explicitly in the modulation of corticospinal excitability during movement preparation.

One of the proposals of sensory attenuation model of fatigue is that, the inability to suppress predicted sensory stimuli (reduced sensory attenuation) results in high perceived effort leading to fatigue (Kuppuswamy, 2017). A previous study has also shown that self-selected ballistic movement speeds are slower and resting corticospinal excitability assessed using transcranial magnetic stimulation (TMS) is reduced in the affected hemisphere of stroke survivors who report high levels of PSF (A. Kuppuswamy et al., 2015; Annapoorna Kuppuswamy et al., 2015). Speed of ballistic movements is dependent on the ability of the motor cortex to activate necessary corticospinal output to initiate movement and are intrinsically linked to corticospinal excitability (Jäncke et al., 2004). Movement preparation plays a crucial role in determining ballistic movement speeds. The theoretical account of PSF and the previously reported experimental evidence from studies on PSF, when taken together, suggest that pre-movement excitability representing predicted proprioceptive consequences of movement may be altered in those who exhibit high levels of fatigue. Indeed, such differences in corticospinal excitability during movement preparation have previously been reported in multiple sclerosis patients with high and low fatigue (Morgante et al., 2011). Behaviourally, such changes may result in reduced movement speeds (mediated by high perceived effort) which has been seen in stroke survivors with high fatigue (A. Kuppuswamy et al., 2015). While previous studies reported no difference in reaction times in PSF, in this study however, I chose to study pre-movement excitability in a reaction time task and not movement time for two reasons. One, it is known that the technique of TMS used to study pre-movement excitability induces a change in reaction time and it is not known if fatigue influences the TMS

induced delay in reaction time. Secondly, reaction time and movement time are inextricably linked, and any influence on reaction time will subsequently influence movement time. Therefore, the aim of this study was to investigate the modulation of corticospinal excitability in a reaction time task in stroke survivors with varying severity of PSF.

5.2 Materials and Methods

5.2.1 Subjects

The study was approved by London Bromley Research Ethics Committee (REC reference number: 16/LO/0714). Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. Stroke survivors were recruited from the database of eligible stroke survivors described in Chapter 2 of this thesis. Seventy-three stroke survivors took part in the experiment between February 2017 and May 2019 (demographics shown in table 5.1).

5.2.2 Surface Electromyogram and Transcranial Magnetic Stimulation

Recordings were carried out on the first dorsal interosseous (FDI) muscle of the affected hand. Following skin preparation using alcohol swabs, EMG recordings were obtained from the FDI muscle using surface neonatal prewired disposable electrodes (1041PTS Neonatal Electrode, Kendell) in a belly-tendon montage with the ground positioned over the flexor retinaculum of the hand. The signal was amplified with a gain of 1000 (D360, Digitmer, Welwyn Garden City, UK), bandpass filtered (100-1000 Hz), digitized at 5 kHz (Power1401, CED, Cambridge, UK) and recorded with Signal version 6.04 software (CED, Cambridge, UK). EMG recordings enabled the measurement of motor evoked potentials (MEPs).

A standard monophasic TMS device (Magstim 2002, Magstim, Whitland, Wales) connected to a figure-of-eight coil (wing diameter, 70 mm) was used to stimulate the hand area of M1 in the hemisphere affected by the stroke. The coil was held tangentially on the scalp at an angle of 45° to the mid-sagittal plane to induce a posterior-anterior current across the central sulcus. The subjects were instructed to stay relaxed with their eyes open and their legs uncrossed. The motor 'hotspot' of the FDI muscle was determined as follows: the vertex (cross-over point between the mid-point between the two tragi and midpoint between nasion and inion) was marked using a dry wipe marker. Four centimetres lateral and 2 cm anterior from the vertex was then marked on the contralateral hemisphere, which is the approximate location of M1. This was used as a rough guide for a starting point for determining the hotspot for the first dorsal interosseous. At 50% maximal stimulator output (MSO) (or higher or lower in some patients) the coil was moved in 1 cm blocks for ~2 cm anterior, posterior, lateral and medial to the marked region. Three stimuli were delivered at each spot and the location with the highest average motor evoked potential response was taken as the hotspot.

5.2.3 Resting motor threshold and 0.5mV intensity

Resting motor threshold (RMT) was defined as the lowest intensity of stimulation (% MSO) required to evoke a peak-to-peak MEP amplitude at the hotspot of at least 50 μ V in a minimum of 5 of 10 consecutive trials while subjects were at rest. The stimulation intensity that produced a visible MEP of approximately 0.1 mV was used as the starting point to define RMT and was adjusted accordingly. Throughout the experiment, the stimulator setting was adjusted to produce a target MEP size of 0.5 mV. This was defined as the stimulator setting (determined to the nearest 1% of MSO) required to evoke a peak-to-peak MEP amplitude of ≥ 0.5 mV in a minimum of 5 of 10 consecutive trials. A 0.5 mV response was preferred to a 1 mV response used previously as some stroke survivors

tend to have higher RMTs than the general population. A 0.5 mV MEP was achieved in all patients.

5.2.4 Simple Warned Reaction Time Task

Participants were seated comfortably in a chair facing away from the computer monitor with their hands palm-down on a pillow on their laps and performed a simple warned reaction time task. In each trial of the experiment, an auditory warning stimulus (WS) preceded an auditory imperative stimulus (IS) by a fixed interval of 500 ms. Participants were instructed to respond quickly and accurately to the IS by making a finger abduction using the index finger of the hemiparetic side. Prior to the start of the experiment, participants completed 15 trials of the warned reaction time task without TMS to determine their mean baseline reaction time (RT). The main experiment consisted of a single block of 70 trials. To prevent anticipation of the IS and premature responses, catch trials were included where a WS was given with no IS and participants were instructed not to respond on these trials (10 trials). TMS was delivered at six different time points (figure 5.1A): together with the WS (10 trials), late during the foreperiod (WP) defined as 167 ms before the IS (10 trials), together with the IS (10 trials) and at 30%, 50% and 70% of the mean baseline RT (10 trials for each). This resulted in six different TMS conditions, which will be referred to as the following from now on: WS, WP, IS, RT30, RT50, RT70. This allowed us to measure corticospinal excitability during movement preparation. The order of trials was pseudorandomized across the five different TMS timings. Following the completion of 70 trials, a separate single block of 10 trials of unwarned reaction time task was completed. This was not included in the main experiment in order to maintain the effect of the WS. In this task, participants were given an auditory IS with no WS (IS-WS) and were instructed to make a finger abduction using the same finger as previously described as quickly and accurately as possible. TMS was delivered together with the IS

(figure 5.1B). In both experiments, stimulus timings were controlled using Signal version 6.04 software connected to a data acquisition system (Power1401, CED, Cambridge, UK). Each trial was 1.5 seconds long and the inter-trial interval was set to 5.5 ± 1.5 seconds.

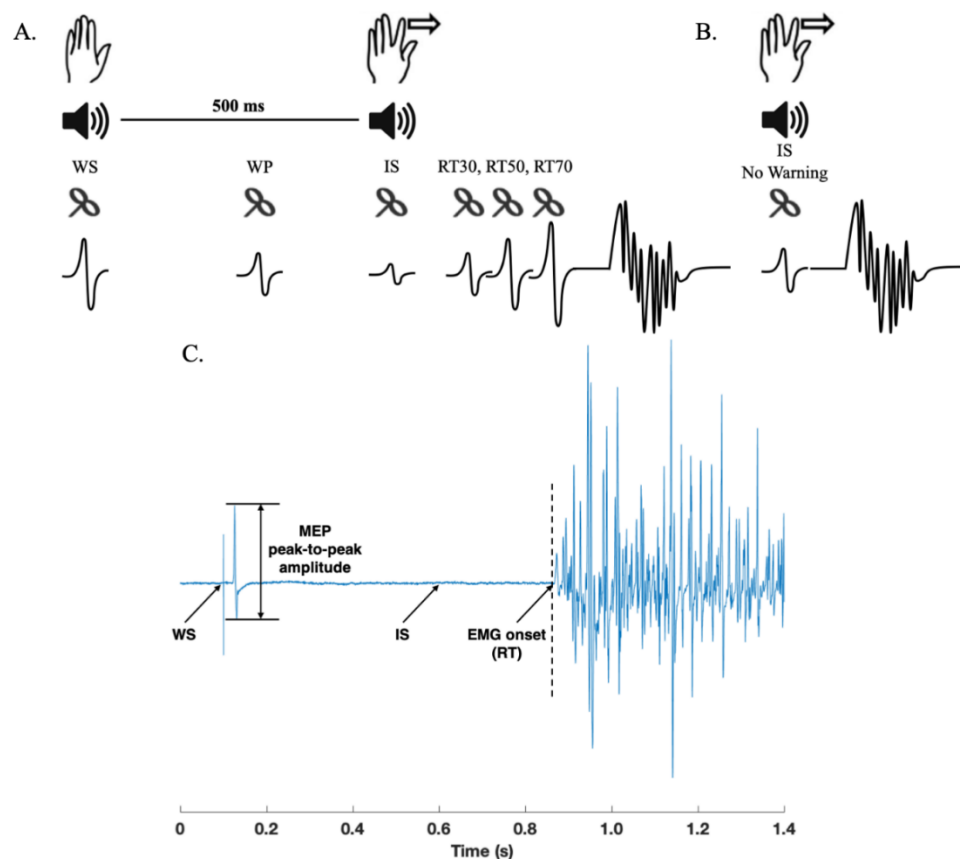


Figure 5.1 – Simple Warned Reaction Time Task and TMS: Study design for the simple auditory warned reaction time task (A) and the auditory unwarned reaction time task (B) used to study the modulation of corticospinal excitability during movement preparation. Warning Stimulus (WS), Warning Period (WP), Imperative Stimulus (IS), Imperative Stimulus (IS) No Warning, 30% RT (RT30), 50% RT (RT50) and 70% RT (RT70) indicate the different time points of stimulation across each task. Participants were instructed to carry out a ballistic index finger abduction after the auditory IS. An example electromyogram (EMG) trace indicating an motor evoked potential (MEP) and reaction time (RT) is shown in panel C.

5.2.5 Questionnaires

Trait fatigue was quantified at the very start of the experimental session using the Fatigue Severity Scale (FSS-7), a seven-item questionnaire asking for ratings of fatigue ranging from one to seven (strongly disagree to strongly agree) over the preceding week from the day of administration. An average score of seven being the highest fatigue and a score of one being no fatigue (Johansson et al., 2014). Stroke survivors also completed the HADS, a 14-item questionnaire with a depression and anxiety subscale, prior to the study. A score of 0 to 7 for either subscale could be regarded as being in the normal range, with a score of 11 or higher indicating probable presence of the mood disorder (Snaith, 2003).

5.2.6 Data Processing and Statistical Analysis

5.2.6.1 Screening Test Scores

Spearman's Rank Correlations between FSS-7 and a number of measures (age, anxiety, depression, grip strength, NHPT, symbol digit modalities test (SDMT), RMT and RT) were calculated. Wilcoxon rank sum tests were used to assess the difference in FSS-7 across different groups divided based on gender, hemisphere affected, and dominant hand being affected. The level of significance was set at $p = 0.05$ and p -values were adjusted for multiple comparisons using Bonferroni correction.

5.2.6.2 TMS Data

The data files were extracted from Signal into MatLab and were analysed offline using custom-written routines in MatLab (2018a, Mathworks). Two dependent variables were measured on a trial-by-trial basis as follows: (1) MEP peak-to-peak amplitude (figure 5.1C) and (2) reaction time (RT) measured from the time of the IS to the onset of volitional muscle activity (figure 5.1C). Peak-to-peak MEP amplitudes for each condition were estimated from the acquired EMG signal without applying any additional filters.

	data (N = 73)	P-value
FSS-7		
Mean (SD)	3.69 (1.84)	
Gender		<i>P</i> = 0.5637
Females Males	24 49	
Hemisphere Affected		<i>P</i> = 1.0000
Left Right	40 33	
Dominant Hand		<i>P</i> = 0.3775
Right Left	67 6	
Age (years)		
Mean (SD)	61.55 (12.11)	<i>P</i> = 1.0000
Grip (% unaffected hand)		
Mean (SD)	91.49 (18.82)	<i>P</i> = 1.0000
NHPT (% unaffected hand)		
Mean (SD)	89.70 (23.66)	<i>P</i> = 1.0000
SDMT		
Mean (SD)	1.19 (0.43)	<i>P</i> = 1.0000
Depression - HADS		
Mean (SD)	4.56 (2.95)	<i>P</i> < 0.0001
Anxiety - HADS		
Mean (SD)	5.04 (3.86)	<i>P</i> = 0.0069
RMT (% MSO)		
Mean (SD)	47.81 (10.69)	<i>P</i> = 1.0000
0.5mV Intensity (% MSO)		
Mean (SD)	59.03 (13.19)	<i>P</i> = 1.0000
Reaction Time (s)		
Mean (SD)	0.18 (0.06)	<i>P</i> = 0.3963

Table 5.1 – Demographics of stroke survivors for SWRT study: Demographics of all stroke survivors that took part in the study. Significance values for FSS-7 are reported for continuous and categorical data respectively. (NHPT = Nine Hole Peg Test; SDMT = Symbol Digit Modalities test; HADS = Hospital Anxiety and Depression Scale; RMT = resting motor threshold; MSO = maximum stimulator output).

A logarithmic transformation (to the base of *e*) of single-trial MEP amplitudes was performed before the statistical tests to ensure normality of the samples. Resting EMG was defined as the root mean square (rms) across all trials for each participant in the first 100 ms of each trial (prior to the WS). Thresholds set at five times these levels were used to determine the RT. All trials were then visually inspected and manually corrected to

ensure that RT was estimated properly, there was no undue influence of the silent period following stimulation and that no build-up of EMG was apparent before the TMS. Trials in which RT was less than 75 ms or greater than 500 ms were excluded from the final analysis as they represented premature and late responses respectively. Trials were also excluded if the MEP amplitude was less than 0.025 mV. Trials containing outlier MEP amplitudes (Grubb's test, $p < 0.005$) were also excluded from the final analysis. On average, 15.4% of TMS trials and 16% of catch trials were excluded across all stroke survivors with a minimum of 7 trials per stimulation condition.

To examine the effect of fatigue on corticospinal excitability and RT, log-transformed MEP amplitudes and RTs were labelled according to the time at which TMS was delivered (WS, WP, IS, RT30, RT50, RT70) and analysed by means of generalized mixed effects models carried out within the R environment for statistical computing, using the 'lme4' package (Bates et al., 2014). The 'lmerTest' package (Kuznetsova et al., 2017) was used to estimate the p-values for the t-test based on the Satterthwaite approximation for degrees of freedom. A stepwise ANOVA based on Satterthwaite's approximation of degrees of freedom for model selection (lowest AIC value and p-value) was used to identify the combinations of variables that best predicted the outcome variables (MEP amplitude and RT). Based on previous studies we had reason to believe that the change in MEP amplitude over time would follow a quadratic trend whereas RT would follow a linear trend (Bestmann and Duque, 2016; Hannah et al., 2018; Ibáñez et al., 2020). Therefore, we compared the AIC for both the linear and quadratic fit for both MEP amplitude and RT (table 5.2). The quadratic model with a random slope and intercept was a better fit for the MEP amplitude data while a linear model with a random slope and intercept was a better fit for the RT data and the effect of Warning. A similar analysis was used to examine the effect of fatigue and condition (Warning condition vs No Warning condition) on corticospinal excitability and RT (table 5.2). Assumptions of normality and

homoscedasticity of the residuals for each model were assessed visually using quantile-quantile normal plots and fitted- versus residual-value plots. Individual spearman's rank correlations were carried out between FSS-7 and the dependent variable in each model.

Fixed effects	Model Df	AIC	Chisq	Chi Df	Pr(>Chisq)
<i>Corticospinal Excitability</i>					
Time	5	6394.4			
Time ²	6	6334.4	61.6765	1	4.05e-15***
Time ² + FSS	7	6334.3	2.4676	1	0.11622
Time ² * FSS	9	6331.3	6.9242	2	0.03136*
Time ² * FSS + Anxiety + Depression	11	6336.9	0.4249	2	0.80862
<i>Reaction Time</i>					
Time	5	-6569.3			
Time ²	6	-6570.3	2.3481	1	0.12543
Time + FSS	6	-6567.5	0.2015	1	0.65351
Time * FSS	7	-6572.3	6.8826	1	0.008704*
Time * FSS + Anxiety + Depression	11	-6571.8	7.4255	4	0.11504
<i>Effect of Warning – Corticospinal Excitability</i>					
Time	6	3009.5			
Time + FSS	7	3008.7	2.7585	1	0.09674
Time * FSS	8	3009.2	1.5054	1	0.21985
<i>Effect of Warning – Reaction Time</i>					
Time	6	-2715.8			
Time + FSS	7	-2715.1	1.2095	1	0.2714
Time * FSS	8	-2713.6	0.5360	1	0.4641

Table 5.2 – Mixed effects model parameters and selection: The result of generalized mixed effects model comparisons across the corticospinal excitability data, the reaction time data and the effect of warning on both corticospinal excitability and reaction time. Participants nested in time are the random effect in each model. Significance levels are indicated by * (* < 0.05). Df=degrees of freedom; AIC = Akaike's information criterion; Chisq = chi-squared statistic; Chi Df = chi-squared degree of freedom; Pr(>Chisq) = probability value.

For a graphical representation of the results, stroke survivors were divided into two groups, high and low fatigue, based on their FSS-7 scores. A cut-off score of less than four on the FSS-7 was classified as low-fatigue and a score equal or greater than four was classified as high fatigue (Valko et al., 2008). Throughout the analysis, FSS-7 was treated as a continuous scale.

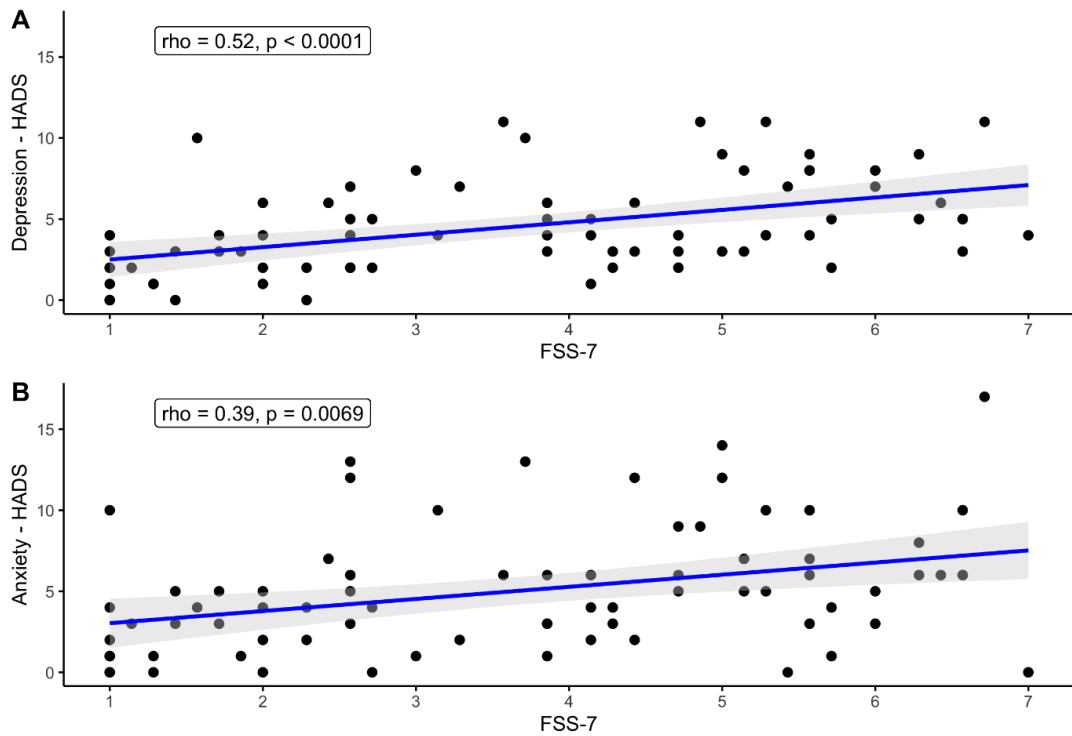


Figure 5.2 – PSF versus Depression and Anxiety: Associations between fatigue as measured by the Fatigue Severity Scale (FSS-7) and (A) depression and (B) anxiety.

5.3 Results

5.3.1 Demographics

There was a significant positive association between FSS-7 and anxiety ($\rho = 0.39, p < 0.0069$), depression ($\rho = 0.52, p < 0.0001$), figure 5.2. There was no association between FSS-7 and age, RMT, 0.5mV intensity and reaction time. There was no difference in FSS-7 in left hemisphere strokes compared to right hemisphere strokes and no difference between males and females.

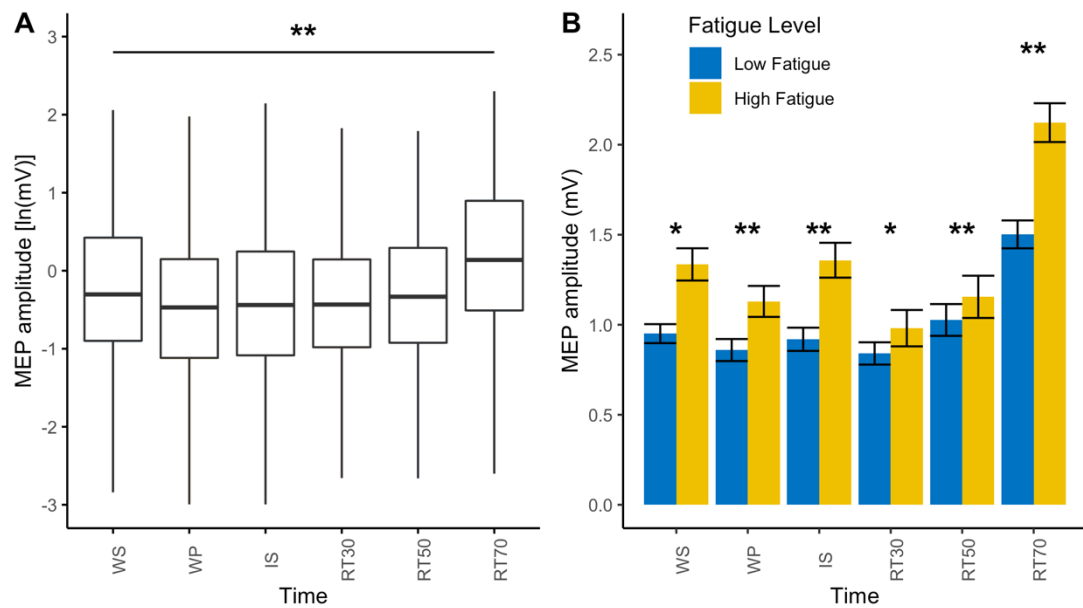


Figure 5.3 – PSF and MEP amplitude during movement preparation: The effect of time and fatigue on motor evoked potential (MEP) amplitude. A. Boxplot for MEP amplitude across all stroke survivors for each time point indicating the significant effect of time on MEP amplitude. B. Bar plots with standard error bars representing MEP amplitude across all time points with stroke survivors grouped based on their fatigue score indicating the significant interaction between time² and fatigue on MEP amplitude. Fatigue was measured using the Fatigue Severity Scale (FSS-7). Low fatigue patients (FSS-7 < 4) are represented in blue and high fatigue patients (FSS > 4) are represented in yellow. The association between fatigue (FSS-7) and MEP amplitude for each time point is also shown. Significance levels are indicated by * (* < 0.05, ** < 0.001).

5.3.2 Corticospinal excitability

A non-linear (quadratic) mixed effects model with time (WS, WP, IS, RT30, RT50 and RT70) and FSS-7 as fixed effects and participant nested in time as random effects best described the rate of change of corticospinal excitability during movement preparation. Including covariates that significantly correlated with FSS-7 (anxiety and depression) did not significantly improve the model. The mixed effects model showed that time² was a significant predictor of MEP amplitude ($\beta = -0.44$, $t = -4.73$, $p < 0.001$), FSS-7 did not significantly predict MEP amplitude ($\beta = -0.068$, $t = 0.321$, $p = 0.75$) and the interaction between time² and FSS-7 was a significant predictor of MEP amplitude ($\beta = -0.0066$, $t = -2.22$, $p = 0.0263$) such that stroke survivors with higher fatigue showed less modulation

of corticospinal excitability during movement preparation. There was a significant positive correlation between FSS-7 and MEP amplitude across all time points (WS: $\rho = 0.1$, $p = 0.02$, WP: $\rho = 0.13$, $p = 0.003$, IS: $\rho = 0.21$, $p < 0.001$, RT30: $\rho = 0.18$, $p = 0.006$, RT50: $\rho = 0.20$, $p = 0.003$, RT70: $\rho = 0.13$, $p = 0.005$). All corticospinal excitability data is presented in figure 5.3.

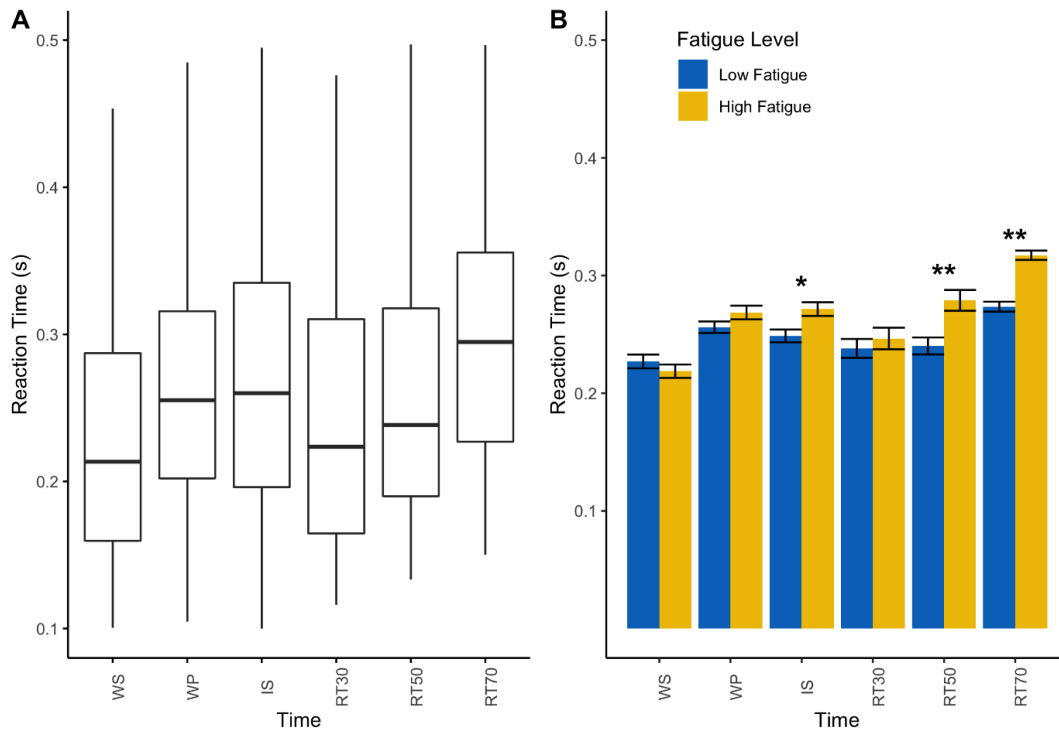


Figure 5.4 – PSF and RT during movement preparation: The effect of time and fatigue on reaction time (RT). A. Boxplot for RT across all stroke survivors for each time point indicating no significant effect of time on RT. B. Bar plots with standard error bars representing RT across all time points with stroke survivors grouped based on their fatigue score indicating the significant interaction between time and fatigue on RT. Fatigue was measured using the Fatigue Severity Scale (FSS-7). Low fatigue patients (FSS-7 < 4) are represented in blue and high fatigue patients (FSS > 4) are represented in yellow. The association between fatigue (FSS-7) and MEP amplitude for each time point is also shown. Significance levels are indicated by * (* < 0.05, ** < 0.001).

5.3.3 Reaction Time

A linear mixed effects model with time (WS, WP, IS, RT30, RT50 and RT70) and FSS-7 as fixed effects and participant nested in time as random effects best described the rate of change of reaction time during movement preparation. Including covariates that

significantly correlated with FSS-7 (anxiety and depression) did not significantly improve the model. The mixed effects model showed that the fixed effects of time ($\beta = 0.0039$, $t = 0.980$, $p = 0.363$) and FSS-7 ($\beta = -0.0033$, $t = -0.854$, $p = 0.396$) did not significantly predict RT. The interaction between time and FSS-7 ($\beta = 0.0024$, $t = 2.47$, $p = 0.0159$) was a significant predictor of RT such that stroke survivors with higher fatigue showed slower RTs the closer the stimulation time to movement onset. There was a significant positive correlation between FSS-7 and RT only at the IS ($\rho = 0.1$, $p = 0.01$), RT50 ($\rho = 0.31$, $p < 0.001$) and RT70 ($\rho = 0.32$, $p < 0.001$) time points. All RT data is presented in figure 5.4.

5.3.4 Effect of Warning

A linear mixed effects model with condition (Warning, No Warning) as a fixed effect and participant nested in condition as random effects best described the difference in corticospinal excitability and RT across the two conditions. FSS-7 did not significantly improve the model in either of the two cases. The mixed effects model showed that the fixed effect of condition ($\beta = 0.101$, $t = 4.072$, $p < 0.001$) was a significant predictor of MEP amplitude across the two conditions (figure 5.5a). The fixed effect of condition ($\beta = -0.004$, $t = -1.92$, $p = 0.0592$) was not a significant predictor of RT across the two conditions (figure 5.5b). There was a significant positive correlation between FSS-7 and MEP amplitude across both conditions (Warning: $\rho = 0.21$, $p < 0.001$, No Warning: $\rho = 0.11$, $p = 0.004$) and a significant positive correlation between FSS-7 and RT in the Warning condition ($\rho = 0.1$, $p = 0.001$), figure 5c-d.

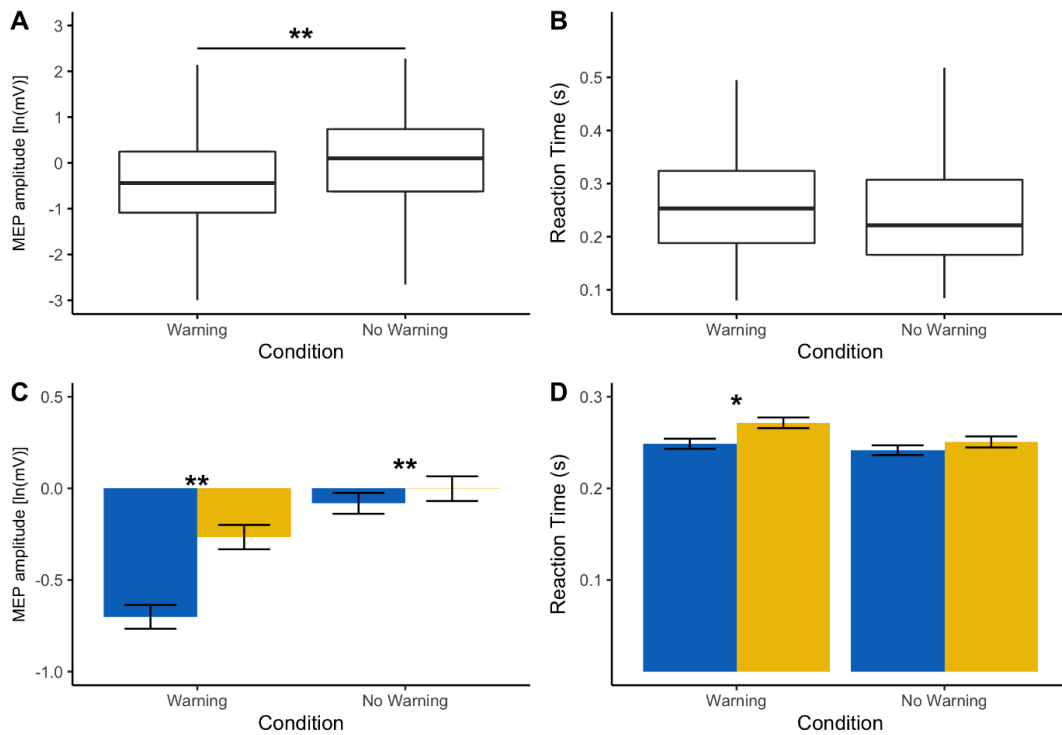


Figure 5.5 – Effect of PSF and Warning cue on MEP amplitude and RT during movement preparation: The effect of condition (Warning vs No Warning) and fatigue on motor evoked potential (MEP) amplitude and reaction time (RT). A, B. Boxplots for MEP amplitude and RT across all stroke survivors for each condition indicating a significant effect of condition on MEP amplitude but not on RT. C, D. Bar plots with standard error bars representing MEP amplitude and RT across both conditions with stroke survivors grouped based on their fatigue score. Fatigue was measured using the Fatigue Severity Scale (FSS-7). Low fatigue patients (FSS-7 < 4) are represented in blue and high fatigue patients (FSS > 4) are represented in yellow. The association between fatigue (FSS-7) and MEP amplitude for each time point is also shown. Significance levels are indicated by * (* < 0.05, ** < 0.001).

5.4 Discussion

In this study I show that the modulation of corticospinal excitability during movement preparation changes as a function of fatigue in stroke survivors. Specifically, the higher the level of fatigue, the lower the suppression of corticospinal excitability during movement preparation and the higher the pre-movement facilitation of corticospinal excitability immediately before EMG onset. Reaction times were also greater in stroke survivors with greater fatigue during movement preparation. This was more apparent when TMS was delivered at time point closest to onset of EMG. I also showed that

corticospinal excitability is higher in the absence of the warning cue in all stroke survivors. Analysis on the demographics of our patient cohort showed that the higher the levels of anxiety and depression the higher the severity of fatigue.

5.4.1 Corticospinal excitability during movement preparation

A number of different models have been put forward to explain the reported modulation in corticospinal excitability during movement preparation from a motor control perspective (Burle et al., 2004; Duque et al., 2010; Duque and Ivry, 2009; Greenhouse et al., 2015; Lebon et al., 2019). Recent studies in nonhuman primates show that neural activity during movement preparation is a necessary component of movement generation and the time spent in the preparatory state can change depending on task demands (Lara et al., 2018). During cue driven movements, such as reaction time tasks where time is available, neuronal activity reaches the preparatory state well before movement onset. The ability to rapidly and consistently reach the correct preparatory state in advance, may allow time to correct small inaccuracies or even speed up movements before the movement itself (Churchland and Shenoy, 2007). Similar results have been reported in the mouse motor cortex as well as in humans, where the amount of preparatory inhibition, as measured by pre-movement cortical inhibition, positively correlated with reaction time (Hannah et al., 2018; Hasegawa et al., 2017). Stroke survivors with low levels of fatigue appear to follow a similar pattern of preparatory inhibition as healthy volunteers as has previously been described (Duque et al., 2017). However, with increasing fatigue, there is both reduced preparatory inhibition and earlier pre-movement facilitation before EMG onset. Both peripheral and central components of fatigue have an influence on MEP amplitude (Brasil-Neto et al., 1993). In the current study, any peripheral components of fatigue can be excluded as the cohort of stroke survivors studied were all mildly physically impaired. The differences observed in the modulation of corticospinal excitability as a

result of fatigue are primarily driven by central fatigue. Given that the model with the best predictive capacity did not include anxiety and depression scores, suggests that changes seen in motor cortical neurophysiology is exclusively related to fatigue and may be an independent mechanism that drives chronic pathological fatigue.

5.4.2 Reaction time and PSF

In the absence of TMS, there is no association between fatigue severity and reaction times. In the TMS conditions however, reaction times are also slower with increasing severity of fatigue. Slower reaction times with greater fatigue during the warned reaction time task maybe due to inability to reach the appropriate preparatory state, indicated by reduced preparatory inhibition, from which to initiate a movement. This could also explain why stroke survivors with high fatigue also have slower self-selected ballistic movement speeds (A. Kuppuswamy et al., 2015). Given the undue influence of the stimulation itself on reactions times, particularly at time points close to EMG onset, I was not able to examine the relationship between reaction times and corticospinal excitability in the current experiment. Whether the relationship between reaction times and changes in corticospinal excitability is causal should be explored further. Also, I cannot exclude the possibility that the silent period following stimulation influenced reaction times. The relationship between silent period duration and fatigue has not been explored previously, but given that reaction times were slower with higher severity of fatigue when the stimulation was delivered together with the imperative stimulus, this is unlikely.

5.4.3 Corticospinal excitability, effort, and fatigue

A number of studies have attempted to explain the changes reported in corticospinal excitability during movement preparation from a decision making and sensory processing perspective (Chiu et al., 2014; Cos et al., 2014; Freeman et al., 2014; Klein et al., 2012; Klein-Flügge et al., 2013; Klein-Flügge and Bestmann, 2012). MEP amplitudes may be

influenced by other non-motor areas such frontal, parietal and subcortical regions that have projections to the pre-motor and motor cortex. Such influences include decision-related variables such as prior probabilities, subjective expected values or sensory evidence, which are computed elsewhere but ultimately influence the state of the motor system. When humans make choices between reaching actions, they tend to choose the one that is less effortful (Cos et al., 2014). This suggests that prior to movement initiation, one can predict the estimated action cost of different movements. Estimated action cost, normally experienced as 'effort', can therefore inform both implicit and explicit action choices towards the least effortful one. The estimated action cost of the upcoming movement is inversely proportional to the amplitude of MEPs (Cos et al., 2014). It has previously been suggested that PSF is a result of altered perceptual processing, specifically altered perception of effort, associated with actions (Kuppuswamy, 2017). The results of the current study, altered modulation of corticospinal excitability, lend support to this hypothesis. The lack of preparatory inhibition and increased pre-movement facilitation may reflect a higher estimated action cost associated with the upcoming movement resulting in the movement being perceived as more effortful. On the contrary, reduced pre-movement facilitation of corticospinal excitability in a visual reaction time task has also been reported in multiple sclerosis fatigue (Morgante et al., 2011). The authors conclude that impairment of areas engaged in motor planning might give rise to fatigue. The contradictory result between the aforementioned study and the current study might be explained by physiological differences previously reported between warned and unwarned reaction time paradigms (Ibáñez et al., 2020).

5.4.4 Effect of Warning cue on neurophysiology and reaction time

MEP amplitudes were lower in the warned RT condition compared to the unwarned RT condition irrespective of fatigue severity, while reaction times remained unchanged.

Higher MEP amplitude in the unwarned condition is not surprising as the stimulation was given at the time of the imperative stimulus and movement “preparation” was yet to take place, unlike the warned condition. Given the difference in MEP amplitude between the two conditions I would also expect a difference in reaction times. One would expect reaction times to be slower in the unwarned condition when compared to the warned condition. The lack of difference in reaction times across the two conditions could be explained by the inclusion of catch trials in the warned condition experiment, whereas there were no catch trials in the unwarned condition. It has previously been reported that the presence of catch trials slows reaction times²⁵⁵. RTs appear to be longer in the warned condition with increasing severity of fatigue but unchanged in the unwarned condition. This might suggest that stroke survivors with high fatigue are capable of responding as quick as those with low fatigue when time is not available to prepare.

5.4.5 PSF, other affective symptoms and resting motor threshold

The relationship between RMT of the affected hemisphere and self-reported fatigue may be influenced by other variables than previously suggested (Annapoorna Kuppaswamy et al., 2015). Corticospinal excitability of the left and right hemispheres behave differently during motor control with asymmetries seen between the two hemispheres (Davidson and Tremblay, 2013; Klein et al., 2016). The asymmetry in corticospinal excitability between the two hemispheres may be driven by altered inter-hemispheric network dynamics that subsequently influence corticospinal excitability (Netz et al., 1995; Ondobaka et al., 2019; Ziemann and Hallett, 2001).

The current study further highlights the overlap of fatigue with other affective symptoms such as anxiety and depression previously described in the literature (De Doncker et al., 2018). Despite the overlap, the mechanisms underlying fatigue appear to be distinct as anxiety and depression scores did not improve the predictive capabilities of the model.

This highlights the importance of using a strictly controlled patient cohort when trying to draw conclusions from studies and attempting to develop a mechanistic understanding of affective symptoms.

5.4.6 Limitations

Despite providing us with useful insights into the mechanisms of post-stroke fatigue, this study is not without limitations. The findings are limited to the affected hemisphere of non-depressed, mildly impaired stroke survivors. Future studies must investigate corticospinal excitability during movement preparation in a wider stroke population in both the affected and unaffected hemisphere. The intensity of stimulation to produce a 0.5mV response was determined at rest. However, when engaged in a task, corticospinal excitability at baseline, despite no EMG activity appears to be different across patients introducing variability into the paradigm. Future studies should ensure that all patients have a similar task-dependent baseline which they can use as a reference to compare the MEP amplitude across different time points. Given the nature of the symptom being investigated, a small number of trials was used at each time point to ensure that all patients could complete the task. I recommend that, given the variability of responses to TMS, future studies should use a block design with sufficient time between blocks to allow patients to rest in order to have a larger number of trials and more robust results. In the current study, I cannot not make a causal link between corticospinal excitability and reaction time due to the effect of the TMS pulse on reaction time. Using study designs in which reaction time is more closely controlled as demonstrated in a recent experiment (Ibáñez et al., 2020), one might be able to study the effect of pre-movement corticospinal excitability on reaction times.

5.5 Conclusion

The modulation of corticospinal excitability during movement preparation assessed using TMS, changes as a function of fatigue in non-depressed, minimally impaired stroke survivors. Reaction times are also longer when given time to prepare for a movement in those who report high levels of fatigue. Preparatory inhibition, when viewed as a measure of sensory processing of expected stimuli, a reduction in preparatory inhibition in high fatigue may indicate poor sensory processing supporting the sensory attenuation model of fatigue.

Chapter 6: Exploring the effect of tDCS on Post-Stroke Fatigue: a potential therapeutic intervention?

6.1 Introduction

Post-stroke fatigue has been identified as the top unmet need among stroke survivors living in the community (McKevitt Christopher et al., 2011). A main contributor to fatigue being such a major issue other than its high prevalence, is the lack of effective interventions and management strategies for PSF. Anti-depressants such as fluoxetine, are commonly prescribed to stroke survivors with PSF as a potential treatment but a number of studies have found such drugs to be ineffective (Choi-Kwon et al., 2007). A systematic review on interventions for post-stroke fatigue, identified a number of pharmacological interventions and non-pharmacological interventions, with no sufficient evidence on the efficacy of any intervention to treat or prevent PSF (Wu et al., 2015a). In order to develop effective interventions for PSF, one must first understand the pathophysiology and mechanisms that underlie PSF, both of which are poorly understood.

Recent work aimed at understanding the underlying neurophysiology of PSF provided a potential target for modulation that may reduce the symptoms of PSF. Cortical excitability at rest, specifically the primary motor cortex (M1) of the affected hemisphere, is reduced in those who report high levels of PSF when assessed using transcranial magnetic stimulation (Annapoorna Kuppaswamy et al., 2015). Motor cortex excitability as measured by TMS is normally associated with motor function of the targeted muscle (Rosso and Lamy, 2018). However, TMS measures of motor cortex excitability have also been associated with non-motor functions such as perception and attention (Ruge et al., 2014; Voss et al., 2007). Given the homogeneity of motor function in the investigated

stroke cohort, it has been argued that reduced motor cortex excitability was a reflection of altered perceptual processing in relation to muscle contraction i.e. altered effort perception (Kuppuswamy, 2017).

I have previously shown that stroke survivors with high severity of fatigue show greater perceived effort (PE). Increased PE may be driven by altered precision afforded to bottom-up prediction errors (as described in the introduction of this thesis), as measured by motor cortex excitability (Kuppuswamy, 2017). I therefore hypothesised that altering the gain i.e. increasing motor cortex excitability, will reduce PE and subsequently reduce fatigue symptoms.

Transcranial direct current stimulation (tDCS) has promising potential therapeutic applications due to its ease of use, low cost and lack of physiological and behavioural side effects (Brunoni et al., 2012; Fregni et al., 2015). tDCS modulates cortical excitability in stroke survivors and has been widely used in the treatment of various neurological and psychiatric disorders, including the treatment of multiple sclerosis fatigue (Ayache et al., 2016; Bastani and Jaberzadeh, 2012; Chalah et al., 2015; Charvet et al., 2018; Ferrucci et al., 2014; Kuo et al., 2014; Nitsche et al., 2009; Saiote et al., 2014; Tecchio et al., 2015, 2014). tDCS has also been used to enhance sport performance and has been shown to reduce rate of perceived exertion in healthy individuals (Angius et al., 2018).

The primary aim of this exploratory study was to use anodal tDCS over the M1 to reduce PSF. The secondary aim was to investigate the potential mechanisms that underlie the hypothesised effect on PSF.

6.2 Methods

6.2.1 Study design

This was a double-blind, sham-controlled study with a single session of bilateral anodal tDCS chosen as the method of intervention. Patients visited the laboratory on three separate occasions, with tDCS applied only on the first visit. The second visit took place one week later with the third visit taking place one month after visit two and will be termed week and month throughout the manuscript (figure 6.1). The primary outcome measure was a change in trait fatigue. Secondary outcome measures included state fatigue, explicit and implicit measures of PE and motor cortex physiology measures of resting motor thresholds (RMT) and slope of recruitment curves (IO_{slope}) of the affected and unaffected hemisphere assessed using TMS. The primary outcome measure was recorded at three distinct time points (pre stimulation, week, and month). All other outcome measures were recorded at four distinct time points (pre stimulation, immediately post stimulation, week, and month).

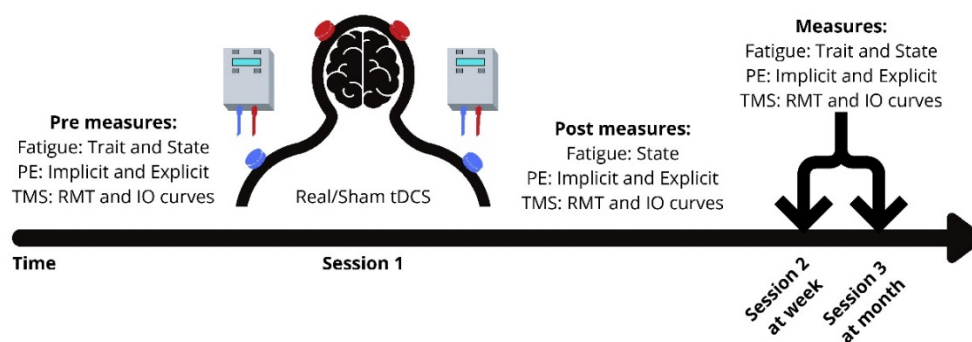


Figure 6.1 – tDCS study design: Study Design indicating the sequence in which procedures were done for each of the sessions at the 4 different time points (pre tDCS, immediately post-tDCS, week and month time points).

6.2.2 Subjects

The study was approved by London Bromley Research Ethics Committee (REC reference number: 16/LO/0714). Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. Stroke patients were recruited from the database of eligible stroke survivors described in Chapter 2 of this thesis. An additional inclusion criterion in this study was the presence of clinically significant fatigue. A score of ≥ 4 on FSS-7 indicates the presence of clinically significant fatigue (Valko et al., 2008). Therefore, only patients that had scored greater than 4 on the FSS-7 on the day of testing were recruited into the study.

	Real (N = 20)	Sham (N = 10)
Age (years)	56.95 (13.17)	59.83 (11.66)
Time Since Stroke (years)	4.19 (5.43)	4.83 (6.47)
FSS-7	5.84 (0.63)	5.14 (0.74)
HADS – Depression	6.15 (3.31)	6.20 (3.39)
HADS – Anxiety	5.80 (2.78)	7.10 (4.31)
Grip (% unaffected hand)	85.83 (22.09)	80.00 (29.32)
NHPT (% unaffected hand)	85.14 (27.91)	77.37 (23.36)
Gender		
Females Males	11 9	4 6
Hemisphere Affected		
Left Right	10 10	4 6
Type of Stroke		
Ischemic Hemorrhagic	16 4	8 2
Lesion Location Territory		
ACA	1	1
MCA	16	5
PCA	2	0
Brainstem and Cerebellum	1	4
Dominant Hand		
Right Left	19 1	10 0

Table 6.1 – Demographics of stroke survivors for tDCS study: Patient demographics and clinical data for the real and sham stimulation groups. FSS-7 = Fatigue severity Scale-7; HADS = Hospital Anxiety and Depression Scale; NHPT = Nine-hole peg test; ACA = Anterior Cerebral Artery; MCA = Middle Cerebral Artery; PCA = Posterior Cerebral Artery.

The minimal clinically important difference on the FSS-7 is 0.45, with differences greater than 0.45 predicting a significant effect on quality of life (Nordin et al., 2016; Rooney et al., 2019). Based on previous studies using tDCS as a potential intervention for fatigue in MS patients, in order to detect the minimal clinically important difference in fatigue with 80% power (0.80) and a significance level alpha of 0.05 using a non-parametric tests, a sample size of 11 subjects per group is needed (Saiote et al., 2014). Twice the number of patients were allocated to the real stimulation group than necessary, as previous studies using tDCS in multiple sclerosis fatigue and healthy individuals showed that approximately 50% of patients respond to tDCS (Saiote et al., 2014; Wiethoff et al., 2014). Thirty-three patients were recruited into the study and were randomly allocated to the real (n = 22) or sham (n = 11) stimulation groups (figure 6.2). All patients gave written informed consent in accordance with the Declaration of Helsinki. Patient demographics for both groups are found in table 6.1.

6.2.3 Questionnaires

Trait and state measures of fatigue were captured during the study. Trait fatigue represents the experience and impact of fatigue on day to day living for a pre-determined time period leading up to the day of testing, whereas state fatigue characterizes fatigue at a given moment in time. Trait fatigue was quantified using the FSS-7, a seven-item questionnaire asking for ratings of fatigue ranging from one to seven (strongly disagree to strongly agree) over the preceding week from the day of administration (Krupp et al., 1989). An average score of one indicates no fatigue while an average score of seven indicates very severe fatigue. State fatigue was quantified using a visual analogue scale (VAS) ranging from zero to ten (Not at all tired to extremely tired). Patients also completed the HADS, a 14-item questionnaire with a depression and anxiety subscale, prior to the stimulation.

A score of 0 to 7 for either subscale could be regarded as being in the normal range, with a score of 11 or higher indicating probable presence of the mood disorder (Snaith, 2003).

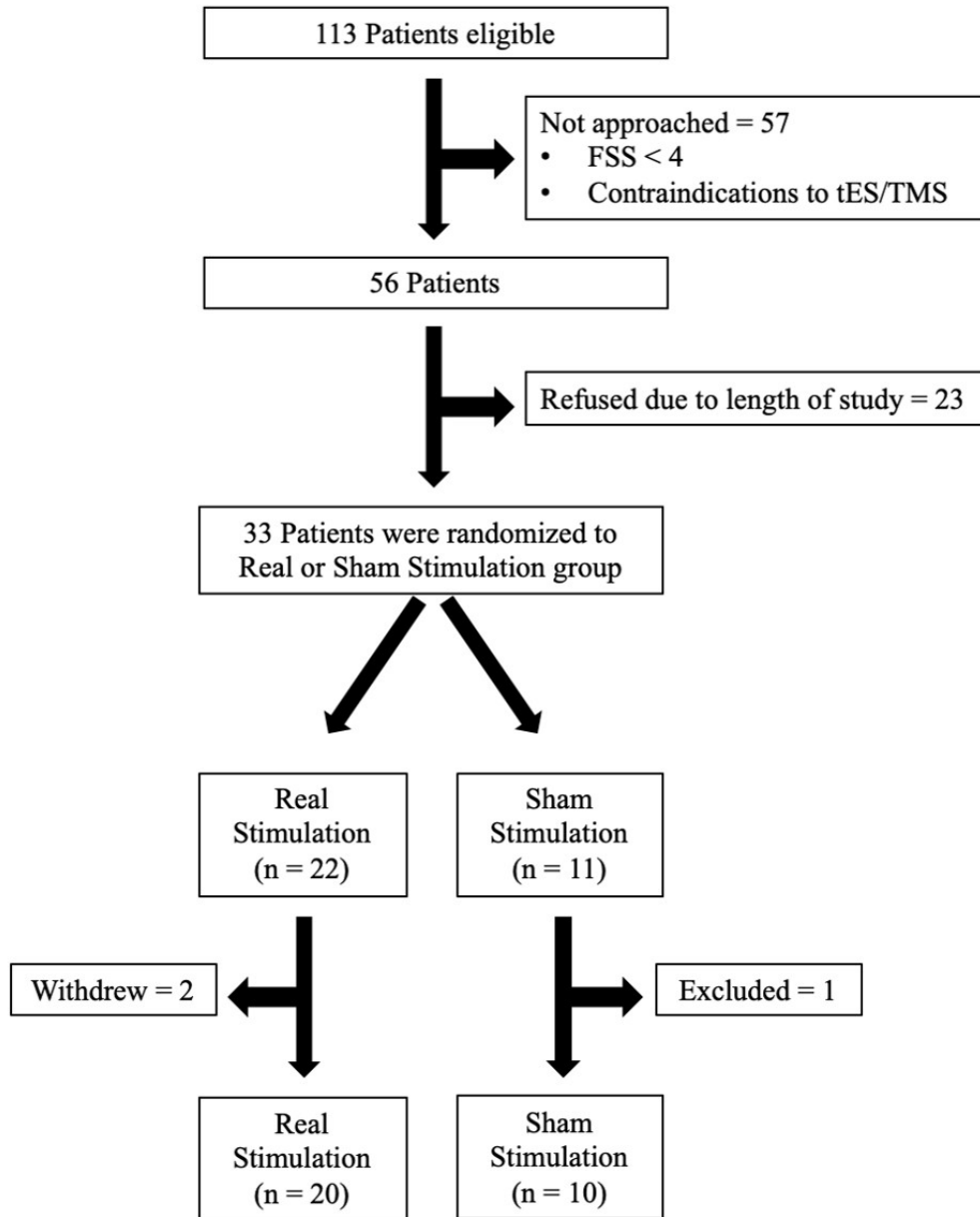


Figure 6.2 – Patient recruitment and randomisation: Study recruitment and randomisation (HADS = Hospital Anxiety and Depression Scale; FSS = Fatigue Severity Scale; tES = transcranial Electrical Stimulation; TMS = Transcranial Magnetic Stimulation).

6.2.4 Stimulation

tDCS was applied using two battery-driven stimulators (DC-Stimulator Plus, NeuroConn, Germany) while patients were awake and at rest. Four 35 cm² rubber electrodes coated

with conductive paste were secured with self-adhesive bandages. The anode of each stimulator was placed over the left and right M1 (C3 and C4 according to the 10-20 EEG system), while the cathode of each stimulator was placed over the ipsilateral left and right shoulders. This tDCS montage has previously been shown to reduce perception of effort and increase corticospinal excitability in healthy individuals (Angius et al., 2018). Real tDCS involved two 20-minute sessions of stimulation at 2 mA separated by a 10-minute break in between. The current was ramped up for 30 seconds until reaching 2 mA and ramped down for 30 seconds at the end of the stimulation period. Stimulation intensity and duration complied with current safety recommendations (Bikson et al., 2016). For sham stimulation, the current was ramped down immediately after ramping up, providing effective blinding (Ambrus et al., 2012). The patient and researchers were blind to the applied stimulation (real or sham). At the end of stimulation, patients were explicitly asked whether they thought they received real or sham stimulation. Patients were not told in which group they were in until the very end of the study.

6.2.5 Perceived effort

PE was measured in an isometric hand grip task with a hand-held dynamometer (Biometrics Ltd, Newport, UK) performed using the dominant hand (Doncker et al., 2020). Force data from the dynamometer were acquired at 500 Hz via a data acquisition interface (Power1401, CED) and recorded in MATLAB (2016b, MathWorks). Each trial was 5 seconds long, in which patients were required to sustain a grip force for 3 seconds at 20%, 40%, or 60% of their maximum voluntary force. Immediate force feedback was shown on the monitor as filling of a red bar, which turned green once the minimal required target force, indicated by a cross on the screen, was reached. The grip force–visual feedback relationship was individually adjusted for every patient to eliminate potential influence on PE. Before the experiment, patients practiced each force level with

their dominant hand to familiarize themselves with the effort required and performed a line familiarization. In the line familiarization, patients were shown 3 “short” lines (1, 2, and 3 cm), and 3 “long” lines (10, 11, and 12 cm). After presentation of the 6 lines, patients were shown each of the learned lines without information about the category it belonged to, and were asked to judge the line length. Patients responded using the keyboard: left arrow key for “short” and right arrow key for “long”. They were then asked to rate their confidence in their response using a VAS. If patients’ response was <100% correct, the procedure was repeated until they were able to distinguish between short and long lines.

During the PE task, each grip was followed by a line length estimation. The line presented could have a length of 3.5 to 8.5 cm with a total of 24 different line lengths, 12 short and 12 long. Twenty-four lines presented under the 3 force conditions resulted in a total of 72 trials divided into 3 blocks. The order of forces and line lengths was randomized with equal numbers of the 3 different force levels in each block. Participants reported if the presented line was short or long based on the length of lines presented during the familiarization phase. If they determined the presented line to be shorter than half the length of the longest line presented during the familiarization (12 cm), they reported short; otherwise, they reported long. These blocks were used as an implicit measure of PE.

After 3 blocks, participants performed a final block of 9 trials. This block was used as an explicit measure of PE. Each trial consisted of a 5-second grip with visual feedback at the 3 different force levels, 20%, 40%, or 60% of maximum voluntary force, with 3 trials for each force level. This was followed by the question, “How effortful was the squeeze?” Patients had to respond using a VAS ranging from “not at all” to “very hard.”

6.2.6 Surface electromyogram and TMS

Electromyogram (EMG) recordings were obtained from the first dorsal interosseous (FDI) muscle using surface electrodes (1041PTS Neonatal Electrode, Kendell) in a belly-tendon montage with the ground positioned over the flexor retinaculum of the hand. The signal was amplified with a gain of 1000 (D360, Digitmer, Welwyn Garden City, UK), bandpass filtered (100-1000 Hz), digitized at 10kHz (Power1401, CED, Cambridge, UK) and recorded with Signal version 6.04 software (CED, Cambridge, UK).

TMS (figure-of-eight coil with wing diameter, 70mm; Magstim 2002, Magstim, Whitland, UK) was used to stimulate the hand area of the M1. The coil was held tangentially on the scalp at 45° to the mid-sagittal plane to induce a posterior-anterior current across the central sulcus. The subjects were instructed to stay relaxed with their eyes open and their legs uncrossed. The motor 'hotspot' of the FDI muscle was determined as follows: the vertex (cross-over point between the mid-point between the two tragi and midpoint between nasion and inion) was marked using a dry wipe marker. Four centimetres lateral and 2 cm anterior from the vertex was then marked on the contralateral hemisphere, which is the approximate location of M1. This was used as a rough guide for a starting point for determining the hotspot for the first dorsal interosseous. At 50% maximal stimulator output (MSO) (or higher or lower in some patients) the coil was moved in 1 cm blocks for ~2 cm anterior, posterior, lateral and medial to the marked region. Three stimuli were delivered at each spot and the location with the highest average motor evoked potential response was taken as the hotspot. RMT was defined as the lowest intensity required to evoke a motor evoked potential (MEP) at the hotspot of at least 50µV in a minimum of 5 of 10 consecutive trials while subjects were at rest. IO curves were acquired at rest at the hotspot using TMS intensities set at 100, 110, 120, 130, 140 and 150% of RMT. Six pulses at each of the 6 intensities were delivered in a randomized

order with an inter-trial interval of 4 seconds, giving thirty-six trials in total. This procedure was repeated for both the affected (RMT-A, IO_{slope}-A) and unaffected (RMT-U, IO_{slope}-U) hemispheres.

6.2.7 Analysis of questionnaires

The FSS-7 score was calculated by averaging all items for each of the three time points.

The total score was taken for the anxiety and depression subscales of HADS, HADS-Anxiety and HADS-Depression respectively, and were considered as independent measures.

6.2.8 TMS analysis

The data were analysed using custom-written routines in Matlab (2018a, Mathworks). Peak-to-peak MEP amplitudes for each condition were estimated from the EMG recordings. All trials were visually inspected and approximately 7% of trials with pre-contraction and size ≤ 0.025 mV were excluded across all participants. A linear fit was applied to all the MEP data across the six conditions (100-150% RMT) for each participant at each session. The quality of the linear fit was evaluated by calculating the r-squared value for each participant across each session. The grand mean r-squared value across all individuals and all session and the resulting standard deviation ($R^2 = 0.86 \pm 0.12$) demonstrate an overall good fit of the MEP data with little variability within conditions. The gradient of the linear fit was subsequently calculated for each participant in each of the four sessions and for each hemisphere (affected and un-affected hemisphere) giving us the slope of the recruitment curve.

6.2.9 PE analysis

To obtain a measure of explicit PE, VAS scores were averaged across all trials in each force level in each individual. As there was no difference across force level, the average

VAS score across all force levels was used as an explicit measure of PE for each of the four time points. To obtain a measure of implicit PE, the sum of the number of lines reported as long for each individual in each force level was calculated. As there was no difference across force level, the average number of lines across all force levels was used as an implicit measure of PE for each of the four time points.

6.2.10 Statistical analysis

All statistical analysis was performed using R (RStudio Version 1.2.5033). Assumptions of a normal distribution of the primary and all secondary outcome variables was assessed using the Shapiro-Wilk test. All data were non-normally distributed ($p < 0.05$). To test for changes over time, a non-parametric Friedman test was performed for the primary outcome variable (trait fatigue) and all secondary outcome variables (state fatigue, RMT-A, RMT-U, $IO_{\text{slope-A}}$, $IO_{\text{slope-U}}$, PE-implicit and PE-explicit), separately for the sham and real intervention groups as in Saiote et al (Saiote et al., 2014). When significant results were found, pairwise comparison between baseline and each post-measurement day were performed using Wilcoxon signed-rank test. To analyse the effect of real stimulation versus sham stimulation across both primary and secondary outcome measures, the changes in scores were calculated by normalising each day to baseline (pre stimulation), and then compared within each day using a Wilcoxon signed-rank test. Adjustment for multiple comparisons was performed using Bonferroni correction.

A spearman correlation was used to examine the association between baseline trait fatigue scores and the change in trait fatigue a week after stimulation in both the sham and real stimulation groups. To identify the potential mechanisms that drive the change in trait fatigue in the real stimulation group a multiple linear regression was used with demographic data and secondary outcome variables that were significantly different between the real and sham stimulation groups used as predictors. Collinearity amongst

the predictors used in the multiple regression model was assessed by computing the variance inflation factor (VIF). No VIF value exceeded a score of 5, demonstrating that there was no collinearity amongst the predictors used. Goodness of fit was assessed using the BIC (lower BIC indicates a better fitting model) to identify the combination of variables that best predicted the outcome variable, the change in trait fatigue. Assumptions of normality and homoscedasticity of the residuals for each model were assessed visually using quantile-quantile normal plots and fitted- versus residual-value plots.

6.3 Results

Two patients from the real stimulation group decided to withdraw from the study during visit 1 as they found the stimulation uncomfortable and one patient from the sham stimulation group was excluded because they started taking antidepressants after session 1. No serious adverse events were reported. Thirty patients were included in the final analysis, with twenty in the real stimulation group and ten in the sham stimulation group. When asked whether they thought they had received the real or sham stimulation, 12 of the 20 patients in the real stimulation group reported real and 6 of the 10 patients in the sham stimulation group reported real. Given that 60% of patients in the sham and real groups thought they had received the real stimulation, indicates a successful sham condition.

6.3.1 Trait and State Fatigue

The Friedman test showed a significant effect of time on trait fatigue in the real stimulation group ($\chi^2(2)=15.5$; $p<0.001$) but not in the sham stimulation group ($\chi^2(2)=0.154$; $p=0.926$). Post-hoc analysis with Wilcoxon signed-rank tests showed that FSS-7 scores decreased compared to baseline both at the week ($V=198$, $Z=0.777$,

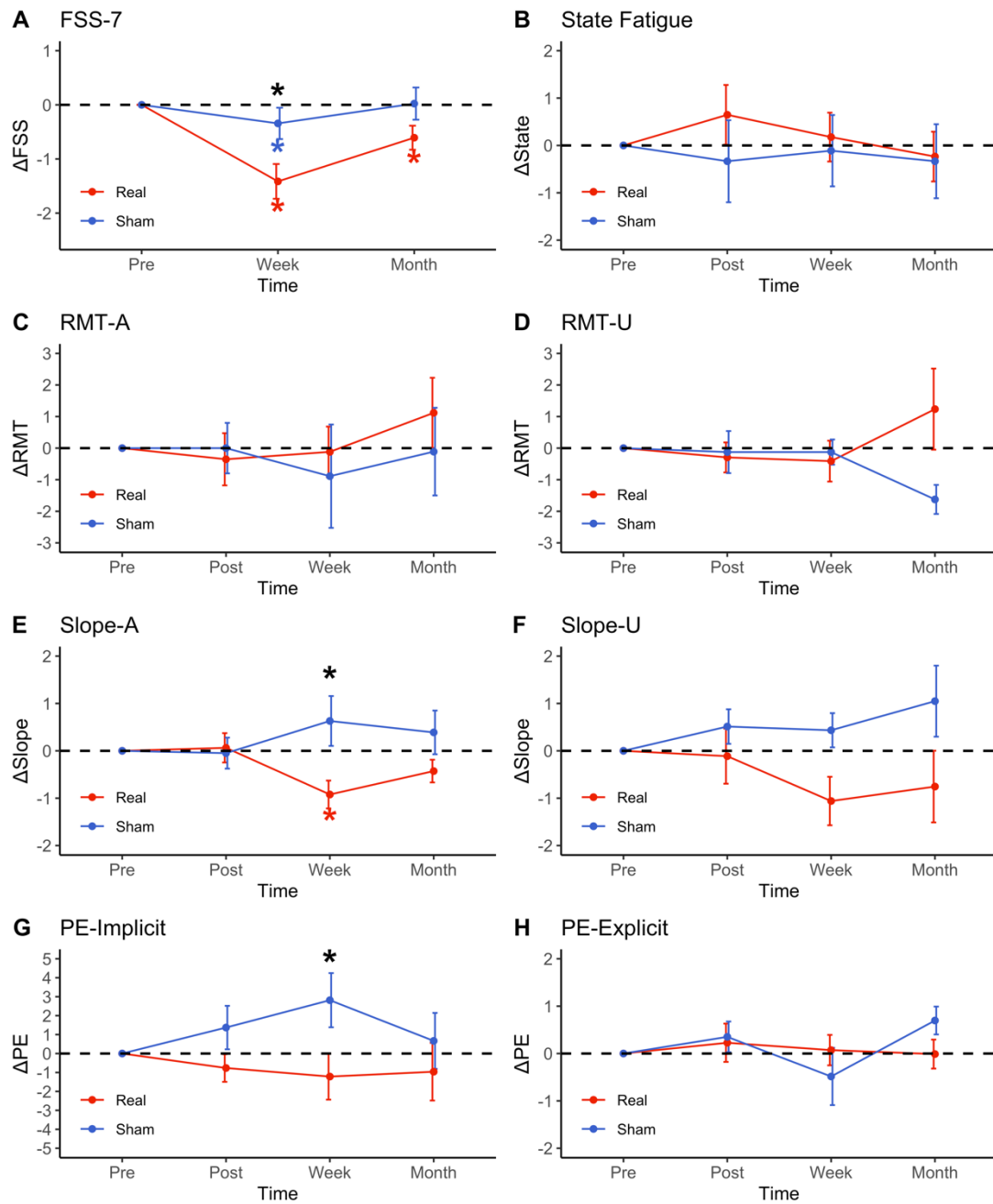


Figure 6.3 – Effect of tDCS on fatigue, neurophysiology, and behaviour: Changes in trait fatigue (A), state fatigue (B), resting motor threshold of the affected and unaffected hemisphere (C-D), slope of the recruitment curve of the affected and unaffected hemisphere (E-F), implicit perceived effort (G) and explicit perceived effort (H) compared to baseline (pre stimulation time point) across the different time points for both the real (red) and sham (blue) stimulation group. Error bars represent standard error of the means. Significant differences from baseline for the real and sham stimulation groups are indicated by red and blue asterisks respectively. Significant differences between the sham and real stimulation groups are indicated by black asterisks ($p < 0.05$). FSS-7 = Fatigue Severity Scale-7; RMT-A = Resting Motor Threshold of Affected Hemisphere; RMT-U = Resting Motor Threshold of Un-affected Hemisphere; $IO_{Slope-A}$ = recruitment curve slope of Affected Hemisphere; $IO_{Slope-U}$ = recruitment curve slope of Un-affected Hemisphere; PE = Perceived Effort.

$p=0.002$) and month ($V=142$, $Z=0.535$, $p=0.047$) time point in the real stimulation group. FSS-7 at the week time point was also lower than at the month time point ($V=21$, $Z=0.639$, $p=0.016$). Post-hoc Wilcoxon signed-rank test of the normalised FSS-7 scores revealed a significant difference between the sham and real stimulation group at the week time point ($W=52.5$, $Z=0.382$, $p=0.0386$) but not at the month time point ($W=65.5$, $Z=0.277$, $p=0.134$), seen in figure 6.3A.

The Friedman test showed no significant effect of time on state fatigue in the real ($\chi^2(3)=0.97$; $p=0.809$) or sham ($\chi^2(3)=3$; $p=0.392$) stimulation group. Post-hoc Wilcoxon signed-rank test for the normalised state fatigue scores revealed no significant difference between the sham and real stimulation group at any time point (figure 3B).

6.3.2 Neurophysiology

The Friedman test showed a significant effect of time on $IO_{\text{slope-A}}$ in the real stimulation group ($\chi^2(3)=11.2$, $p=0.0106$) but not in the sham stimulation group ($\chi^2(3)=0.75$, $p=0.861$). Post-hoc analysis with Wilcoxon signed-rank tests showed that $IO_{\text{slope-A}}$ decreased compared to baseline at the week ($V=96$, $Z=0.730$, $p=0.024$) but not at the immediate post and month time point in the real stimulation group. Post-hoc Wilcoxon signed-rank test of the normalised $IO_{\text{slope-A}}$ scores revealed a significant difference between the sham and real stimulation group at the week time point ($W=23$, $Z=0.480$, $p=0.024$) but not at the immediate post and month time point. The Friedman test showed no significant effect of time on RMT-A in the real ($\chi^2(3)=2.62$, $p=0.454$) or sham ($\chi^2(3)=2.06$, $p=0.560$) stimulation groups. Post-hoc Wilcoxon signed-rank test for the normalised RMT-A revealed no significant difference between the sham and real stimulation group at any time point.

The Friedman test showed no significant effect of time on RMT-U or IO_{Slope-U} in the real ($\chi^2(3)=2.71$, $p=0.438$; $\chi^2(3)=3.38$, $p=0.337$) or sham ($\chi^2(3)=5.62$, $p=0.132$; $\chi^2(3)=2.2$, $p=0.552$) stimulation groups. Post-hoc Wilcoxon signed-rank test for the normalised RMT-U and IO_{Slope-U} scores revealed no significant difference between the sham and real stimulation group at any time point (figure 6.3C-3F).

6.3.3 Perceived Effort

The Friedman test showed no significant effect of time on PE-implicit or PE-explicit in the real ($\chi^2(3)=5.60$, $p=0.905$; $\chi^2(3)=0.2$, $p=0.978$) or sham ($\chi^2(3)=4.24$, $p=0.237$; $\chi^2(3)=6.73$, $p=0.0809$) stimulation groups. Post-hoc Wilcoxon signed-rank test for the normalised PE-explicit scores revealed no significant difference between the sham and real stimulation group at any time point. Post-hoc Wilcoxon signed-rank test for the normalised PE-implicit scores revealed a significant difference between the sham and real stimulation group at the week time point ($W=39.5$, $Z=0.391$, $p=0.0491$) but not at the immediate post and month time point (figure 6.3G-3H).

	Beta coefficient	2.5% CI	97.5% CI	P-value
(Intercept)	-2.775	-4.344	-1.207	0.002
ΔSlope-A	0.436	-0.212	1.085	0.170
HADS-Anxiety	0.285	0.066	0.505	0.015

Table 6.2: Multiple linear regression results with change in FSS-7 at the week time point as the outcome variable and change in IO_{Slope-A} and HADS-Anxiety as predictors. Table includes beta coefficients, 95% confidence intervals and the associated p-values for each predictor. FSS-7 = Fatigue Severity Scale-7; IO_{Slope-A} = recruitment curve slope of the affected hemisphere; HADS = Hospital Anxiety and Depression Scale; CI = confidence interval.

6.3.4 Change in trait fatigue

There was no association between baseline FSS-7 scores and the change in FSS-7 score at the week time point in the real ($r_s = -0.2$, $p=0.39$) and sham ($r_s=0.2$, $p=0.57$) stimulation group (figure 6.4A). The multiple linear regression model with normalised IO_{Slope-A} at the

week time point and baseline HADS-Anxiety scores as predictors was the best fitting model ($\Delta\text{FSS}_{\text{week}} = -2.775 + 0.436\Delta\text{IO}_{\text{slope-A}} + 0.285\text{HADS-Anxiety}$). A significant regression equation was found ($F(2,13) = 5.345$, $p = 0.020$), with an adjusted R^2 of 0.37. Baseline HADS-Anxiety significantly explained the change in FSS-7 scores ($t = 2.925$, $p = 0.013$), whereas normalised $\text{IO}_{\text{slope-A}}$ at the week time point ($t = 1.760$, $p = 0.104$) was not a significant predictor of the change in FSS-7 scores (figure 6.4B). Beta coefficients of the predictors used in the model together with their associated 95% confidence intervals and p-values are found in table 6.2.

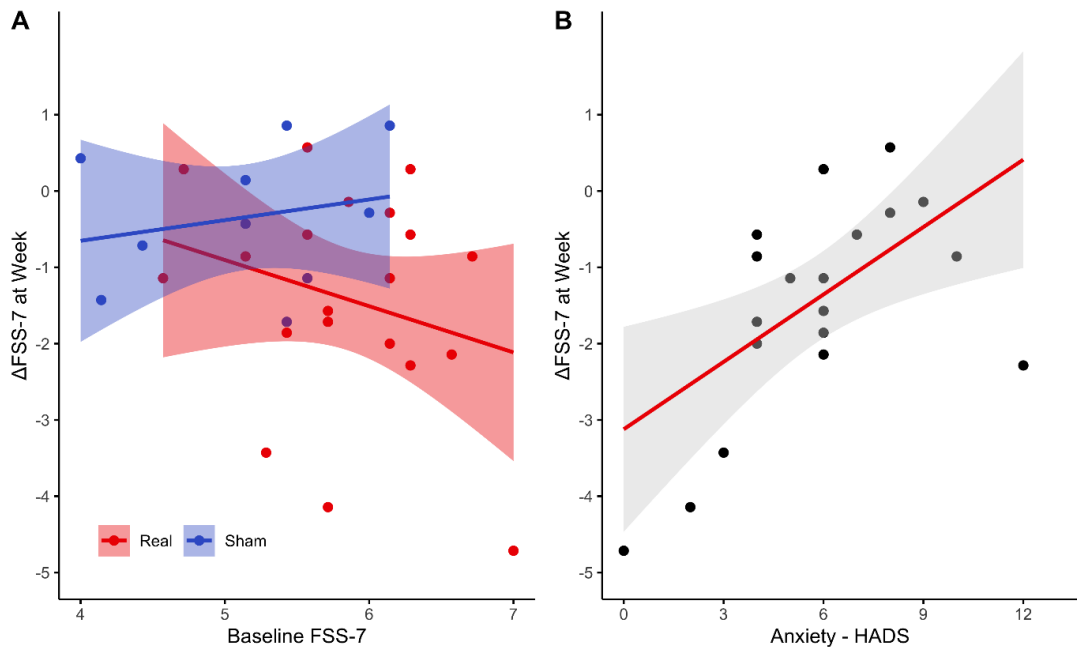


Figure 6.4 – Predictors of the change in FSS-7: Correlation between baseline FSS-7 and the change in FSS-7 at the week time point for the real (red) and sham (blue) stimulation groups with the 95% confidence interval (A). The association between the baseline HADS-Anxiety levels and the change in FSS-7 at the week time point for the real stimulation group with its associated 95% confidence interval (B). FSS-7 = Fatigue Severity Scale-7; HADS = Hospital Anxiety and Depression Scale.

6.4 Discussion

In this study, I aimed to improve fatigue symptoms in minimally impaired, non-depressed stroke survivors using bilateral anodal tDCS over the M1. I show a significant reduction in trait fatigue a week following anodal tDCS. There were also significant differences between the real and sham stimulation groups in IO_{slope} of the affected hemisphere and

implicit measures of PE a week after stimulation. Those with the greatest drop in trait fatigue a week after anodal tDCS also had the lowest anxiety scores prior to stimulation.

6.4.1 tDCS and fatigue

Anodal tDCS increases cortical excitability (Bastani and Jaberzadeh, 2012) and reduce perception of effort in healthy participants during an endurance performance task (Angius et al., 2018). The effects of tDCS are not specific to the targeted brain regions but spread to distinct cortical and subcortical structures (Lang et al., 2005). A single session of anodal tDCS was expected to increase motor cortex excitability temporarily resulting in reduction of PE by modulating excitability and connectivity of regions upstream of M1 (Marcora, 2009; de Morree et al., 2014, 2012). By resetting PE in a physical task, the carry over effects on behaviour would accumulate eventually reducing fatigue levels. This reduction in fatigue levels would be evident by changes in trait fatigue but not necessarily state fatigue. The current results partly support this theory by showing a reduction in trait fatigue a week post-tDCS. Fatigue has been identified as one of the top unmet needs for chronic stroke survivors within the community and interferes most with their activities of daily living (McKevitt Christopher et al., 2011; Rudberg et al., 2020). Currently there are no effective interventions for PSF (Aali et al., 2020; Hillis, 2020). The proposed intervention, if confirmed to be effective in larger and a more heterogeneous cohort of patients, will represent a simple, low-cost and risk-free procedure for reducing fatigue symptoms (Brunoni et al., 2012; Kuo et al., 2014).

6.4.2 Neurophysiology

RMT is a measure of motor corticospinal excitability and anodal tDCS reduces RMT (Bastani and Jaberzadeh, 2012). The lack of effect of tDCS on RMT in this study could have been driven by the split stimulation paradigm of two 20-minute periods, with the second 20-minute stimulation reversing the effects of the first 20 minutes (Karabanov et

al., 2015). The slope of IO curves following real tDCS reduced significantly in the affected hemisphere when compared to sham tDCS. IO curves are thought to measure the excitability of pathways upstream of motor cortex, therefore a measure of inputs to the motor cortex (Chen and Huang, 2018; Potter-Baker et al., 2016). The slope of IO curves represents the gain of descending corticospinal tract, possibly driven from higher motor areas (Ridding and Rothwell, 1997; Ward et al., 2006). However, a reduction and not an increase in slope is puzzling. Steeper IO represent greater recruitment of higher order motor areas such as the supplementary motor area and pre motor cortex (Potter-Baker et al., 2016). As there are no normative values for IO curves, it is hard to speculate if tDCS induced shallowing of IO curves is a reflection of homeostatic normalisation of inputs to the motor cortex, but offers one possible explanation of the IO results.

6.4.3 Perceived effort

PE has mostly been tested in post-exercise paradigms where measures such as VAS and Borg Scales have been validated against physiological measures of exertion such as heart rate and maximal aerobic capacity (Smith et al., 2016; Van Cutsem et al., 2017). They conclude PE is less subject to bias in some populations (Jones et al., 2015; Moore and Picou, 2018). However, in the current study PE is measured in a non-exercise paradigm and in a disease population with a condition that is highly stigmatised and under recognised (Crosby et al., 2012; Walsh et al., 2015). Hence, we expected to see a response bias in PE. Therefore, in addition to an explicit measure of PE, a novel implicit measure of PE based on line-length perception was also used. This measure takes advantage of the susceptibility of visual perception to physical effort where high effort unfavourably biases distance estimation (Proffitt et al., 2003). On similar lines, a line length estimation task was developed and shown to be biased by prior exertion, which is used as a measure of implicit PE (Clark et al., 2016; Doncker et al., 2020). In Chapter 3, showed that trait

fatigue is explained by implicit PE but not explicit PE in a physical task (Doncker et al., 2020). In the current study I show a significant difference between real and sham stimulation in implicit PE but not in explicit PE a week after anodal tDCS. It could be that implicit, perceived effort is the first to respond to tDCS and if the effects were maintained, would result in a reduction in explicit PE. A second possible explanation is that reducing implicit PE that is sufficient to alleviate fatigue. This difference appears to be primarily driven by an increase in implicit PE in the sham stimulation group. Perhaps in the real stimulation group this task specific increase in PE was suppressed. The test-retest reproducibility of the paradigm used to measure implicit PE has not been examined in the absence of tDCS, and could potentially shed light on the current finding. It is important to note that all patients in this study were physically well recovered, evident from their upper limb clinical scores (grip and NHPT, table 1). Therefore, I did not expect there to be an effect of hemiparetic side on their ability to perform the task successfully.

6.4.4 Mechanism driving the change in trait fatigue

One of the aims of this work was to identify the potential mechanisms that underlie the reduction in trait fatigue following anodal tDCS. The expectation was that a change immediately post stimulation in M1 neurophysiology and PE will result in reduction in trait fatigue a week later. However, no change immediately post stimulation, but only a week later in these measures, makes it harder to interpret the neurophysiology and perception results. The results of the multiple linear regression model suggest that measures of M1 neurophysiology, specifically of the affected hemisphere a week after stimulation, appear to be related to the improving fatigue symptoms. Whether the change in fatigue is a consequence of a change in neurophysiology or whether they occur via independent mechanisms cannot be inferred from the current study. Therefore, from a mechanistic point of view, there are still questions to be addressed with regards to how

anodal tDCS results in reduced trait fatigue. The improvement in fatigue symptoms does however appear to be modulated by anxiety levels prior to the stimulation itself. PSF and anxiety co-occur more often than any other problems such as pain, depression and sleep (Naess et al., 2012b). In chronic pain, anxiety exacerbates pain (Ploghaus et al., 2001). Similarly, anxiety levels may exacerbate fatigue which manifests as a small or no change in fatigue in those with high baseline anxiety. Anxiolytic medication (e.g. diazepam, lorazepam) targets the neurotransmitter GABA and anodal tDCS enhances cortical excitability by decreasing GABA concentration (Antonenko et al., 2017). This could have prevented the efficacy of tDCS in reducing fatigue, however, patients included in the current study were not on any centrally acting medication. Therefore, the true interaction between anxiety and effect of tDCS remains unclear.

6.4.5 Limitations

Despite providing a potential intervention to improve fatigue symptoms after stroke, this study is not without limitations. Firstly, the current study is limited to non-depressed, minimally impaired stroke survivors. Given the nature of the symptom being investigated and the heterogeneous cohort that are stroke survivors, the effect of anodal tDCS on post-stroke fatigue should be investigated in a wider range of stroke survivors. This highlights the need to replicate such findings before tDCS can be used as a tool for management of PSF. Secondly, due to the nature of the symptom being investigated, a small number of trials was used for the recruitment curve data and only a single session of anodal tDCS was performed to ensure that all patients could complete the study. Having multiple sessions of tDCS as in previous studies in multiple sclerosis (Ayache et al., 2016; Cancelli et al., 2018; Chalah et al., 2020; Charvet et al., 2018; Ferrucci et al., 2014; Saiote et al., 2014; Tecchio et al., 2015, 2014) might result in improvement in fatigue scores lasting longer than a week. Finally, despite differences in neurophysiological and

PE measures between the real and sham stimulation groups, the reduction in fatigue scores is not fully explained by these measures, leaving the question of mechanism of tDCS-induced reduction in fatigue, still open.

6.5 Conclusion

The current results show that a single session of bilateral anodal tDCS over the primary motor cortex improves fatigue symptoms for up to a week after stimulation. Therefore, tDCS could be a useful addition for management of PSF. For effective interventions to be developed, we must improve our understanding of the structural and functional neural networks associated with altered effort perception, neurophysiological variables and PSF.

Chapter 7: The role of the left motor cortex in Post-Stroke Fatigue: a corticospinal excitability study

7.1 Introduction

In the normal functioning brain, there is an asymmetry between the two hemispheres within and outside primary motor areas characterized by a net inhibitory dominance from the left hemisphere (Corbetta and Shulman, 2002; Giovannelli et al., 2009; Mevorach et al., 2006; Ziemann and Hallett, 2001). The interhemispheric inhibition balance (IIB), a measure of interhemispheric network dynamics, is altered in PSF, with a shift from a net left-to-right inhibition dominance to a net right-to-left inhibition dominance (Ondobaka et al., 2019). This shift in IIB has also previously been shown to account for clinical depression, with overall lower corticospinal excitability seen in the left hemisphere compared to the right hemisphere (Lefaucheur et al., 2008). Non-invasive brain stimulation studies have shown that IIB has an influence of corticospinal excitability of both hemispheres (Schambra et al., 2003). Dysfunctional functional connectivity within sensorimotor networks, particularly of the left hemisphere, appear to also play a crucial role in mediating MS fatigue (Chalah et al., 2015; Cogliati Dezza et al., 2014; Dell'Acqua et al., 2010; Vecchio et al., 2017). Targeting the connectivity within these regions using non-invasive brain stimulation has shown to reduce the severity of fatigue (Porcaro et al., 2019; Tecchio et al., 2014).

Given the directionality of IIB in PSF, the overlap between fatigue and depression and the role of the left hemisphere in mediating fatigue in other neurological disorders, I aimed to investigate the influence of fatigue on corticospinal excitability in stroke survivors with left and right hemisphere strokes. I hypothesised that stroke survivors with left hemisphere strokes will have lower corticospinal excitability while stroke survivors

with right hemisphere strokes will have higher corticospinal excitability with increasing severity of fatigue.

7.2 Methods

7.2.1 Subjects

Stroke survivors that took part in the experiments highlighted in Chapters 4 and 5 of this thesis were included in this subsequent experiment. In the scenario where stroke survivors participated in both experiments, only one dataset was included. Ninety-eight stroke survivors were included in the current analysis (Table 7.1).

Demographics	N = 98 ¹	Statistic ²	p-value ²
FSS-7	3.83 (1.91)		
Hemisphere Affected (Left Right)	51 47	1379	0.200
Sex (Females Males)	32 66	661	0.003
Age (years)	60.93 (12.65)	-0.198	0.050
Time Post-Stroke (years)	4.51 (4.74)	-0.097	0.348
Grip (% of unaffected hand)	91.37 (22.93)	-0.204	0.044
NHPT (% of unaffected hand)	88.48 (24.63)	-0.123	0.229
HADS - Depression	4.83 (3.23)	0.498	<0.001
HADS - Anxiety	5.26 (3.93)	0.367	<0.001

¹n (%); Mean (SD)

²Spearman rank correlations; Kruskal-Wallis rank sum test

Table 7.1 – Demographics of stroke survivors for RMT study: Mean (SD) values are displayed for all continuous variables and number of patients are displayed for categorical variables (Hemisphere affected and gender). P-values indicate the significance of spearman rank correlations between FSS-7 and continuous variables and Wilcoxon rank sum tests comparing the FSS-7 score within categorical values.

7.2.2 Statistical Analysis

The association between FSS-7 and time post-stroke, age, grip strength, NHPT, HADS-Depression and HADS-Anxiety was assessed using Spearman's Rank Correlations.

Wilcoxon rank sum tests were used to assess the difference in FSS-7 across different groups divided based on lesioned hemisphere and sex.

To explain individual differences in fatigue, a multiple linear regression was used (RStudio Version 1.2.5033) with RMT and the interaction between lesioned hemisphere (left vs right) and RMT as explanatory variables. The interaction term was included to test for a potential confounding effect of lesioned hemisphere. HADS-Depression scores and sex significantly improved the model, assessed using the BIC (lower BIC indicates a better fitting model) and were included as independent explanatory variables. Multicollinearity of the explanatory variables was assessed by computing the variance inflation factor (VIF). Assumptions of normality and homoscedasticity of the residuals for each linear regression model were assessed visually using quantile-quantile normal plots and fitted-versus residual-value plots.

7.3 Results

7.3.1 Demographic data

There was a significant association between FSS-7 and grip strength ($\rho=-0.204$, $p=0.044$; figure 7.1C), HADS-Anxiety ($\rho=0.367$, $p<0.001$; figure 7.1E) and HADS-Depression ($\rho=0.498$, $p<0.001$; figure 7.2B) in the 98 stroke survivors. There was no association between FSS-7 and time post-stroke ($\rho=-0.097$, $p=0.348$; figure 7.1A), age ($\rho=-0.198$, $p=0.050$; figure 7.1B) and NHPT ($\rho=-0.123$, $p=0.229$; figure 7.1D). There was a significant difference in median FSS-7 scores between males and females ($W=661$, $p=0.003$; figure 7.2C) but no significant difference between left and right hemisphere strokes ($W=1379$, $p=0.200$; figure 7.1F) in the cohort of stroke survivors (demographics in table 7.1).

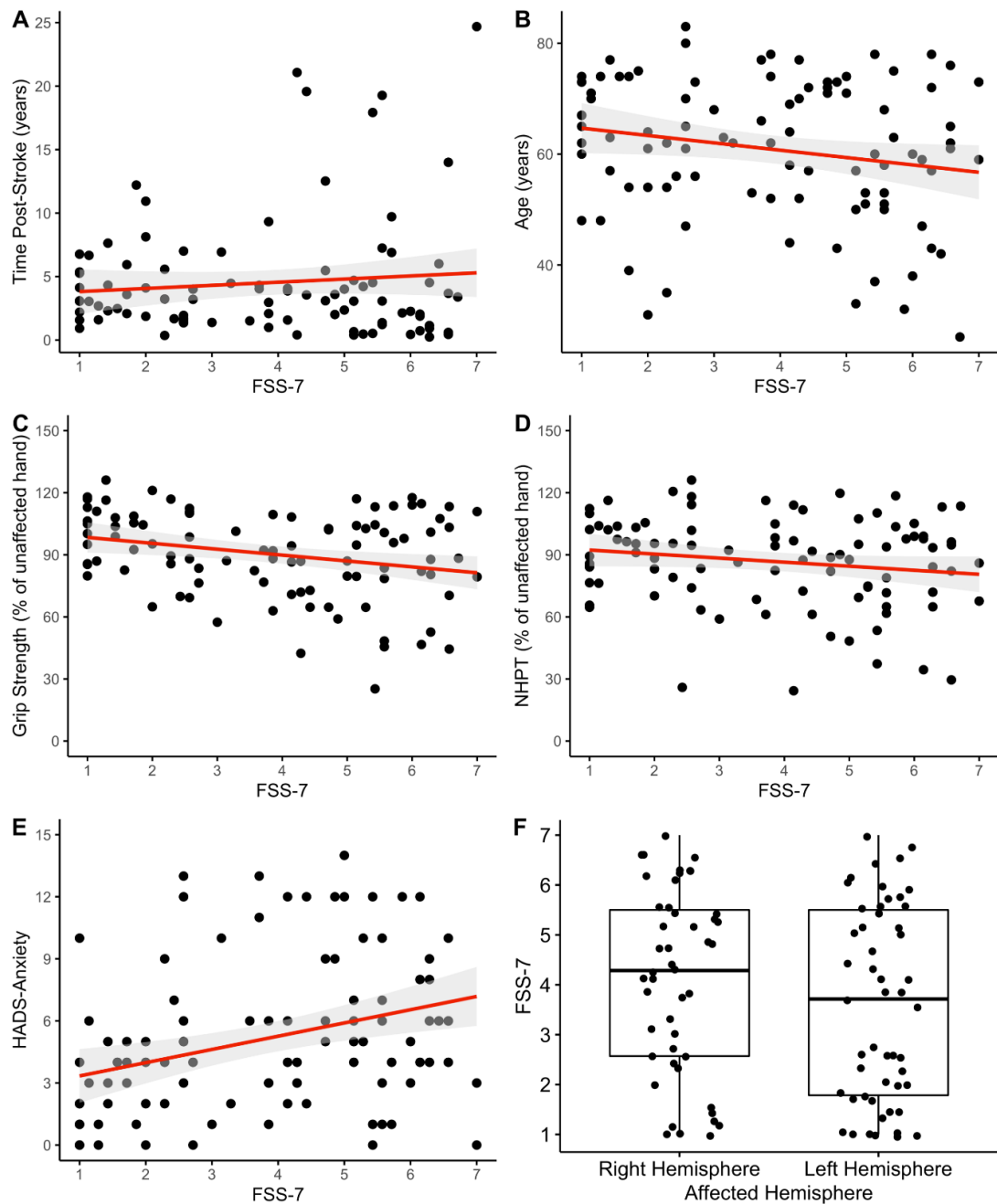


Figure 7.1 – Demographics and FSS-7: Association between fatigue (FSS-7) and demographic data across the entire cohort of stroke survivors (n = 98). For panel A-E, the red line indicates the regression line and its associated 95% confidence interval in grey for continuous data. For panel F, boxplots displaying the median and interquartile range for categorical data (hemisphere affected).

7.3.2 Corticospinal excitability

The multiple linear regression equation explained 31.3% of the variance in fatigue ($F(4,93)=12.04, p<0.001, \text{adj } R^2 = 0.313$). RMT was not a significant predictor of FSS-7 ($\beta = -0.063, p = 0.706, \text{CI}[-0.394, 0.268]$), while the interaction between lesioned

hemisphere and RMT was a significant predictor of FSS-7 ($\beta = 0.339$, $p = 0.039$, $CI[0.018, 0.659]$; figure 7.2A). The additional explanatory variables of HADS-Depression (figure 7.2B) and sex (figure 7.2C) were also significant predictors of FSS-7 ($\beta = 903$, $p < 0.001$, $CI[0.584, 1.223]$ and $\beta = 1.127$, $p = 0.002$, $CI[0.425, 1.830]$ respectively).

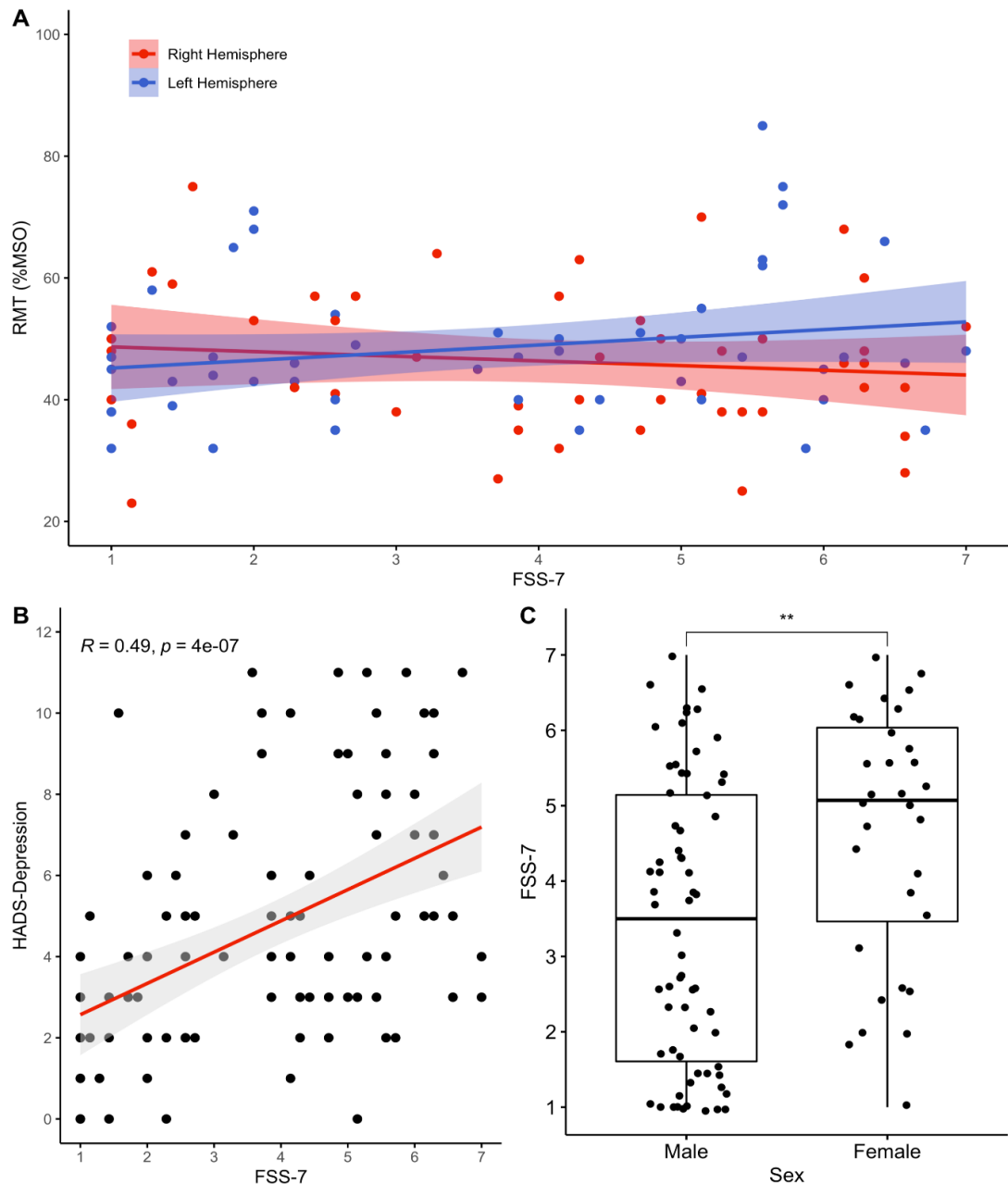


Figure 7.2 – Multiple linear regression model predictors: A) The association between resting motor threshold (RMT) and fatigue (FSS-7). Stroke survivors are displayed based on the hemisphere affected by the stroke with right hemisphere strokes in blue and left hemisphere strokes in blue. Regression lines and the associated 95% confidence interval is displayed is shown for both groups. B) Scatter plot with a regression line and 95% confidence interval showing the association between fatigue (FSS-7) and HADS-Depression. C) Boxplot displaying the effect of sex on fatigue (FSS-7) in the cohort of stroke survivors. ** indicate a significance level of <0.01 .

7.4 Discussion

Stroke survivors with left hemisphere strokes and high fatigue have lower corticospinal excitability than those with low levels of fatigue and right hemisphere strokes. Stroke survivors with high severity of fatigue scored higher on both the anxiety and depression subscales of HADS and also had less grip strength on their affected hand when compared to their unaffected hand. Fatigue severity was higher in female stroke survivors compared to males.

7.4.1 Influence of interhemispheric connectivity on resting motor threshold

Corticospinal excitability assessed using TMS resting motor threshold is highly variable in the general population (Wassermann, 2002). The two hemispheres behave differently during motor control. The left hemisphere appears to have a dominant role during motor control characterized by higher corticospinal excitability, broader activating patterns during movement and greater thickness of the motor cortex (Davidson and Tremblay, 2013; Hammond, 2002; Hervé et al., 2009; Klein et al., 2016; Verstynen and Ivry, 2011). This is in line with the asymmetry in inter-hemispheric connectivity, a net left-to-right inhibitory dominance and a net right-to-left excitatory dominance, seen in normal functioning brains. In PSF, there is a shift of inter-hemispheric effective connectivity within primary motor cortices from a net left-to-right to a net right-to-left inhibitory dominance (Ondobaka et al., 2019). In multiple sclerosis fatigue, sensorimotor networks within the left hemisphere show the biggest change following neuromodulation techniques (Porcaro et al., 2019). The authors suggest that re-balancing the inter-hemispheric difference between sensorimotor networks in the left and right hemispheres reduces fatigue severity. One would therefore expect to see lower corticospinal excitability in the left hemisphere and higher corticospinal excitability in the right hemisphere of stroke survivors with high severity of fatigue. In line with this prediction,

I show stroke survivors with high fatigue and left hemisphere strokes had lower corticospinal excitability than those with low fatigue and right hemisphere strokes.

Corticospinal excitability does not only reflect the output of the motor cortex but also the excitability of inputs that drive the output. The motor cortex has strong anatomical connections with other cortical and subcortical regions such as the pre-motor cortices, supplementary motor areas, cingulate motor areas, basal ganglia and the cerebellum, all of which can modulate corticospinal excitability (Kirimoto et al., 2011; Lee et al., 2013; Strick et al., 1998). Higher motor areas of the left-hemisphere specifically have a dominant role in motor attention and movement selection (Rushworth et al., 2003) and disrupting neural activity within the supplementary motor area of the left hemisphere results in a decrease in effort perception (Zénon et al., 2015a). A model of PSF has recently been proposed whereby poor sensory attenuation leads to increased perceived effort and subsequently high fatigue (Kuppuswamy, 2017). In fact, artificially reducing corticospinal excitability by stimulating the primary motor cortex of the left hemisphere using theta-burst stimulation reduces sensory attenuation (Voss et al., 2007). Corticospinal excitability is therefore closely associated to motor attention, effort perception and sensory attenuation. The results of the current study, reduced corticospinal excitability of the left hemisphere of stroke survivors with high fatigue, provides evidence to support the sensory attenuation model of fatigue.

7.4.2 PSF, other affective symptoms, sex and physical disability

The association seen between fatigue and the anxiety and depression subscales of HADS is not surprising. There is significant overlap between affective symptoms in neurological disorders (Cumming et al., 2018; De Doncker et al., 2018), suggesting that fatigue, anxiety and depression may share common underlying mechanisms resulting in a cluster of symptoms (Ayache and Chalah, 2019). This is also evident from similar findings of lower

corticospinal excitability in the left hemisphere of patients with clinical depression (Lefaucheur et al., 2008). It is important to note however, that despite the overlap, fatigue can exist independently of other affective symptoms (van der Werf et al., 2001). This highlights the importance of using a strictly controlled patient cohort when trying to draw conclusions from studies and attempting to develop a mechanistic understanding of affective symptoms.

The finding of greater fatigue in women than men has previously been reported in the stroke population (Mead et al., 2011; Schepers et al., 2006). Whether the imbalance is reflective of report bias with men considering less acceptable to report fatigue related symptoms or a difference in physiology remains unknown. It is important to consider that in the current cohort of stroke survivors there were twice as many males than females. The difference in fatigue between males and females observed in this study may therefore be a sampling issue. Our finding that higher levels of upper limb impairment, indicated by lower grip strength of the affected hand compared to the unaffected hand, are associated with PSF also supports previous studies (Choi-Kwon et al., 2005). It is important to note that all stroke survivors that took part in the study were fully independent and did not consider themselves to have a physical disability. Despite having lower grip strength, the manual dexterity of those with high fatigue was relatively high as stroke survivors that had less than 60% grip strength and dexterity on the affected hand were excluded from the study. Therefore, we do not consider muscle weakness as a cause of reported fatigue.

7.5 Conclusion

The relationship between corticospinal excitability of the affected hemisphere and self-reported fatigue may be influenced by other variables than previously suggested (Annapoorna Kuppaswamy et al., 2015). I show that the hemisphere affected significantly

contributes to the association between corticospinal excitability and fatigue. Identifying the functional role of the left hemisphere in mediating fatigue across a range of neurological and psychiatric disorders makes it a potential target for developing effective interventions of fatigue.

Chapter 8: General Discussion

Fatigue is a major but neglected issue across a range of neurological disorders. The role of the brain, an organ of perception, in mediating fatigue has been acknowledged since the time of Angelo Mosso in the late 19th century. What remains unclear however is how the brain generates the subjective experience of fatigue in the absence of a stimulus, as seen in chronic pathological fatigue. PSF was highlighted as a major issue in the 'Life After Stroke' priority setting partnership in 2010, run by the Stroke Association in the UK and has led to increased research funding in the field of fatigue. A major driver of PSF being a major issue in stroke survivors is the lack of currently available treatments and the lack of effect of previously used interventions of PSF, such as anti-depressants. Over the last decade, PSF has received its much-deserved attention and has been acknowledged as a primary symptom that needs to be addressed independently. This has led to the emergence of new theoretical frameworks to explain chronic pathological fatigue that subsequently impact how we investigate and treat fatigue. The new theoretical frameworks have previously been used to explain brain function and have been repurposed to explain chronic pathological fatigue. Such models lead to hypothesis driven experiments that can be performed with the aim to identify the neural mechanisms that underlie fatigue, ultimately resulting in successful interventions of this persistent and highly debilitating symptom.

The sensory attenuation model of fatigue is one such theoretical framework that has been used to explain the mechanism that underlies PSF. The model proposes that inflammation, the commonest cause of fatigue in the acute stage of stroke recovery, results in altered neurotransmission and neuromodulation which sets in motion a series of changes that include alterations in sensorimotor processing that underlie the perception of effort. Failure of homeostatic mechanisms to reverse such alterations,

namely the inability to attend away from predictable sensory input or sensory attenuation, results in the perception of high effort for what are usually low effort activities and subsequently in the self-reported symptom of fatigue. Throughout my PhD, I have performed a number of experiments to test whether the sensory attenuation model of fatigue is true. What follows is a brief summary of all the results presented throughout earlier parts of this thesis.

Chapter 3 investigated the association between the perception of effort in the absence of prior exertion in stroke survivors with varying severity of fatigue. This is the first study to show that perceived effort, namely the implicit and not explicit perception of effort, is influenced by fatigue. I have also shown that stroke survivors with high severity of fatigue show alterations in motor control and behaviour, particularly in low effort tasks which may mediate the observed differences in effort perception.

Chapter 4 examined the effect of sensory attenuation as quantified using the force matching paradigm on PSF. Despite not providing definitive evidence in support of the sensory attenuation model of fatigue, this study provided some useful insights into specific sensory modalities that might be implicated, namely sensory attenuation of proprioceptive input. This study also highlighted some key methodological considerations that should be addressed when performing classic behavioural experiments such as the force matching paradigm. Providing detailed descriptions of the set up used that can be assembled across different research facilities will help in the replication of the sensory attenuation effect and is something that should be explored further.

Chapter 5 explored the influence of fatigue on neurophysiology when preparing for an action, during movement preparation. I found that corticospinal excitability during movement preparation changes as a function of fatigue in chronic stroke survivors.

Stroke survivors with high severity of fatigue had less suppression of corticospinal excitability during movement preparation and higher excitability immediately before movement onset when compared to stroke survivors with low severity of fatigue. Stroke survivor with high fatigue, also had longer reaction times during the task. Modulation of corticospinal excitability during movement preparation can be viewed as a measure of sensory processing of expected sensory input and therefore sensory attenuation. Less modulation of corticospinal excitability during movement preparation can thus be interpreted as reduced sensory attenuation.

Chapter 6 used a neuromodulatory technique, anodal tDCS applied bilaterally over the two primary motor cortices with the aim to reduce fatigue severity and provide insights into the mechanisms that might underlie fatigue. Such techniques have been shown to increase corticospinal excitability, reduce the perception of effort in exercise induced fatigue and reduce fatigue severity in MS. I show that anodal tDCS significantly improves the subjective experience of fatigue when compared to a sham stimulation, with effects lasting for one week post stimulation. Despite seeing an improvement in fatigue, the mechanisms that might underlie the improvement in fatigue and hence the mechanisms that underlie fatigue as a symptom remain unclear.

Chapter 7 examined the association between corticospinal excitability and fatigue. Despite previous studies showing an association between corticospinal excitability assessed using TMS and PSF, this was not replicated in Chapter 5. Using the data collected in Chapter 5 and Chapter 6, the relationship between corticospinal excitability and PSF was examined taking into consideration the hemisphere affected by the stroke. Stroke survivors with left hemisphere strokes and high fatigue have lower corticospinal excitability than stroke survivors with right hemisphere strokes and low levels of fatigue.

This highlights the functional role of the left hemisphere and the interhemispheric connectivity between the two hemispheres in mediating fatigue.

In what follows, I will attempt to unify the findings across the different studies included in this thesis with findings in other neurological conditions in which fatigue is a prominent symptom and discuss potential mechanisms that underlie the chronic nature of fatigue in disease state.

8.1 Effect of acute inflammation on cortical neurophysiology

Following a stroke there is a global inflammatory response in the brain as the metabolic demands of the affected and surrounding brain area are not met. Inflammation is the commonest cause of fatigue in the acute stages of stroke recovery (Dantzer et al., 2014). Inflammation affects a number of neurotransmitters such as dopamine, serotonin, GABA and glutamate as well as directly affecting voltage gated sodium channels, all of which are responsible for the normal functioning of the brain and implicated in measures of cortical neurophysiology (Dantzer et al., 2014; Zhou et al., 2011; Ziemann, 2004). Dysregulation of the abovementioned neurotransmitter systems and ion channels can result in alterations in cortical neurophysiology, and failure of homeostatic mechanisms to reverse these changes, may explain the persistence and chronic nature of fatigue.

8.1.1 Cortical neurophysiology at rest

Reduced cortical excitability of the affected hemisphere, reflected by higher RMTs using TMS, has previously been associated with fatigue severity in chronic stroke survivors (Annapoorna Kuppuswamy et al., 2015). Higher RMTs assessed using TMS reflect the excitability of both cortical M1 neurones and spinal motor neurones, while measures of AMT are thought to reflect only cortical M1 neurone excitability (Rothwell et al., 1991). Given that both measures of RMT and AMT were associated with fatigue, together with

the fact that the investigated cohort of stroke survivors had minimal physical impairment and therefore intact corticospinal tract integrity, suggests that the observed alterations in cortical excitability are of central origins. Drugs used to block voltage gated sodium channels and NMDA receptors, such as lamotrigine and ketamine, are affected by inflammation and known to directly influence corticospinal excitability (Boroojerdi et al., 2001; Ziemann, 2004). Lower cortical excitability seen in PSF, might therefore be a result of voltage gated sodium channel or NMDA receptor dysfunction resulting in changes within M1 or due to a failure to drive M1 output by brain regions that input into M1 such as the SMA and premotor cortex. Both these neurotransmitter systems are excitatory and are in line with a recent model of fatigue in neurological diseases which suggests that suppression of the excitatory sensorimotor system may lead to the development of fatigue (Tanaka and Watanabe, 2012). In Chapter 7 of this thesis, I show that the association between cortical excitability and fatigue only holds true in the left hemisphere. Although dysfunction of neurotransmitter systems other than glutamate mediated neurotransmission do not directly influence measures of motor threshold assessed using TMS, they do impact other measures of cortical and corticospinal excitability that may influence measures of motor threshold and be reflected in cortical excitability changes. One such measure is that of interhemispheric inhibition.

The corpus callosum is the largest white matter structure in the brain that connects homologous cortical areas of the two cerebral hemispheres and plays a critical role in transfer of sensory, cognitive and motor information. The transcallosal influence of each M1 on its homologue in the opposite hemisphere is predominantly inhibitory mediated by transcallosal glutamatergic pathways linking with pyramidal tract neurones through GABAergic interneurons (Hui et al., 2020; Perez and Cohen, 2009b; Reis et al., 2008). Optimal interhemispheric communication is fundamental for normal and effective functioning of brain networks. Studies in healthy subjects show that the left hemisphere

exhibits a stronger inhibitory influence on the right hemisphere than the inhibitory influence of the right hemisphere on the left (Giovannelli et al., 2009; Netz et al., 1995; Ziemann and Hallett, 2001). Inflammatory mediated changes in glutamatergic and GABAergic neurotransmission may therefore affect the interhemispheric communication and subsequently cortical excitability. A recent study in PSF demonstrated a shift in interhemispheric inhibition in those with higher severity of fatigue. Fatigue was associated with a stronger inhibitory influence from the right hemisphere onto the left hemisphere (Ondobaka et al., 2019). A stronger inhibitory influence from the right hemisphere onto the left hemisphere seen in those with high fatigue severity could therefore result in reduced cortical excitability specifically of the left hemisphere. Results reported in Chapter 7 of this thesis confirm this is indeed the case.

8.1.2 Cortical neurophysiology during movement preparation

Cortical excitability changes associated with fatigue are not only seen at rest but also when preparing for a voluntary movement. When preparing for a voluntary movement, cortical excitability undergoes distinct modulation that is dependent on the excitation/inhibition balance of not only the M1 but also of areas upstream of M1 that feed into M1 (Tanji and Evarts, 1976). Studies using TMS over M1 to probe corticospinal excitability changes at different time points relative to movement onset report a period of reduced corticospinal excitability observed prior to movement in muscles that are both involved and uninvolved in an action, termed preparatory inhibition (Bestmann and Duque, 2016; Duque et al., 2017, 2010; Greenhouse et al., 2015; Hasbroucq et al., 1999; Touge et al., 1998). The preparatory inhibition observed when preparing for a voluntary movement is not caused by direct inhibition of corticospinal output neurones but instead is thought to reflect reduced excitability in one of the excitatory input pathways to corticospinal neurones (Hannah et al., 2018). Physiologically, the role preparatory inhibition before voluntary

movement onset may be to attenuate irrelevant input to motor cortices and help the motor cortex reach a preparatory state from which to achieve faster and more accurate movements (Churchland and Shenoy, 2007; Hannah et al., 2018; Hasegawa et al., 2017; Seki and Fetz, 2012). Disruptions in interhemispheric communication and areas upstream of M1 such as the SMA which have projections into M1 can both influence preparatory inhibition and behaviour (Hinder et al., 2018, 2012; Zimnik et al., 2019). It is therefore plausible that inflammatory mediated changes in interhemispheric inhibition and altered activity of neurotransmitter pathways both within and outside of M1 will result in a different time course of corticospinal excitability during movement preparation. This is in line with the results of Chapter 5 of this thesis where the modulation of corticospinal excitability during movement preparation changes as a function of fatigue in stroke survivors. Specifically, the higher the level of fatigue, the lower the suppression of corticospinal excitability during movement preparation and the higher the pre-movement facilitation of corticospinal excitability immediately before EMG onset that could account for the longer reaction times in those with greater fatigue. This suggests that stroke survivors with fatigue are not able to reach the appropriate preparatory state (lower suppression of corticospinal excitability) from which to initiate the movement and as a result a greater input into M1 is required to drive motor output (higher pre-movement facilitation of corticospinal excitability). The lack of preparatory inhibition can be interpreted as an inability to attenuate irrelevant, or predictable, sensory input that might arise from within the body (proprioceptive information from the muscles) or from the external environment (task-related cues). As a result, the greater drive required to initiate a movement from a reduced preparatory state will be reflected behaviourally by slower reaction times and perceptually by the movement feeling harder or more effortful.

Changes in cortical excitability, at rest and when preparing for a movement, influenced by dysfunctional connectivity within sensorimotor networks might therefore be related

to altered sensorimotor processing, specifically the inability to modulate attention away from predictable sensory input, resulting in a greater perception of effort.

8.2 Cortical excitability as a surrogate of sensory attenuation

The sensory attenuation model of fatigue proposes that reduced sensory attenuation underlies altered perception, namely the perception of effort, resulting in PSF. Within predictive coding schemes, top-down predictions are used to form prediction errors at each level of the cortical and subcortical hierarchies. Prediction errors encode the newsworthy information from a lower hierarchical level that was not predicted by the higher level and is returned to the level above to update future predictions in a Bayesian sense. Prediction errors are precision-weighted and prediction errors with a higher precision (or gain) have a stronger influence over higher levels of processing (Bastos et al., 2012). The function of altering the gain of prediction errors is known as sensory attenuation (Brown et al., 2013). Sensory attenuation quantifies the effect of pre-synaptic input on post-synaptic output and is therefore mediated by the effects of various neurotransmitter systems. In fact, neurotransmitter systems implicated in sensory attenuation are also known to affect cortical excitability and within the sensorimotor system, cortical excitability might be a surrogate measure of sensory attenuation (Adams et al., 2013b; Ziemann, 2004).

In Chapter 7, I have shown that resting cortical excitability of the left hemisphere is reduced in stroke survivors with high severity of fatigue. Rest is a term often used to describe lack of explicit behaviour. However, even when at 'rest' the brain is constantly receiving bottom-up afferent input from within the body, proprioceptive projections from contracted muscles to maintain resting muscle tone, and the external environment in the form of visual, auditory or somatosensory input. Reduced sensory attenuation (high precision afforded to bottom-up prediction errors) of the abovementioned afferent input

at rest, reflected as reduced cortical excitability at rest, might account for some of the experiences of stroke survivors with fatigue that will be discussed in a later section. The altered time course of cortical excitability during movement preparation in stroke survivors with high fatigue might also be a reflection of reduced sensory attenuation. The state of cortical excitability prior to a movement is thought to be influenced by the level of uncertainty associated with the upcoming movement (Bestmann et al., 2008; Bestmann and Duque, 2016). In cue driven paradigms the stimulus to act (usually an auditory or visual stimulus), as well as the proprioceptive and somatosensory input associated with upcoming movement are highly predictable. The degree of preparatory inhibition of cortical excitability before movement onset is associated with the degree of predictability, with greater preparatory inhibition associated with higher predictability and more accurate or faster movements (Churchland and Shenoy, 2007; Hannah et al., 2018; Kilner et al., 2005). By reducing the predictability of upcoming cues to act, the preparatory inhibition within the motor cortex is suppressed (Bestmann et al., 2008; Kilner et al., 2005). This effect is primarily thought to be driven by input into M1 from brain areas further upstream (Hannah et al., 2018). In post-stroke fatigue, reduced preparatory inhibition may indicate greater uncertainty afforded to predicted afferent input and therefore higher precision afforded to bottom-up prediction errors. High precision afforded to bottom-up prediction errors, or reduced sensory attenuation, may subsequently result in higher effort perception afforded to the upcoming movement.

Overall, lower cortical excitability of the left hemisphere at rest and lesser suppression of corticospinal excitability when preparing for a movement in stroke survivors with high fatigue provides some evidence in support of the sensory attenuation model of fatigue.

8.3 Sensory attenuation of proprioceptive information and perceived effort

Sensory attenuation provides a general account of perception and is not specific to a single sensory modality. In the context of movement and processing of sensory information resulting from movement, the sensory information that is often attenuated originates from somatosensory organs conveying proprioceptive information and mechanoreceptors conveying information related to touch, pressure and vibration. In Chapter 4, I have shown that the idea of reduced sensory attenuation in post-stroke fatigue does not hold true with regards to sensory information originating from mechanoreceptors, suggesting that stroke survivors with fatigue are still able to attend away from such sensory information. The results of chapter 4 however do not exclude the possibility of a failure to attenuate proprioceptive information originating from somatosensory receptors. In fact, reduced sensory attenuation of bottom-up proprioceptive information resulting in lower cortical excitability, when at rest can account for the sensation of limb heaviness reported in stroke survivors with fatigue (Kuppuswamy et al., 2016). As mentioned previously, when at rest various muscles are contracted to maintain resting muscle tone. This results in proprioceptive information reaching the sensorimotor cortex, which under normal circumstances is attenuated (afforded low precision) as it does not encode newsworthy information. However, if sensory attenuation of proprioceptive information arising from muscles used to maintain muscle tone is reduced, proprioceptive prediction errors are afforded higher precision and can give rise to the sensation of limb heaviness. During movement, or when preparing for an upcoming movement, reduced sensory attenuation of proprioceptive information results in lesser suppression of cortical excitability during the preparatory phase. If one takes the example of a muscle contraction in the healthy brain, under normal sensory attenuation, bottom-up proprioceptive prediction errors that drive the muscle

contraction are suppressed which leads to the perception of less or no effort afforded to the muscle contraction. However, in the absence of, or when sensory attenuation is reduced as has been proposed to be the case in post-stroke fatigue, the same muscle contraction will be accompanied by more precise bottom-up proprioceptive prediction errors resulting in the perception of higher effort afforded to the muscle contraction.

In Chapter 3, I have shown that trait fatigue, a measure of the experience and impact of fatigue on day-to-day living, correlates with the perception of effort associated with low force contractions and not high force contractions. The relationship between perceived effort and fatigue does not appear to be driven by fatigue on the day of testing as there is no association between state fatigue and perceived effort. Higher perceived effort afforded to what are usually low effort activities (e.g. 20% MVC contractions) in those with high levels of trait fatigue and not state fatigue is suggestive that altered perceived effort is the driver of fatigue and not simply an epiphenomenon of fatigue. The association between trait fatigue and perceived effort afforded to low force contractions fits with anecdotal evidence from stroke survivors suffering from fatigue; activities of daily living feel more effortful than they did prior to the stroke. For high force contractions when the motor system is working close to its maximum (close to MVC), sensory attenuation no longer holds true (Walsh et al., 2011) as one cannot attend away from bottom-up proprioceptive information. When taken together, the above support the hypothesis reduced sensory attenuation of proprioceptive information results in higher perceived effort afforded to muscle contractions associated with what are usually low effort activities and subsequently in the sensation of fatigue.

8.3.1 Brain areas implicated in perceived effort and cortical excitability

Taking a closer look at the origins of effort perception afforded to voluntary movements when carrying out certain tasks, highlights the overlap between brain regions implicated

in the abovementioned studies and those mediating the perception of effort. Perceived effort has been primarily studied in the context of movement and exercise induced fatigue, or physiological fatigue, in which subjects are asked to rate the sense of effort afforded to certain tasks. Perceived effort can be altered by manipulating bottom-up afferent input from the peripheral musculature and sensory organs or by disrupting top-down predictions of sensory input (Lafargue et al., 2003; Slobounov et al., 2004; Bridgeman, 2005; Luu et al., 2011; de Morree et al., 2012; Brooks et al., 2013; Takarada et al., 2014; Zénon et al., 2015). Studies focusing on the central contributions of perceived effort highlight the role of the sensorimotor cortex in effort perception. Studies using TMS to disrupt activity within M1 and areas further upstream that have inputs to M1, such as the SMA, have an effect on the sense of effort associated with the subsequent movement. Disrupting M1 increases perceived effort, probably by increasing the drive from areas further upstream into M1, while disrupting SMA reduces perceived effort (Takarada et al., 2014; Zénon et al., 2015). EEG studies looking into the effect of the sense of effort on MRCP, suggest that areas such as the SMA, premotor cortex, M1, sensory cortex and parietal cortex all contribute to the perception of effort (Slobounov et al., 2004; Marcora, 2009; de Morree et al., 2012). It becomes apparent that a number of brain regions located within the sensorimotor network appear to be implicated in mediating the perception of effort. The abovementioned brain areas thought to contribute to the perception of effort, namely the M1 and SMA, are also implicated in preparation and execution of voluntary movements as previously mentioned in earlier parts of this thesis (Hannah et al., 2018; Hinder et al., 2018; Seki and Fetz, 2012; Zimnik et al., 2019). Therefore, it is possible that reduced attenuation of bottom-up proprioceptive input at the level of sensorimotor cortex, reflected as lower cortical excitability at rest and lesser suppression of cortical excitability during movement

preparation, underlies high perceived effort when performing simple tasks as seen in post-stroke fatigue.

8.5 Other evidence of sensorimotor implications and reduced sensory attenuation in fatigue

Research in PSF has primarily focused on correlations with the characteristics of the stroke itself and stroke survivor demographics, with very little research on network level dysfunctions and mechanisms that might be associated with PSF. There is however a large body of work on pathological fatigue and the implicated networks in MS. Similarly to PSF, fatigue in MS has been identified as one of the most troubling symptoms of the disease occurring in up to 80% of people with MS (Kesselring and Beer, 2005). The sensory attenuation model of fatigue is a disease independent mechanism used to explain the emergence and persistence of pathological fatigue across different disease states, and work from MS can be used to provide evidence in support of this framework.

MS patients with fatigue exhibit an overall hyperactivation of the M1 both at rest and during movement, with an overall less inhibition after exercise when compared to MS patients without fatigue and healthy volunteers (Leocani et al., 2001; Liepert et al., 2005). As well as primary motor areas, non-primary sensorimotor areas such as the SMA and premotor cortex are implicated in MS fatigue. Fatigue severity in MS patients is modulated by the activity of the SMA, with increased activation and decreased inhibition of the SMA resulting in more severe fatigue (Filippi et al., 2002; Leocani et al., 2001). The association between SMA activity and fatigue is further evident in patients with chronic fatigue syndrome. Stronger SMA activity and reduced SMA-sensorimotor cortex connectivity is seen in fatigue patients (van der Schaaf et al., 2018). The directionality of activity in SMA and fatigue severity is in line with that of SMA activity and perceived effort. As previously described, the SMA is thought to be responsible for generating predictions regarding the

sensory consequences of the upcoming movement (Haggard and Whitford, 2004; Zénon et al., 2015b) and abnormal activity in SMA may reflect a discrepancy between prior expectations and actual sensory evidence. The abovementioned findings suggest that increased activity of SMA might reflect reduced sensory attenuation of bottom-up proprioceptive input and might underlie the excitability changes seen in MS fatigue and the perception of high effort.

Connectivity of local sensorimotor networks also appears to be altered with fatigue. MS patients with fatigue have lower levels of resting state functional connectivity in the pathways connecting brain areas involved in processing sensory and motor information, namely the SMA and premotor cortex (Cruz Gómez et al., 2013; Engström et al., 2013; Finke et al., 2015; Hidalgo de la Cruz et al., 2017; Jaeger et al., 2019; Stefancin et al., 2019; Vecchio et al., 2017). Connectivity changes with fatigue are not only evident at rest but also before, during and after movement. There is increased activation in motor and premotor circuits, as well as greater cortico-muscular coherence while performing motor tasks in MS patients with fatigue (Benwell et al., 2007; Morgante et al., 2011; Rocca et al., 2009; Tomasevic et al., 2013).

Interhemispheric communication between sensorimotor networks appears to play a role in fatigue in MS patients. Resting state functional connectivity between post-central sensory networks is increased in MS patients with fatigue, with major differences observed in the primary sensory cortex and posterior parietal cortex specifically of the left hemisphere (Buyukturkoglu et al., 2017; Porcaro et al., 2019; Vecchio et al., 2017). Greater functional imbalance between the two hemispheres results in greater fatigue levels both at rest and during movement, with the primary sensory area of the left hemisphere generating higher power than the right hemisphere (Cogliati Dezza et al., 2014).

All of the above findings in MS fatigue share many similarities to the findings in PSF both in this thesis and in the existing literature. A network level dysfunction, specifically within the sensorimotor network, resulting in reduced attenuation of the sensory consequences of movement originating from somatosensory organs, underlies the perception of high effort in such tasks and the experience of fatigue. The work in MS provides evidence in support of the sensory attenuation model of fatigue.

8.6 Therapeutic interventions of fatigue

Chronic pathological fatigue is a prominent symptom across a range of neurological diseases and has a major impact on quality of life. Developing effective interventions based on a sound understanding of the mechanisms that underlie fatigue is therefore of major importance. Throughout this thesis, I have demonstrated that PSF is associated with sensorimotor network level dysfunction, altered cortical excitability both at rest and when preparing to carry out a movement, that underlies sensory attenuation and the perception of effort. This is in line with previous work both in PSF and MS fatigue. Interventions aimed at modifying cortical excitability and restoring sensorimotor network balance such as NIBS are easy to use, low cost, interventions that can be administered within a home setting and are therefore an attractive proposal. By increasing cortical excitability, the precision afforded to bottom-up proprioceptive input will be reduced (high sensory attenuation), and therefore reduce perceived effort and fatigue severity. Such techniques are useful not only for their therapeutic potential, but also offer a means for developing a better understanding of the mechanisms that underlie fatigue.

In Chapter 6 of this thesis, I have shown that a single session of anodal tDCS results in an improvement in fatigue (a reduction in fatigue severity) in chronic stroke survivors. One of the aims of the study was to identify the potential mechanisms that underlie the reduction in trait fatigue following anodal tDCS. The expectation was that a change

immediately post stimulation in M1 neurophysiology and PE will result in reduction in trait fatigue a week later. The results from chapter 6, provide some support of this claim but from a mechanistic point of view, there are still questions to be addressed with regards to how anodal tDCS results in reduced trait fatigue. The results in this thesis are in line with tDCS studies aimed at improving fatigue in MS patients. Anodal tDCS applied to the sensorimotor cortices with a shoulder reference reduces fatigue severity in MS patients, with the effects lasting a couple of weeks (Ferrucci et al., 2014; Porcaro et al., 2019; Tecchio et al., 2014). What is interesting is that anodal tDCS applied to the dorsolateral prefrontal cortex, a common target used for the treatment of depression, does not improve fatigue (Saiote et al., 2014). These studies highlight the role of sensorimotor network dysfunction in mediating fatigue and when targeting these networks, such techniques are able to restore the connectivity patterns to normal range and reduce fatigue severity possibly by modulating effort perception.

A very important factor that needs to be considered when using such techniques is the duration of the desired effect. In Chapter 6 and in the previous studies reported in the literature, the effect of reduction of fatigue severity is short-lived lasting only a few weeks to a month. From a patient's perspective, these effects need to be longer lasting to offer a meaningful improvement in quality of life. Developing ways of extending the effects of such interventions, is therefore essential before they can be used in a clinical setting as an effective treatment for fatigue.

One potential method for getting a more robust effect with regards to fatigue reduction is to use more targeted stimulation approaches. The differences in intra and inter-hemispheric connectivity reported in MS fatigue are all within the beta frequency band which appears to play a crucial role in sensorimotor control (Buyukturkoglu et al., 2017; Cogliati Dezza et al., 2014; Engel and Fries, 2010; Vecchio et al., 2017). In predictive

coding schemes, neural oscillatory activity determines the synaptic gain and at the level of the sensorimotor cortex, beta band oscillatory activity might be a reflection of precision afforded to bottom-up proprioceptive input (Chawla et al., 1999). Transcranial alternating current stimulation (tACS) allows for stimulation at specific frequencies. Therefore, tACS in the beta frequency, which has previously been shown to increase cortical excitability (Wischnewski et al., 2019), could potentially be a more effective intervention in reducing fatigue.

8.7 Future directions

The field of fatigue research is very young and there is a lot of work to be done in order to develop a sound understanding of the mechanisms that underlie chronic pathological fatigue. With increasing recognition of fatigue as a primary and significant problem by both patients and health care professionals across different disease states, including “long Covid”, more resources will be invested to progress the field. The work done as part of this PhD introduces an avenue on which we can build our understanding of fatigue. Although the work presented here is in line with the sensory attenuation framework of fatigue, other frameworks also exist which can account for some of the reported results.

The central sensitization model of fatigue proposes that excessive activation of excitatory systems in the acute stages of stroke recovery results in sensitization of the inhibitory system as a means to counteract prolonged stress, resulting in a constant need to rest and the experience of fatigue (Tanaka et al., 2013). This framework can account for the neurophysiological findings of lower cortical excitability at rest and altered modulation of corticospinal excitability when preparing for a movement reported in this thesis, as well the use of excitatory NIBS techniques to reduce fatigue severity. Another neurocognitive framework takes into accounts the impact of effortful exertion on subsequent motivation (Müller and Apps, 2018). It is not the percept per se that is altered resulting in fatigue,

but the affinity afforded to effort. In other words, how willing is an individual to exert a certain amount of effort to obtain a specific ‘reward’; Do I engage in an action or do nothing? The higher perception of effort afforded to what are usually low effort voluntary contractions seen in PSF in Chapter 3 of this thesis, might therefore reflect a higher subjective value of exerting effort. Participants were not given an option of exerting effort and were instructed to complete the task at hand; therefore, a higher subjective value of effort will be reported in the task as being more effortful. If given the option, participants might have chosen not to engage in the task. A defining feature of fatigue is the reduction in self-initiated voluntary activity, with the motivational system being essential for the self-initiation component of voluntary action. The areas of the brain implicated in effort based decision-making and motivation have previously been implicated in apathy and depression which as mentioned in the introduction of this thesis has significant overlap with fatigue in a number of neurological disorders including stroke (Bonnelle et al., 2015; Husain and Roiser, 2018; Le Heron et al., 2017; Muhammed et al., 2015). A lack of engagement in voluntary activities requiring effort might therefore be a result of motivational dysfunction due to the cost (inverse of reward) afforded to effort. Although such frameworks can explain some of the results reported in this thesis, there is strong evidence in support of the sensory attenuation model of fatigue, and when considered together, these frameworks can explain the multidimensional nature of fatigue.

As well as providing evidence in support of the sensory attenuation model of fatigue, the experiments carried out highlight the potential of future work and experiments that can be done that could provide further support of this framework. One such experiment includes investigating the role of attenuation of proprioceptive input originating from muscle spindles on effort perception, and how inability to attend away from proprioceptive prediction errors might give rise to limb heaviness, increased effort perception and subsequently fatigue. Another important step is to examine the use of

NIBS approaches resulting in more robust and longer lasting effects on fatigue reduction. Examining the functional role of oscillatory activity in mediating fatigue will allow for the use of more targeted NIBS approaches, such as tACS at specific frequencies, that may be more effective in reducing fatigue severity than previously used methods.

Finally, exploring the role of sensory attenuation across other sensory modalities and its association of fatigue may allow us to better understand the multidimensional nature of fatigue. Throughout this thesis I have mainly focused on the perception of effort in a manual task and movement related processing of afferent input. However, anecdotal evidence from stroke survivors suffering from fatigue suggests that processing of afferent input across other sensory domains such as vision and hearing is also affected. Stroke survivors with fatigue feel overwhelmed when in crowded places and are unable to filter out background sound.

"If we are talking about sound, I say the worst thing for me is conversations. I can handle one person talking but If I am in a busy environment or an office, there is no way to filter out all the conversations and it is very, very tiring to be in a room with lots of people. I pray for silence"

The same holds true with regards to vision when looking at a visually cluttered scene. Sensory attenuation, as highlighted in the introduction of this thesis, is not specific to proprioception and hold true for predictable sensory input across various sensory modalities. Is fatigue a result of reduced sensory attenuation across all sensory modalities or is it specific to certain domains? Exploring the role of visual effort and auditory effort in fatigue is therefore an avenue worth exploring further that might provide further support for the sensory attenuation model of fatigue.

There is a lot of work to be done if we are to understand the neural mechanisms that underlie chronic pathological fatigue. Research on fatigue should be a top priority given

its prevalence across various disease states and its impact on quality of life, and only then will we see a significant improvement in the strategies used to manage and treat fatigue.

A letter to fatigue

Dear Fatigue,

You test me, punish me, control me, and teach me. I swing between being thankful for you teaching me patience and tolerance and detesting you for taking over my life. For preventing me from living for stopping me from working, seeing my friends and my family. But mostly, being the woman, I knew and loved. You took that away from me. You stole everything I knew and recognised.

I imagine that **I was once a spectacular castle set in the most beautiful grounds,** Walled gardens and wildflowers. **But now I am a dilapidated castle.** You can see where I started but it has started to crumble away. It is now exposed, bare and fighting for its life.

I didn't know or understand it before. I cringed at people who said they were tired. I didn't know or recognise what that was. **I was bursting with life, bursting with endless energy. Nothing was going to stop me or take me down.** Stroke you arrived and crippled me. You stilted my speech and left me with the dreaded F. Yes, fatigue I'm talking about you!

Fatigue, for you I have no fight, no defence. I can work on my movement in rehab. Aided by doctors and therapists. I can do my speech work and practice. But you fatigue? What can I do? You leave me alone and frightened with no fight. I can't fight you! Because I don't have the energy and I don't know what causes you. I don't understand you and that cripples me.

Sarah, a stroke survivor

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