THE MENFAS STUDY

Understanding Mental Fatigue after Stroke

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This thesis is submitted in partial fulfilment of the requirements of the award of Doctor of Philosophy.

June 2023

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Abstract

Mental fatigue is a highly distressing symptom after stroke, and motor factors alone cannot explain the persistence of severe fatigue even many months after the stroke. Evolving theories

suggest that mental fatigue is associated with cognitive impairment in general, and perhaps dysfunction in the cognitive domain of attention in particular. However, the relationship between attention and mental fatigue after stroke has rarely been examined and given the negative impact of mental fatigue on participation, an understanding of underlying mechanisms mediating mental fatigue is clinically significant. Furthermore, there is insufficient evidence of the efficacy of any intervention strategy to treat or prevent post-stroke fatigue (PSF) that considers real world context and environment, such as attention or contextual factors and their potential effect on PSF.

A systematic review to describe the full extent of the evidence, was extended across the post Acquired Brain Injury (ABI) fatigue literature, which included stroke populations. Analysis found sustained attentional performance had stronger associations with fatigue after ABI, though inconsistencies in measurement were shown. A synthesis of the theory base underlined the complexities involved in the domain of attention, and the need for focused measurement strategy to understand the mechanisms of fatigue. Taken together insights gained supported the development of a novel measurement strategy designed to capture the momentary lived experience of fatigue and traits of fatigue (mental and physical fatigue) within the context of the task, in the home environment.

A cross sectional observation study pre-trialling the use of a novel measurement strategy involving 32 patients at the early phase (>2 months) post-stroke experiencing PSF, confirmed a relationship between sustained attention and mental and physical fatigue within a very short time-frame, in the home environment. Linear regressions (R^2) revealed a statistically significant relationship between sustaining attention on the MCCPT and trait fatigue: Accuracy & FSMC sum score (R^2=.141, $p = .034$), Accuracy & FSMC cognitive score (R^2=.153, $p = .027$), Accuracy & FSMC motor score (R^2=.152, $p = .027$). The pre/post study design provided insights into the mutli-dimensional facets of fatigue, with further burdens on executive attentional involved in motor control indicated. Participants experienced higher levels of fatigue in the moments following completion of the attentional task (R^2=.107, p = .068), rather than before.

A novel occupation-focused intervention support system to manage PSF was developed to investigate, in a sample of 29 stroke survivors at the early phase of stroke (> 2months), the extent of the impact of altering attentional focus on both fatigue levels and subsequent task

performance. This feasibility trial demonstrated how investigating the impact of altering attentional focus (with noise-cancelling earphones) is feasible, acceptable, and safe within the community. Study findings supported the use of this trial design within the community. Preliminary findings offer potential further insights into how attentional mechanisms and contexts interact at the sub-acute phase of recovery. In a short time-frame (>12 minutes), increased focus appears to place greater demands on attentional processes involved in motor functioning processes, i.e. Inhibition. Over the longer term (such as a standard therapy session, <45 minutes) altering contextual noise (with noise-cancelling earphones) led to better performance (-12.6, 95% CI [-7.1, -4.7], t (28) = - 4.7, p = <.001) but at a higher cost in terms of fatigue.

Conclusion: This thesis provides novel insights into the role played by sustained attention in the development of mental fatigue at the early phase post-stroke. The initial findings are promising for both research and clinical practice with potential implications for furthering knowledge of who is at risk of developing symptoms of mental fatigue. A larger definitive trial replicated with this trial design, would add to the generalisability of the findings. Furthermore, it may shed a light on possible prevention strategies, and provide suitable guidance on self-management strategies for those affected by mental fatigue that is grounded in empirical evidence.

Acknowledgments

Special thanks to:

The Elizabeth Casson Trust for funding this Thesis for three years. This has enabled me to work within the subject of Occupational Science and Occupational Therapy I am most passionate about, and, to work with my heroes within this field:

First to Helen Dawes, my primary supervisor. Through your guidance, insights and oodles of energy you've patiently supported me to deliver a Thesis that contributes novel insights to the stroke evidence base, the field I am most passionate about working in, and in particular, the subject of Attention. Having the opportunity to create from scratch, deliver and view the outcome of my own research trials has fulfilled a long-held ambition for me. A huge thanks to you.

To my extended supervisory team of Professor Avril Drummond, Professor Nele Demeyere and Dr Johnny Collett whose guidance and support steered me towards completion of each study and the overall thesis. Through your vast intellectual, practical and timely support, your expertise has greatly expanded my knowledge across a number of specialist areas. To my mentors, Professor Derick Wade and the late Dr Ken Howells - we had endless fun creating and shaping each phase of this thesis.

To my postgraduate tutors, Shelly Coe and Stuart Whigham

To all the stroke survivors for their participation and sharing their experience which provided valuable insights towards developing this intervention. The research team at Oxford University Hospital and clinical support from their Early Supported Discharge Service for stroke.

I wish to also thank a great number of people, the completion of this thesis would not have been possible without this support, and it took the village:

All the PhD students and staff at Centre for Movement, Occupational and Rehabilitation Sciences (MOReS). To all the staff in the OT Department at OBU, and particularly Jenny Butler for igniting this passion in this subject area.

To Kevin, Shane and Ronan, Zita and Lucy. To Zoe, Helen G, and my Oxford Gals, all of who supported me from the get-go through all the stresses and strains that being a PhD student involves, on top of battling through a global pandemic. My athletics team and larger IMAA community.

To Glen for his attention to detail, his creative resourcefulness and importance of inclusion when developing an intervention that is affordable to all.

To Aisling, John and Greg for their editing, IT skills and steadfast support throughout.

To Dad, for everything in-between.

Declarations

I declare that unless otherwise stated, all work presented in this thesis is my own.

Submitted abstract

Publications

Is there evidence for a relationship between cognitive impairment and fatigue after Acquired Brain Injury: a systematic review and meta-analysis.

Dillon, A., Casey, J., Gaskell, H., Drummond, A., Demeyere, N. and Dawes, H., 2022. *Disability and rehabilitation*, pp.1-14.https://doi.org/10.1080/09638288.2022.2152503. E.pub. 10th December 2022

Purpose: Fatigue is a major symptom of ABI. Greater fatigue is associated with cognitive impairment. Our aim was to systematically review, describe and analyse the literature on the extent of this relationship. **Methods:** Five databases were searched from inception. Studies were included where: participants had a defined clinical diagnosis of ABI which included TBI, stroke or subarachnoid haemorrhage; a fatigue measure was included; at least one objective cognitive measure was used. Three reviewers individually identified studies and determined quality using the Quality Assessment Tool for Observational Cohort and Cross-sectional Studies. **Results:** Sixteen of the 412 identified studies, investigating the relationship between cognitive dysfunction and fatigue, comprising a total of 1,745 participants, were included. Quality ranged from fair to good. Meta-analysis found fatigue was significantly associated with an overall pattern of cognitive slowing on tasks of sustained attention. A narrative synthesis found weak associations with fatigue and information processing, attention, memory and executive function. **Conclusion:** Analysis found sustained attentional performance had stronger associations with fatigue after ABI. Whereas, weak associations were found between fatigue and information processing, attention and to some extent memory and executive function. More focused research on specific cognitive domains is needed to understand the mechanisms of fatigue.

Contents

Abbreviations

ABI	Acquired Brain Injury
ANT	Attention Network Test
CPT	Continuous Performance Task
CRT	Complex Reaction Time Task
CNS	Central Nervous System
ESD	Early Supported Discharge service for stroke
FAI	Fatigue Assessment Inventory
FSS	Fatigue severity scale
FSMC	Fatigue Scale for Motor and Cognition Functions
GCS	Glasgow Coma Scale
ICSS	Integrated Community Stroke Service Team
ICF	International Classification of Functioning
ITT	Intention To Treat principle
LC	Locus-Coeruleus
MCCPT	Masked Conjunctive Continuous Performance Task
MD	Multi-Dimensional
MFI	Modified Fatigue Inventory
MFIS	Modified Fatigue Impact Scale
MOCA	Montreal Cognitive Assessment
MMSE	Mini-Mental State Examination
MRC	Medical Research Council
mRS	Modified Rankin Scale
NE	Neural Efficiency
OCS	Oxford Cognitive Screen
PASAT	Paced Auditory Serial Addition Test
PFC	Prefrontal Cortex
POMS-f	Profile of Mood States fatigue subscale
PRISMA	Preferred Reporting Items for Systematic Reviews
PROSPERO	International Prospective Register for Systematic Reviews

PSF	Post-stroke Fatigue
PVT	Psychomotor Vigilance Task
RTs	Reaction Times
SAH	Subarachnoid Haemorrhage
SMDT	Symbol Digit Modalities Test
SRT	Simple Reaction Task
STROBE	Strengthening The Reporting of Observational Studies in Epidemiology
TBI	Traumatic Brain Injury
TIA	Transient Ischaemic Attack
TMT	Trail Making Task
VAS-f	Visual Analog Scale - fatigue

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Chapter 1 Introduction

1.1 Overview of Chapter 1

This chapter sets out the general background to and significance of this chosen field of research, post-stroke fatigue (PSF). First, the scale of the challenges presented by stroke and post-stroke fatigue are outlined (1.2). Second, the current situation regarding rehabilitation and the evidence-base for post-stroke fatigue interventions is outlined (1.3), and an argument is put forward for a novel approach to understanding and measuring fatigue for the future development of effective post-stroke mental fatigue interventions (1.4). Third, the rationale is given for the structure of this thesis and the approach used (1.5). Fourth, the aims and objectives of the thesis are presented (1.6).

1.2 Defining the problem: An overview of stroke and the challenges presented by post stroke mental fatigue

1.2.1 Stroke

A stroke is a disturbance of the blood supply to the brain causing an immediate loss of oxygen and glucose to the brain cells (cerebral tissue) resulting in death of or damage to the brain cells [1]. The most common cause of stroke is the sudden occlusion of a blood vessel by a thrombus or embolism, and accounts for 85% of the incidence in stroke, with the remainder due to intracerebral bleeding (haemorrhagic stroke) [1]. Stroke is one of the single largest causes of adult disability in England [1]. Each year approximately 110,000 people experience a stroke, which equates to one stroke every five minutes [1]. In all, over 1.2 million people living in England have experienced a stroke, with almost two thirds of stroke survivors living with moderate to severe disability as a result of stroke [1]. The advances in stroke medical and surgical management means that people are surviving and subsequently living with the long-term consequences of stroke [2]. Long-term effects can comprise cognitive, physical and psychological deficits [3]. These difficulties all have a direct effect on the patient's ability to regain previous levels of independence, participate in the activities involved in daily living and to engage in meaningful life roles and responsibilities [4]. Moreover, the number of people experiencing stroke at a younger age is resulting in stroke being considered as an epidemiological shift toward stroke being a long-term health condition [5]. Indeed, people are two to three times more likely to be unemployed 8 years following their stroke with indirect cost of stroke to society now around £26 billion per year [1].

1.2.2 Post-stroke Fatigue

Globally, there are 33 million survivors of stroke, and at least half of these experience fatigue [6]. Indeed, many survivors rate post-stroke fatigue (PSF) as their most severe symptom among other post-stroke sequelae of both ischemic and haemorrhagic stroke [4, 6-8]. A large prospective cohort study completed by Glader and colleagues highlights the profound negative relationship of PSF on long-term functional outcomes [9]. PSF is a predictor for increased dependency for activities of daily living at two-year follow up [7] and even for greater mortality [9]. A greater understanding and management of this distressing post-stroke symptom is one of the priorities of the Stroke James Lind Alliance Priority setting partnership [10].

The quest to define PSF has challenged researchers and clinicians for over a century with no clear consensus reached [7] [11]. This inconsistency affects approximations of the incidence and prevalence of PSF with broad estimations in stroke research ranging in value from 27-73% [6, 8]. This may likely be attributed to the fact that the underlying mechanisms for PSF are unclear [6, 11].

Understanding mechanisms of PSF is a relatively new field of research. Its casual mechanisms are not yet known [7]. De Doncker (2018) explains how physical deconditioning is a common post-stroke sequela, which can result in fatigue, and subsequently lead to a cycle of avoidance of physical activity, further physical deterioration and more fatigue [120]. The authors highlight how evidence now shows how physical factors alone cannot explain the persistence of fatigue post-stroke. Indeed, preliminary evidence supports how several factors have been reported to be associated with the development of PSF including 1) predisposing factors (prestroke fatigue or prestroke depression); 2) early biological factors (brain lesions, stroke-related inflammatory and neuroendocrine changes); and 3) perpetuating factors (affective disorders, residual neurological deficits, cognitive decline, passive coping, reduced physical activity, locus of control, and self-efficacy) [7, 30].

Within the literature, it is becoming increasingly evident that stroke research is moving away from viewing PSF as a unified construct, with the emerging perspective being that PSF is a multifaceted, multidimensional construct. Distinctions have been made between peripheral and central fatigue [7]. Peripheral fatigue is defined as a failure to sustain force which suggests neuromuscular dysfunction outside of the central nervous system [7, 12]. Muscle fatigability is restored, at least partially by rest. By contrast, central fatigue implicates dysfunction in Central nervous system (CNS) neurotransmitter pathways, that is to say a failure to achieve

and maintain the recruitment of high-threshold motor units. According to the Mayo dictionary (2015) [13] "Central fatigue is regulated by brain pathways associated with arousal and retention, reticular and limbic systems, and basal ganglia" and goes on to say "lesions in these pathways result in deterioration and fluctuation in severity of fatigue under physiological and psychological stimuli producing the perception of physical and perception of mental fatigue" [13]. Chadhuri & Behan (2004) made a clear distinction between both perceptions and explain PSF as "a failure to initiate and/or sustain attentional tasks (mental fatigue) and physical activities (physical fatigue) requiring self-motivation, and is experienced without any peripheral motor impairment" [14]. These definitions suggest that mental fatigue and physical fatigue whilst inter-related may have distinct features that may provide insight in the development of strategies to improve functioning and life quality.

1.2.3 Mental versus physical fatigue

Increasingly, studies have been dedicated to quantifying and understanding, in a more precise way, the physical and mental dimensions of fatigue. There is no single agreed-upon taxonomy for classifying fatigue. However, there is an increasing consensus on the terms used to describe physical fatigue within the literature: physical fatigue is viewed as a 'performance decrement', with a 'feeling of heaviness' and 'fatigued muscles', which seems more predictable, and easier to quantify than perceived mental fatigue [7]. Whilst there have been extensive investigations into physical functioning and fatigue, the potential correlates of mental fatigue after stroke have received limited attention. Mental fatigue is a highly distressing and persuasive post-stroke symptom [15] with many patients rating mental fatigue as their most frustrating symptom [11].

Mental fatigue is described as increased 'mental effort' during prolonged periods of sustained cognitive activity [16, 17]. What is interesting is that in many cases, physical factors alone cannot explain the persistence of severe fatigue even many years post stroke [7, 18, 19]. The emerging perspective in research is that mental fatigue is associated with a variety of factors including cognitive impairment after stroke, and possibly also with the domain of attention in particular [8, 15, 20]. According to Mayo, N.E. (2015) mental fatigue "is the cognitive component of central fatigue characterized by inability to sustain concentration and endure mental tasks" [13].

The relationship of a cognitive impairment, and specifically a domain-specific attentional impairment, to mental fatigue after stroke has rarely been examined. Attention is a core domain

within a hierarchy of cognition and any changes to attention may affect appropriate functioning of higher-level cognitive abilities, such as executive function, and possibly new learning [21-23]. Correlates have been found between post-stroke attentional difficulties across our life span including learning, return to work and driving. Sustained attentional impairments and fatigue are core to dysexecutive syndrome, and merit investigation [24, 25]. Attention is one of the most studies cognitive functions of the human mind: As our environment is constantly changing over time it is essential to remain vigilant, or sustain attention, to detect these changes, and be ready to react accordingly [22]. Contemporary neuropsychologists detail the dynamic temporal aspects involved sustaining attention over time [26]. However, difficulties with engaging these attentional processes may result in previously effortless activities of daily living that require sustained attention becoming exhausting. Given the negative impact of mental fatigue on participation, an understanding of underlying mechanisms mediating mental fatigue is of clinical importance.

In addition, it has been suggested that attentional dysfunction significantly overlaps with and exacerbates any changes in physical abilities [3, 27]. Voluntary intentional movement requires executive motor functioning to anticipate, predict, produce and correct actions. Such movement involves a complex sensorimotor neural network of cortical and subcortical regions. Previous reports have highlighted the specific importance of cortico-cerebellar and cortico-striatal loops in movement and motion [28]. Emerging evidence suggests the critical importance of the Prefrontal Cortex (PFC) in motor regulation, particularly during tasks requiring executive control, visual guidance, and sustained attention [28]. In non-disease states, increased PFC activity during motor tasks of increasing complexity and greater cognitive effort leads to an improvement in task performance [29]. However, in response to cerebral damage, the brain is now required to reorganise itself and seek additional cerebral resources to carry out previously automatic tasks [7]. This over-activation may be perceived as fatigue [7, 30]. Indeed, there is increasing evidence that in sensorimotor pathology, increased Prefrontal Cortex activity is a compensatory mechanism, which through the cortico-cerebellar and striatal networks, enables task performance to be maintained. We suggest that if higher cognitive effort leads to the same task performance, the individual has elicited a less efficient neural focus indicative of pathology or disease progression, which is measured as a reduction in Neural Efficiency (NE) [28, 31]. Thus, there appears a clear link between cognition and both mental and physical fatigue.

There are increasing investigations into the potential neurophysiological correlates of fatigue (including physical functioning and fatigue) [11, 30]. However, little is known about the impact of cognitive impairment on mental fatigue or whether an impairment in a particular cognitive domain, such as attention, exacerbates mental fatigue, or rather whether mental fatigue impacts concentration or ability to sustain attention. Moreover, it is not clear whether the impact of contextual factors on concentration levels, such as background noise, have been considered. Johansson & Ronnback (2012) highlight that accompanying symptoms experienced such as irritability, sensitivity to stress or noise, and concentration need further research [15]. Eilertsen et al (2013) emphasises the importance of the context in which activities take place and to what extent the environment may influence PSF, including noise levels [32].

1.2.4 Measurement of this relationship: definitions used

The precise nature of the relationship between cognitive impairment and fatigue after stroke is unclear. This may be due to the fact that measuring mental fatigue is not straightforward. Broadly speaking, there are two approaches used when measuring fatigue within the literature, namely *subjective experience* or *performance decrement* [7]. The approach used tends to vary depending on the circumstance in which it is used. First, is the subjective feeling of "always feeling tired" [9]. Self-report measurement strategies are an excellent way of capturing the momentary 'state' of the patient's subjective experience of mental fatigue. Likert scales are the most commonly used instrument to capture the subjective experiences of fatigue in studies, across a variety of study populations including PSF. Multi-dimensional questionnaires are increasingly being utilised to assess the various aspects or 'traits' of fatigue under review, e.g. cognitive fatigue over a period of time. However, there is a disadvantage to using this approach as reports could be influenced by mood and recall bias that could reduce their accuracy [7, 33]. Moreover, this emphasis on self-reporting in measuring fatigue to date has correlated poorly with actual performance [8, 15, 20]. In contrast, decrements in performance can be measured, and are most frequently performed in physical fatigue literature. An array of techniques have been developed to objectively measure physical manifestations of fatigue within the motor fatigue literature [11] with typical measurement of physical fatigue involving the direct measurement of performance decrement during sustained or repetitive motor activity, often referred to as 'fatigability' [13]. Yet there seems to be a scarcity of studies objectively measuring mental fatigability. Johansson & Ronnback (2012) describes mental fatigability as "an inability to repeatedly sustain cognitive performance, or attention, and the need for a long

recovery time after exertion" [15]. De Luca (2005) explains that an analogy in the cognitive domain would be reduced performance during sustained cognitive work [7]. Few studies have used this paradigm to objectively measure mental fatigue [16, 17, 34, 35] and results have been mixed but perhaps an objective measurement of performance decrement could also be performed on cognitive performance [7].

Indeed, emerging research documenting objective domain level cognitive changes post-stroke seems promising for documenting change in mental fatigue [15, 18, 20, 25, 36]. This includes reaction-time based assessment [17, 35]. Traditionally cognitive impairment after stroke has been described as a 'global impairment' and assessed using a global cognitive measure [37]. However in recent research, measurement strategies are shifting focus towards domain-specific impairment, such as attention. Attention is a core domain within a hierarchy of cognition, with correlates found between post-stroke attentional difficulties across our life span including driving and returning to work [21-23]. Contemporary neuropsychologists underline how our environment is constantly changing, and the importance of sustaining attention to detect these changes [22]. The dynamic temporal aspects involved sustaining attention over time are highlighted [22]. Increasingly, studies are using specific measurements that are sensitive in capturing this data, such as cognitive assessment batteries with stand-alone domain specific subtests [20, 38], and complex behaviour paradigms involving reaction-time testing [16, 34, 35], which may be a sophisticated model for future research.

Ultimately, Su et al (2020) recognise how there is currently no specific measurement to identify fatigue and the signs of fatigue are not always obvious to outsiders, it may be difficult to understand how a patient is feeling [40]. The author underline the need for '*early detection and effective interventions are particularly important'* [40].

1.3 Post-stroke rehabilitation and intervention strategies for post-stroke fatigue

The National Stroke Service Model states the importance of addressing issues early post stroke [39]. The specific contribution made by a specialist Integrated Community Stroke Service Team (ICSS) [39] and the provision of tailor-made stroke rehabilitation interventions are seen as a key tenet in the recovery of independence, quality of life and reduction in readmission post-stroke [39]. National guidelines recommend the provision of ICSS therapy to be delivered over six weeks (and up to six months), five days a week, with sessions lasting up to 45mins as tolerated [39]. Yet, service provision continues to vary due to increased volume of work, lack

of expert clinicians or resources with the result that stroke survivors rarely receive the required therapy. This may be due to the lack of effective evidence-based intervention strategies specifically aimed at managing PSF [3, 40]. As a result, there is an unmet need for a fatigue management support system that can be set up within the ICSS team, and used by stroke survivors with minimum interaction by clinicians or carers early after stroke. The National Stroke Strategy called for a redesign of service provision to ensure the best use of current available resources [39] and the ICSS Team are in a prime position to play a vital role here by implementing relevant findings in PSF research in rehabilitation, at point of use, and in daily activities.

For rehabilitation to be effective, Su et al (2020), describes how an intervention needs to '*effectively prevent the occurrence of PSF, reduce the incidence of PSF, and improve the quality of life in stroke patients'* [40]. The evidence-base for effective PSF is limited to date, with just six studies reporting limited evidence for cognitive rehabilitation after PSF [3, 40]. These include a fatigue education programme [41], a mindfulness-based stress reduction programme [15], two combination therapy interventions comprising exercise and cognitive based therapy [42, 43] or stand-alone CBT-based interventions for PSF [44, 45]. Taking together these cognition-related PSF interventions [42-45], it is arguable that these strategies involved general non-specific cognitive processes such as problem solving and decision making [42, 43], cognitive symptom management [15, 41] or relate more to behaviour rather than domain specific cognitive function [44, 45].

At present, the potential effect of general cognition-based intervention strategies for fatigue is limited [40]. However, attentional training with consideration for time on task [46] and attentional load [47] has shown to improve mental slowness [46], learning, working memory and attention [47], reaction time [48], and attention deficits specifically at the early phase post-stroke [49]. As such, the potential for training attention immediately after stroke is potentially most impactful and this approach could be an investigation strategy that could be used in managing PSF. Indeed, DeDoncker (2021) pinpoints how "Any lesion to attention networks could result in fatigue, as poor attention may be a key element of high effort, one feature of fatigue" post stroke [30]. This supports the argument that more focused assessment and treatment is now required.

In the development of interventions, Gupta & Taff (2015), noted how services that are impairment-focused and provided in unfamiliar settings are not appropriate to client-centred practice[50]. Rather, they say that "client-centred practice is best embodied by occupation-

focused interventions in the natural environment of everyday living". This has been long recognised by Elizabeth Yerxa (1990) who identified the essential role of the environment or context in which research is being conducted, as 'it informs how people act' [51]. Patients attribute particular significance to occupations that are meaningful to them, and this is closely linked to the individual's situation, context, and cultural background [50]. Despite these insights, there is insufficient evidence of the efficacy of any post-stroke intervention strategy to treat or prevent PSF that considers real world context and environment [3, 40]. Moreover, despite the potential relationship of cognition to fatigue, to date, no interventions have targeted specific cognitive domains, such as attention or contextual factors and their potential effect on PSF.

1.4 Summary of the problem

PSF is highly problematic and disabling post-stroke sequelae. Mental fatigue is a severe and common symptom and can persist years after the stroke event, which is a very distressing problem for many stroke survivors.

Emerging theories propose that mental fatigue is associated with a cognitive impairment [16, 17, 20]. However, the extent and detail of this relationship remains unclear [15, 25] and consequently, there are few evidence-based strategies to manage PSF, and the evidence of efficacy in preventing or treating PSF has been insufficient to date [3, 40].

The evidence supports that dysfunction in overall cognitive functioning, or certain domains of cognition (i.e. attention) which is a potential modifiable factor, may be related to mental fatigue as well as physical performance and fatigue. As such, the importance of describing the relationship between attentional performance and fatigue is evident. Thus, the remit of this thesis is a focus on the cognitive correlates (i.e. attention) potentially relating to fatigue, as opposed to the potential neurophysiological factors. Furthermore, research from this perspective, and if examined by modifying different environmental contexts, could generate an understanding of how mechanisms and context interact. This may provide evidence that can be applied to inform the development of adaptive or training interventions [52]. This knowledge may help to determine who is at risk of developing symptoms of mental fatigue. Importantly, it may shed a light on possible prevention strategies, and provide guidance in intervention development to those affected by mental fatigue post-stroke. To this end, this thesis presents a novel approach to investigating the extent of the relationship between a cognitive impairment

(attention) and mental fatigue post-stroke and uses findings to investigate the impact of an exposure that could alter attention on performance of activities and fatigue levels.

1.5 Thesis approach

This thesis will utilise a pragmatist paradigm. Pragmatism is a research philosophy based on the epistemology that there is no one single point of view that can give an entire picture because "there are many ways of understanding multiple realities" [53-55]. Pragmatism supports the exploration and interpretation of all research methodologies towards finding practical 'best fit' solutions to the real-world issues. Importantly, research subjects are seen as "active ingredients" in the understanding of a problem [56].

In the development of knowledge related to the complexities of human activity, Kristensen and Petersen (2016) recognise three main assumptions: that people are active entities, that there is a relationship between activity and health, and the importance of context [57]. When researching, knowledge is gained through the integration of a variety of approaches that encompass all biomedical, social and humanistic knowledge [58, 59]. Such is the complexity of health-related interventions, and the variability inherent within and between individuals, that a pragmatic approach is needed to understand the extent of the inter-relationship between the individual, the activity and environmental factors. Given those considerations, this research is underpinned by two multi-dimensional framework models that will conceptualise this inter-relationship towards the development of a complex intervention. Those frameworks are presented below.

1.5.1 Thesis Frameworks

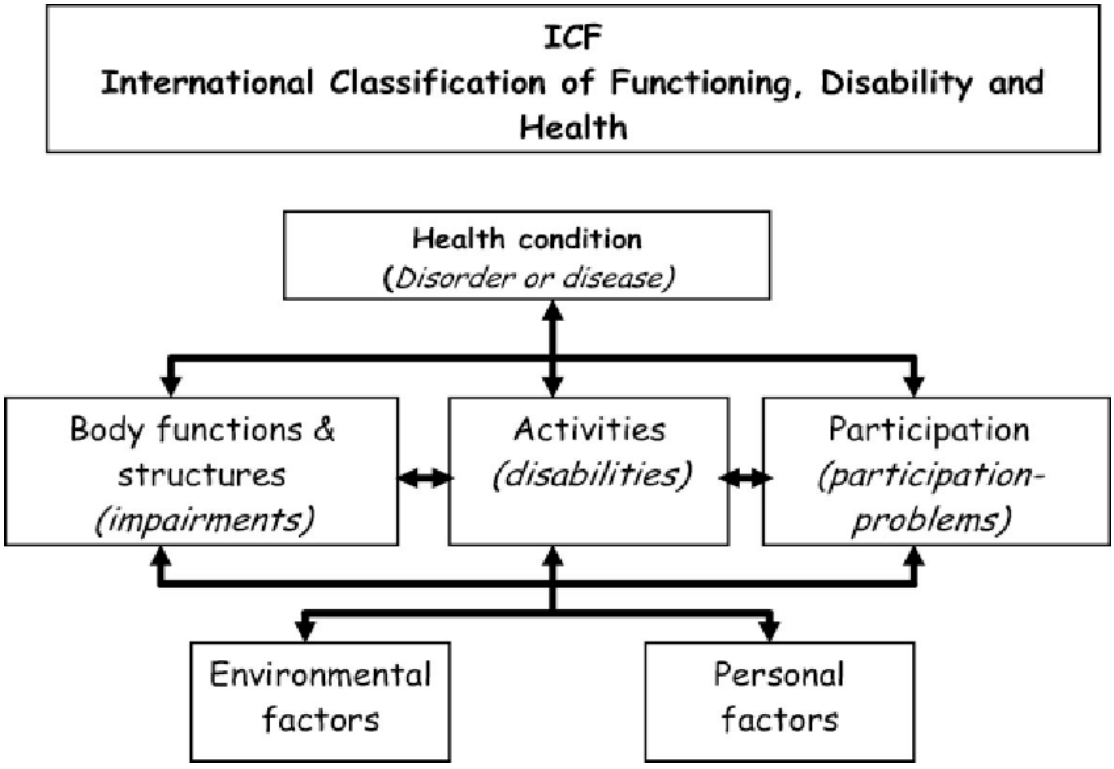
Framework 1: Multi-dimensional conceptualisation of post-stroke fatigue

The dynamic interaction of the multi-dimensional facets of fatigue have been conceptualised across several conditions, with models of practice developed for fatigue in such conditions as Guillain-Barre syndrome [12], stroke [60] and for illness in general [58]. Each model provides insights which are useful in the conceptualisation of fatigue after stroke for the purposes of this thesis.

The International Classification of Functioning, Disability and Health (ICF) [58] offers one such multidimensional model of illness and has been recommended as a valuable tool for research in PSF, as its multi-dimensional approach may shed new light on understanding an individual's fatigue experiences [7] and provide a clear framework to describe outcomes and

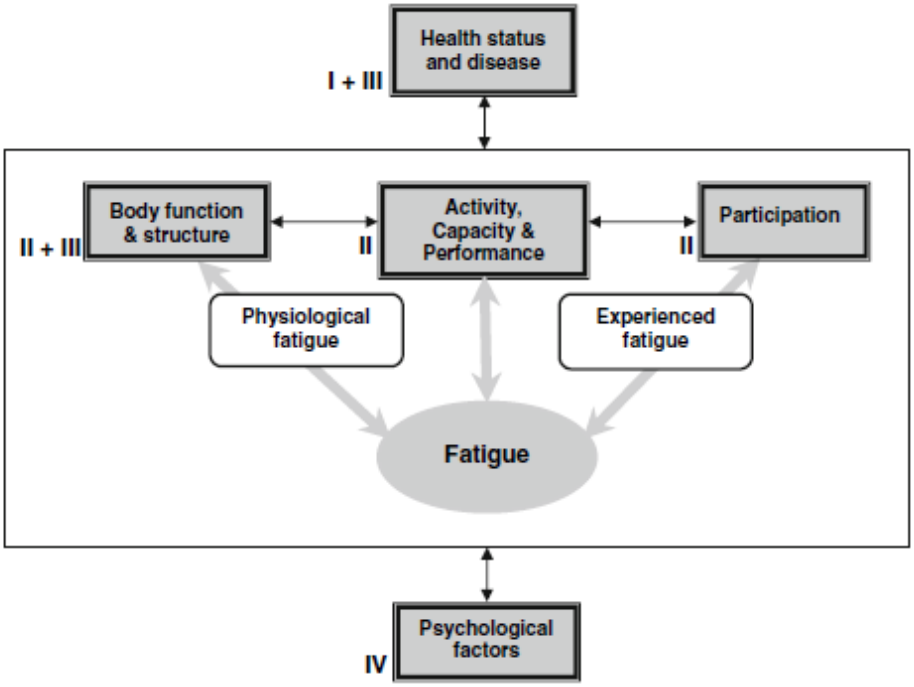
enable a coherent treatment plan to be devised and implemented [59] (fig.1.1). The ICF utilises an ecological model, which is unlike the more commonly used biomedical model for understanding disability as it has less focus on the condition [58]. Rather, it considers the dynamic relationship between the impact of the environment and personal factors on activity, participation and function. Within this model, the ICF defines activities as the execution of a task or action, and participation as the involvement in a life situation. Importantly, the ICF highlights the impact of the social and built environment on participation, a factor not explored in other models [12, 60]. The ICF considers whether the environment promotes or interrupts patients' experience and involvement, which perhaps could be a potential factor for increased fatigue levels.

Figure 1.1 The International Classification of Functioning, Disability and Health framework.



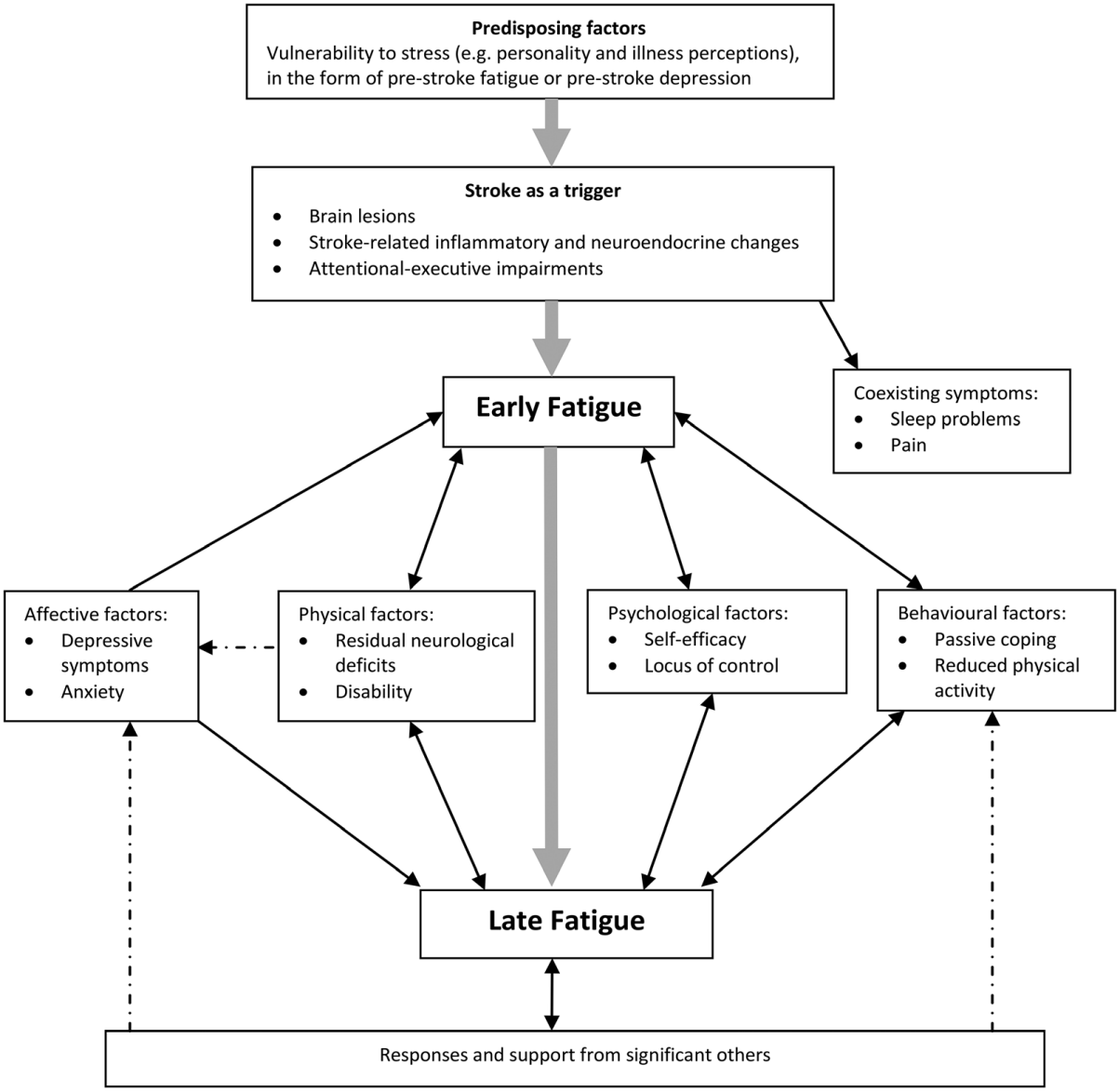
De Vries et al. (2010) [12] describe the facets of experienced fatigue (perceived mental and physical effort) and the physiological fatigue factors of central (mental fatigue) and peripheral fatigue (fatigability) in their model for Guillain-Barre syndrome and align it with the ICF model (fig. 1.2).

Figure 1.2 De Vries et al (2010) describe the effect of aspects of fatigue on activity and participation, and in turn, how psychosocial factors influence fatigue, activity and participation [12].



Wu et al, (2015) [60] offer a conceptualised model of fatigue based on the temporal course of post-stroke fatigue. This model expands on the dynamic interaction of the myriad of factors associated with fatigue, which are evidenced on current research within the stroke literature (fig. 1.3). Within this model, the authors highlight associations found between certain factors at different phases of the stroke event: pre-stroke fatigue (e.g. with early and late post-stroke fatigue); early stroke (e.g. with depressive symptoms) and late stroke (e.g. with residual physical impairment). The authors acknowledge how several factors are likely to interact and consideration of overlap is cautioned, e.g. association of PSF and anxiety may be confounded by effect of depression. Additionally, other symptoms such as pain and sleep disturbance may coexist with and maintain symptoms of fatigue. The authors underline the importance of recognising any related factor early on that may exert most influence on PSF, especially the temporal relationship between such factors (e.g. attentional impairment and early fatigue). Indeed, from the outset, several potentially treatable factors associated with PSF are identified, such as attentional impairment [58]. As attention is a potentially modifiable factor post-stroke [46, 47, 49], an investigation of this relationship early after stroke would be worthwhile.

Figure 1.3 Wu et al (2015) present "A conceptual model of post-stroke fatigue. The unidirectional arrows indicate a causal direction; the bidirectional arrows indicate unknown direction of the association; the dotted arrows indicate potential interactions between factors. Other symptoms may coexist with and maintain PSF [60].



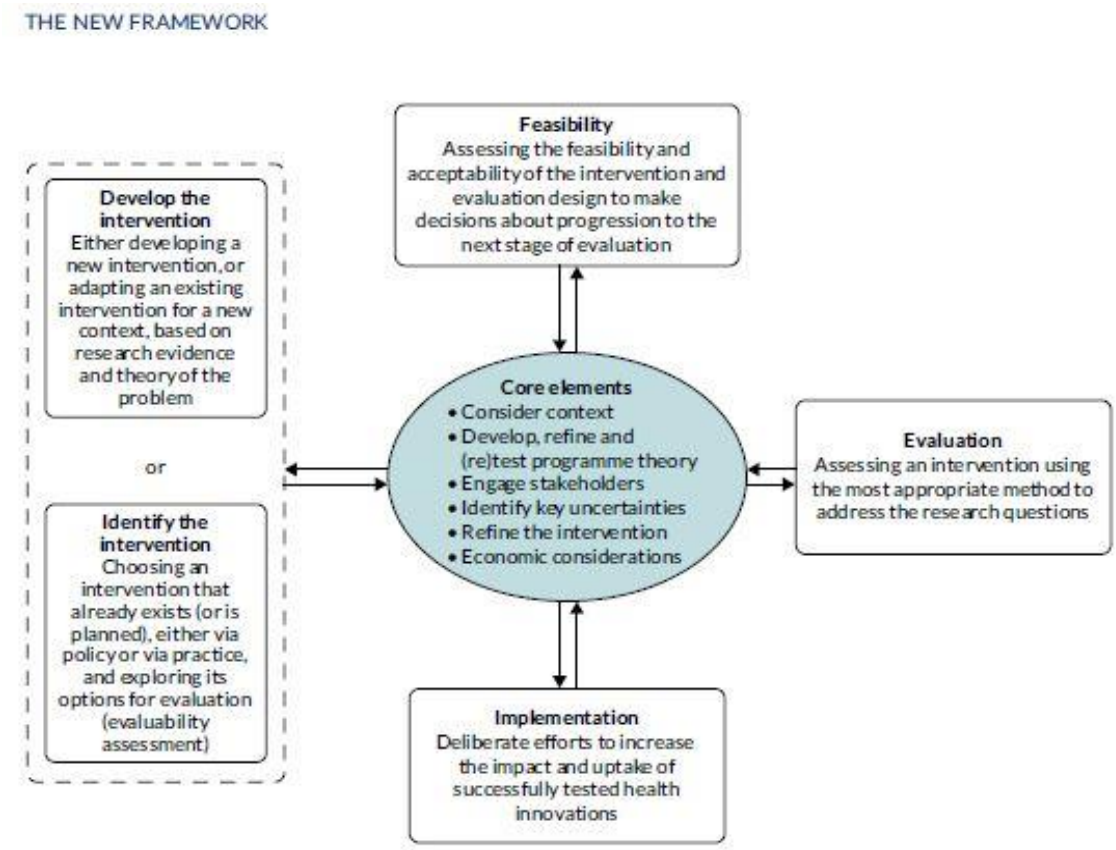
The lack of a universally accepted definition (as outlined earlier) or indeed a comprehensive model for PSF is evident. However, by drawing from the empirical research [12, 58, 60], the insights gained will be used to support and conceptualise PSF in this thesis. In utilising this pragmatic approach, the stroke survivor experiencing PSF is conceptualised with regards to the dynamic interaction of physiological (central fatigue: mental fatigue/ attentional impairment/ early fatigue) [12, 60], psychological (experienced fatigue: mental and physical effort) [12]

and temporal factors (early fatigue/fatigability) [58], and how this inter-relation contributes to participation (as measured by performance) levels [12]. Post-stroke attentional impairment is identified as a potential factor contributing to increased fatigue at the early phase of the stroke event [57]. The built environment, on the other hand, acts as a perpetuating factor for PSF (e.g. noise), with effects on physiological, participation and temporal factors [58].

Framework 2: The Medical Research Council Framework for developing Complex Interventions

The Medical Research Council Framework for Complex Interventions (MRC) is a comprehensive guideline for developing complex interventions [52, 56] (fig 1.4). From the outset, the framework guides the researcher's early decision-making processes, in a bid to create successful interventions [52, 56, 61]. This is particularly important, as adhering to 'best practice' guidelines avoids costly waste of unsuccessful trials which often originate from early stages in intervention development processes [62, 63]. Furthermore, for effectiveness in everyday practice, the authors highlight the need for a degree of flexibility or tailoring of the intervention throughout development processes [52, 56]. The framework supports a dynamic and iterative approach to intervention development, which in turn aligns with the pragmatic paradigm of this thesis [64].

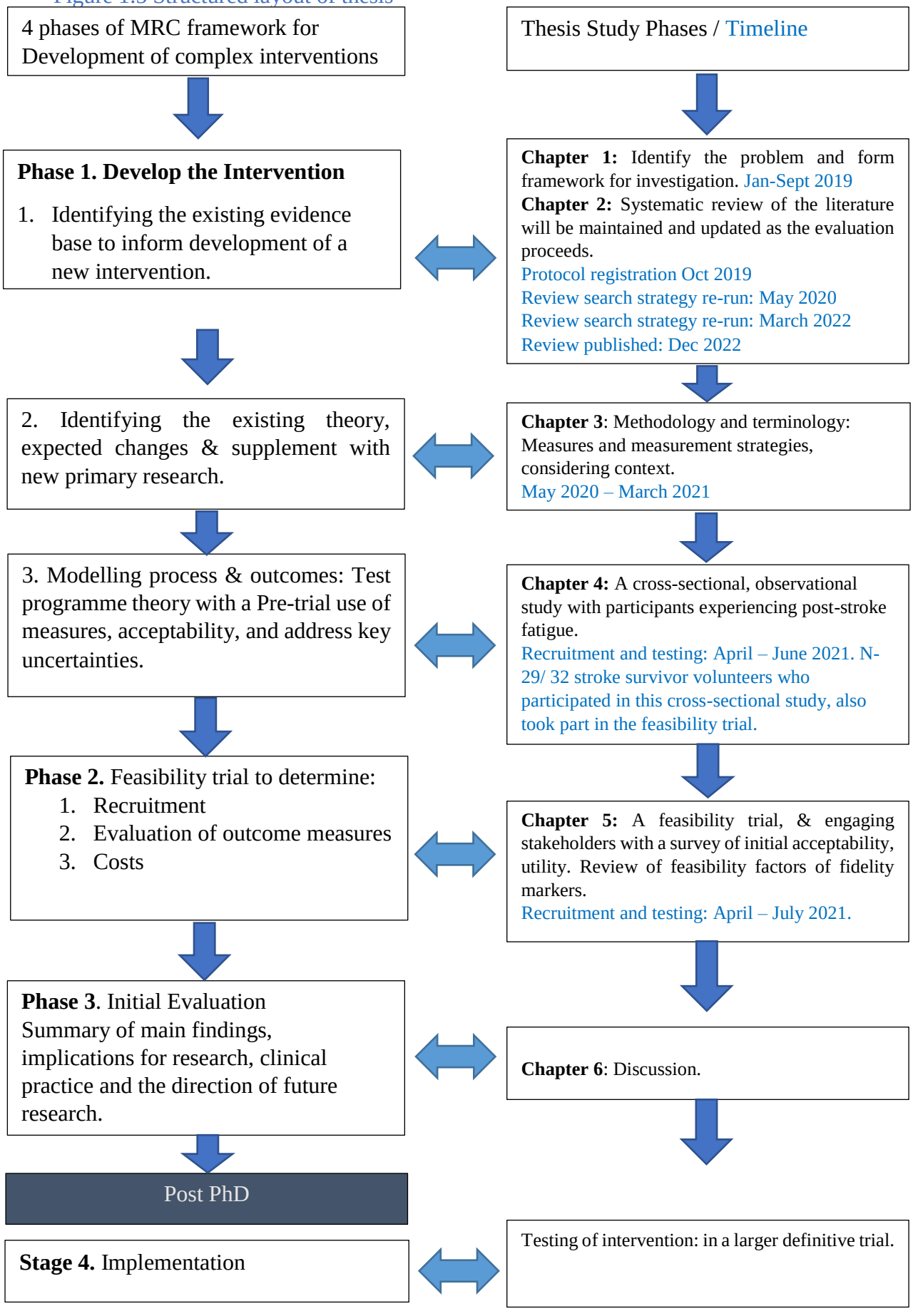
Figure 1.4 The Medical Research Council Framework for Complex Interventions. Main phases and core elements of complex intervention research. The diagram illustrates the non-linear, iterative pathway through the research process [52].



The MRC guidelines link six core principles to four research phases, *Development, Feasibility, Evaluation,* and *Implementation* (fig. 1.4). Central to this framework is the importance of context when developing a complex intervention: "Underestimation of the importance of context, or a failure to take account of all of the relevant contextual dimensions, can lead to difficulties with implementation or a lack of effectiveness".

This thesis follows the four phases of the MRC 2021 guidelines [52] to develop an intervention, with fatigue conceptualised as the model for PSF (fig. 1.5). A description of each phase and core principles of the MRC framework and how they subsequently informed the design of each chapter within this thesis is illustrated in Figure. 1.5 below.

Figure 1.5 Structured layout of thesis



1.6 Aim and objectives of this thesis

The aim of this thesis is to develop greater understanding of the relationship between attention and fatigue in order to inform to the management of post-stroke mental fatigue.

To this end the objectives of this thesis are as follows:

- To systematically and critically review 1) the evidence base and 2) the theory base for the extent of the relationship between cognitive impairment and fatigue after Acquired Brain Injury, which includes stroke literature (chapters 1-3).

- Informed by the review, to formulate and test a measurement approach to determine the extent of the relationship between cognitive impairment (e.g. attention) and post-stroke mental fatigue and physical fatigue (chapters 3 & 4).

- In light of these insights, set out to develop and determine the feasibility and potential effectiveness of a cognitive intervention in a feasibility study, that could potentially be used as a strategy to manage post-stroke mental fatigue (chapter 5).

- To assess the strengths and limitations of the proposed study and its implications for future research in the field (chapter 6).

Chapter 2 Is there evidence for a relationship between cognitive impairment and fatigue after Acquired Brain Injury: a systematic review and meta-analysis

2.1 Overview of Chapter 2

An initial review of the literature in chapter 1 has shown how post-stroke fatigue (PSF) is a highly distressing and persistent symptom for the stroke survivor, and the lack of consensus to define it within research and clinical practice is likely due to its complex and multi-dimensional nature [7]. What is promising is that PSF research is rapidly developing with a growing potential for understanding and measuring fatigue, and development of targeted post-stroke mental fatigue interventions. The finding that cognitive impairment relates to PSF in part is promising and could broaden our understanding of this complex post-stroke symptom.

This chapter sets out to explore the existing evidence base to determine the relationship between cognitive impairment and fatigue. A systematic review in 2016 provides promising findings towards a relationship between these factors, however was limited somewhat in regards to inclusion criteria (see section 2.2 for details). To understand the full extent of the evidence, the review was extended across the post Acquired Brain Injury (ABI) fatigue literature, which included stroke populations. Additionally, as outcomes measures used in post ABI rehabilitation are similar, a systematic review of all measurement strategies may contribute novel insights that could be applied to stroke evidence base. For this, a comprehensive systematic review was completed which included a narrative synthesis and Meta-analysis of the published research, adhering to PRISMA guidelines. The analysis found weak relationships between fatigue and the cognitive domains of information processing, and to some extent memory and executive function. The domain of attention was the most frequently investigated across studies, and revealed stronger associations with fatigue. However, the diversity of measurements strategies used across studies highlights the need for consensus, as more robust domain-specific investigations may strengthen this relationship.

2.1.1 Published paper relevant to this chapter

Is there evidence for a relationship between cognitive impairment and fatigue after Acquired Brain Injury: a systematic review and meta-analysis.

Avril Dillon (ADi), Jackie Casey (JC), Helen Gaskell (HG), Avril Drummond, Nele Demeyere, Helen Dawes (HD)

2.2 Introduction

The full extent of the evidence for a relationship between cognition impairment and fatigue is not yet fully known [7, 60]. For a comprehensive analysis, a broader review of the post Acquired Brain Injury (ABI) fatigue literature which includes stroke populations, was conducted. Within the literature, Acquired Brain Injury is defined as an injury to the brain that is not hereditary, congenital, degenerative, or induced by birth trauma [65]. It is over-arching clinical term which includes Stroke, and Traumatic Brain Injury (TBI), and Subarachnoid Haemorrhage (SAH). By drawing on the literature of fatigue in these conditions alongside stroke, we aim to provide further insights on the extent of the evidence on this issue. Indeed, the incidence of Stroke and TBI alone accounts for 13.7 [66] and 69 million [67] respectively each year worldwide [65-67]. Therefore, these groupings (Stoke, SAH, TBI) will be collectively referred to as ABI within this review.

Advances in medical management mean that more people are surviving and living longer with the consequences of ABI [68, 69]. The number of people experiencing ABI at a younger age is also increasing. ABI is considered a long-term health condition [69] with cognitive, physical, and psychological deficits affecting family, social and vocational roles.

Fatigue is reported by ABI survivors as a highly problematic and persisting experience with many rating it as their most severe symptom amongst post-ABI sequelae [6, 7, 70]. Fatigue can be characterised in a number of ways, including physical, mental and social dimensions, resulting in an associated range of measurement strategies [7, 11, 20, 71, 72]. The complexity of this mechanism, presentation and measurement has led to inconsistency in reporting of fatigue trials in the literature, making it difficult to synthesise evidence. The mental or cognitive manifestations of fatigue are conceptualised by Chadhuri and Behan [14] as a difficulty with initiating or sustaining attentional tasks, which is experienced without any peripheral motor impairment. Including cognitive fatigue is important, as individuals after an ABI often report a state of mental fatigue over physical fatigue, especially around performing a cognitive task which requires sustained effort [16, 73].

An emerging approach, known as the “coping hypothesis,” states that fatigue results from the compensatory effort required by individuals with an ABI to meet the demands of everyday life tasks in the presence of cognitive deficits, namely impaired attention and information processing abilities [17, 73]. Cognitive dysfunction post ABI is also suggested to significantly overlap with and exacerbate any changes in physical, behavioural, or emotional status, and possibly fatigue [3, 7, 18, 27, 60]. However, whilst there have been extensive investigations

into physical functioning and fatigue [11, 74, 75], the nature of the relationship between cognitive impairment and fatigue after ABI has received limited attention. Cognitive impairments are common and troublesome sequelae post ABI with almost 70% of survivors demonstrating at least some cognitive impairment on neuropsychological assessment [8, 32]. Existing research details deficits in core domains such as attention and information processing speed [37], in line with revised definitions of post stroke vascular cognitive impairment [76]. Given the negative impact of fatigue on participation, an investigation into the possible underlying factors mediating mental fatigue after ABI has clinical implications [69, 77, 78]. A systematic review in 2016, investigated the relationship between severity of fatigue, as assessed by questionnaire measures and broad cognitive abilities, after stroke [8]. There was some evidence to indicate associations, however studies which focused on the presence or impact of fatigue were not reviewed as inclusion was restricted to those that captured severity of fatigue. Similarly, no review has examined the extent of the relationship of domain-specific cognitive changes with fatigue across acquired brain injury. Thus, the aim of this systematic review and meta-analysis was to establish the presence and extent of any associations of cognitive impairment and domain specific cognitive impairment to fatigue measures post ABI. The study design and quality of each study will be first described, and then followed by a meta-analysis and narrative summary of the reviewed literature.

2.3 Methods

This review was conducted in compliance with the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines [79]. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) in October 2019 (Registration no: CRD42019156038). A team of reviewers developed a pre-defined search strategy.

2.3.1 Types of participants

Inclusion criteria: Adults aged 18 years and over (no upper age limit) who had a defined clinical diagnosis of ABI which includes TBI (moderate, severe), Stroke (all pathological subtypes), minor stroke, and Subarachnoid Haemorrhage where symptoms persisted over a 24-hour period were included.

Exclusion criteria: Studies with ABI participants with clinical symptoms typically lasting less than 24 hours, and where diagnosis required less than 30 minutes of loss of consciousness, memory loss of less than 24 hours, and GCS of 13 to 15 were excluded. Therefore, ABI studies

with cohorts with a clinical diagnosis of Transient Ischaemic Attack (TIA), Mild Traumatic Brain Injury or concussion were excluded.

Differentiating between the mixed populations and sub-types of ABIs within each study required scrutiny of the individual study groups. Therefore, studies with mixed ABI study populations were initially included if the terms were detailed within the title and abstract of the papers. Following full assessment, papers were then included if at least 75% of participants had a defined clinical diagnosis of ABI which includes TBI (moderate, severe), Stroke or Subarachnoid Haemorrhage. If these participants comprised less than 75% of the study sample, studies were only included if they reported or provided separate data.

2.3.2 Types of studies and information sources

A comprehensive search strategy was developed with the terms Acquired Brain Injury, Stroke, fatigue, and cognitive impairment and their associated synonyms and terms (see appendix 5 for the full search strategy). The search was limited to English language and human studies. Studies were included if a relationship between a cognitive impairment and fatigue was investigated. Any aspect of fatigue was included if it assessed concepts relating to fatigue, such as exhaustion, lack of energy or tiredness. Standardised and non-standardised fatigue measures were included. Studies were included if they reported at least one quantitative outcome measure of cognition. We specified objective outcome measures of cognitive impairment, as subjective measures are known to be related to behavioural responses and mood and might therefore bias the relationship under investigation [80]. To aid interpretation, cognitive assessments and fatigue measures were categorised in accordance to how they have been described in each study.

Randomised control trials, cohort studies, case-control and cross-sectional studies were considered for this review. Systematic reviews, single case studies, reviews and editorials, paediatric studies, dissertations, and articles with no primary data were excluded.

For the purpose of summarising the literature comprehensively, no distinction was made between study setting and timing of assessment of cognitive impairment or fatigue (table 2.1). The following databases were searched from the date of inception to 21st March 2022: PsycINFO, PubMed, CINAHL, OT Seeker, and Web of Science.

2.3.3 Data extraction, charting process and quality assessment

Data were extracted using a pre-defined abstraction form adapted for this review by one of the reviewers (ADi) and then verified by the second and third reviewers (HG, JC). Three reviewers independently screened the title and abstracts against the inclusion criteria (ADi, HG, and JC). Full text articles were obtained for all titles/abstracts that met the inclusion criteria and/or where there was any uncertainty. Three reviewers read the full reports and determined whether they met the inclusion criteria. Any disagreements were resolved by a fourth independent reviewer (HD). Next, the reference lists of all identified studies were hand searched to identify further potentially relevant studies. Data were presented as per PRISMA guidelines, with a PRISMA flow chart used to present the progression of study selection against the inclusion/exclusion criteria (fig. 2.1). Extracted information included population demographics and ABI characteristics (table 2.1), measures of cognitive impairment (table 2.2) and measures for fatigue (table 2.3). Contact was made with authors of primary studies or reviews where further information was required. We hand searched the reference lists of the eligible studies and any papers identified were reviewed against the inclusion criteria.

Three assessors (ADi, JC, and HG) independently assessed for risk of bias using the quality assessment tool for observational and cross-sectional studies [81]. This tool consists of 14 items that examine the key concepts of each study's internal validity and scientific contribution including reliability, implementation and timeframe of outcome measures and assessment strategies used. Confounding variables, selection and attrition bias were also under review. The tool provided a rating for low, fair or high risk of bias and informed the interpretation of our results (table 2.1).

2.3.4 Strategy for data synthesis

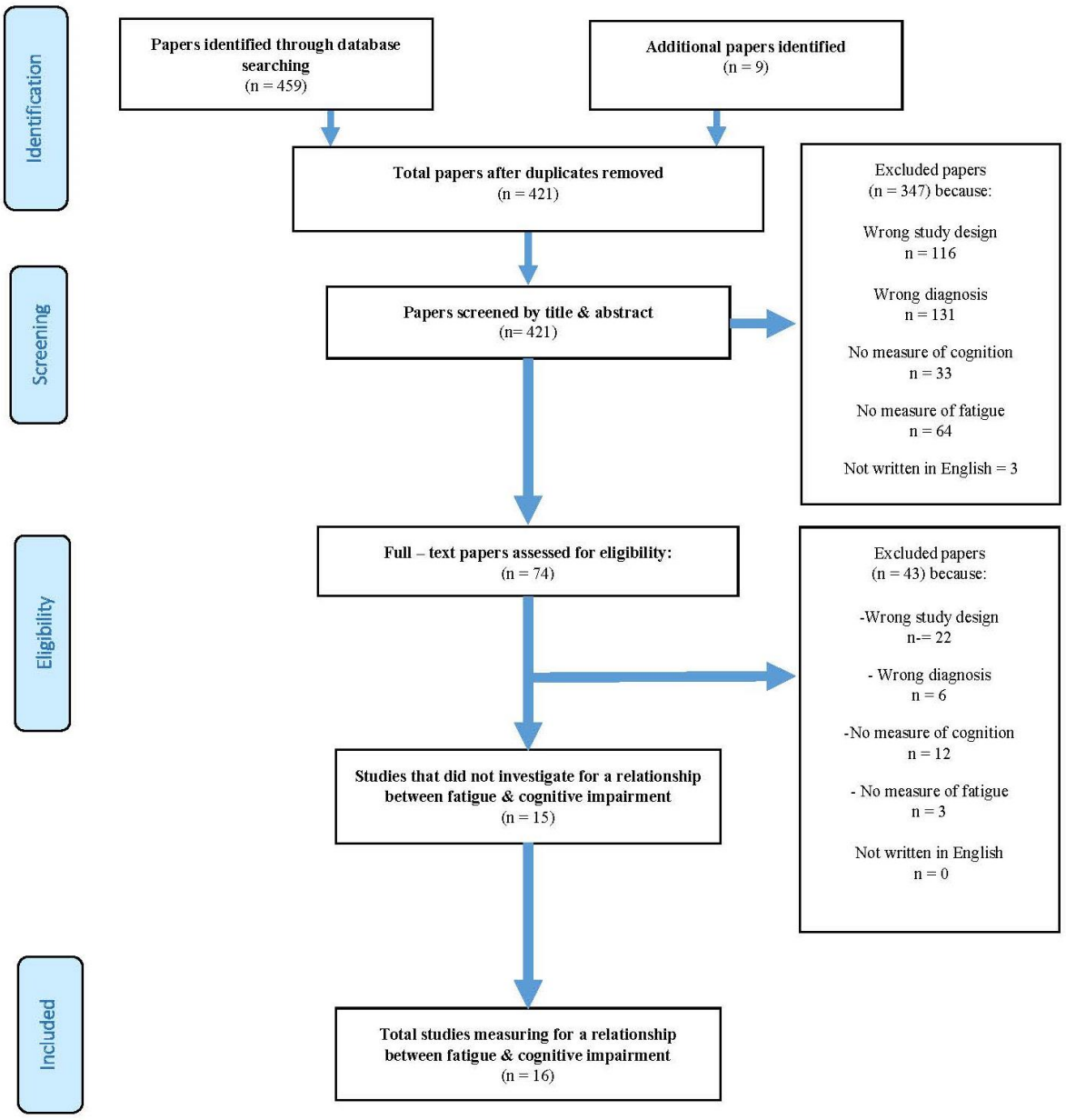
Due to the heterogeneity of measurement approaches and ABI populations, a mixed method approach was used to analyse the data: a narrative synthesis detailed the characteristics and findings of all studies (see also Analysis of Subgroups). Meta-analysis was performed on studies that investigated the relationship between mean reaction times (RTs) and fatigue, if data were available within individual studies and in the appropriate format (Pearson's *r*). A bespoke Exploratory Software for Confidence Intervals for analysis of Pearson r correlations was used [82]. As observed RTs differences are often vulnerable to trade-offs between speed and accuracy [22, 35], only RTs (i.e., scores based on speed of RT) were included in meta-analysis

(fig. 2.2). Also, mean RTs were the most consistent data available and in the appropriate format (correlations, *r*) to complete this analysis.

2.3.5 Analysis of subgroups or subsets

Due to the heterogeneity of ABI populations, it was not possible to explicitly pre-define subgroups in advance. Instead, subgroup analyses were performed where sufficient data on specific cognitive domains, assessments used, and study design were available. For this, the number of associations made in each study were counted. In longitudinal studies with multiple data time points, associations made were counted at each time point. We also determined whether studies were adequately powered. For increased robustness, to detect a medium effect of association an αlpha = 0.05 (2 tailed), and power of 0.9 was used. Therefore, studies with a sample <144 participants were deemed underpowered [83, 84] and not included in this stage of the analysis [85]. Associations that were found to be positive within subgroups were described in percentage. Three main sections are presented: 1) Study designs and study quality; 2) Overview and meta-analysis of associations between cognitive impairment and fatigue; 3) Detailed breakdown of domain specific cognitive impairment, the assessments used and their relationship to fatigue measures.

Figure 2.1 Preferred Reporting Item for Systematic Review and Meta – Analysis flow chart of study selection.



2.4 Results

2.4.1 Study designs

Overall, 16 studies met the inclusion criteria. The ABI populations varied and included four studies with a Traumatic Brain Injury sample [16, 17, 34, 84], ten with a stroke sample [20, 35, 36, 72, 83, 86-90], and two studies in a Subarachnoid Haemorrhage sample [38, 71]. Two further studies had mixed sample populations [91, 92], however, did not meet the inclusion criteria: one had the wrong study design [91] with no separate data available, the other did not investigate for a relationship [92] and could not be included at this point. With regards to study design, eleven studies employed a cross-sectional design with the remaining five studies being longitudinal cohort designs.

2.4.2 Study quality

The study quality ranged from fair to low risk of bias. Justification, power description, or variance and effect estimates was not provided in 89% of studies. Overall, exposure measures were valid and reliable, with the exception of one study using a non-standardised fatigue measure used [86]. Measures were not clearly defined in certain studies [20, 36, 71, 84, 89] . There was a total of 1,745 (M973/F772) participants across these studies: TBI 112 (M36/ F76); Stroke 1,479 (M889/F590); SAH 154 (M48/F106). Seven studies had fewer than 50 participants [16, 17, 34, 36, 72, 83, 84], the larger sample sizes tended to come from stroke studies with 8/10 studies having between 53-325 participants (table 2.1).

Table 2.1 Demographic characteristics, clinical variables in ABI, study participants (n=1,745), and risk of bias.

	Study	Ns	Gender	Time since onset	Education	Country	Relationship Cognitive & Fatique	Risk of bias
	TBI studies							
13	Azouvi et al (2004)	43	♂ 11	10 months	11 years (SD 2.6)	France	Yes	Fair
43	Beaulieu - Bonneau et al (2017)	22	♂ 5	53 months	12.41 yrs (S.D 2.46)	Canada	No	Fair
16	Belmont et al. (2009)	27	♂ 6	9 months	13.45 yrs (SD 2.63)	France	Yes	Low
35	Sinclair et al. (2013)	20	♂ 14	133 days to 13.4 years	15.2 yrs (S.D 3.4)	Australia	No	Low
	Stroke studies							
33	Delva et al. (2017)	156	♂ 73	6 months	34% Higher Ed	Ukraine	Yes	Low - Fair
41	Drummond et al.(2017)	268	♂ 168	24 days	NS	UK	No	Low
47	Goh & Stewart (2019)	53	♂ 35	20 months	0 yrs n = 2%; 6yrs n = 32%; 9 yrs n = 28%; 12yrs n =17%; 16yrs n = 15%; >16yrs n = 6%	USA	Yes	Fair
13	Hubacher et al. (2012)	31	♂ 6	51 days	Secondary Ed n = 16% ; College Ed n= 65% ; University Ed n = 19%	Switzerland	Yes	Fair
39	Park et al. (2009)	40	♂ 26	33 months	NS	South Korea	No	Fair
46	Pihlaja et al. (2014)	133	♂ 86	85 days	12 yrs	Finland	Yes	Low
42	Morsund et al. (2019)	325	♂ 205	3 - 12 months	NS	Norway	No	Low
14	Radman et al (2012)	109	♂ 72	6 months & 12 months	NS	Switzerland	Yes	Low
60	Holmberg et al (2021)	311	♂ 180	3 months	NS	Sweden	No	Low
52	Ulrichsen et al (2020)	53	♂ 38	6-45 months	14.56 yrs (S.D 3.65)	Norway	Yes	Low
	SAH studies							
11	Boerboom et al (2017)	46	♂ 29	4.7 years	41.3% => High school	Netherlands	Yes	Low
51	Passier et al. (2011)	108	♂ 19	11 weeks	Low/Intermediate n = 91 (83.5%), High n = 18 (16.5%)	Netherlands	Yes	Fair
	Total: 16 studies						Total: 10 studies	

2.4.3 Overview of measures

There were a total of 59 measures of cognition used including objective, subjective and reaction time assessments (table 2.2). These measures included cognitive screening measures, neuropsychological assessment and reaction time (RT)-based assessments. In all, 51 assessments were paper-based subtests from detailed neuropsychological batteries of assessment. In total, there were eight measures used to explore fatigue levels, and these were grouped into either unified style scales or multi-dimensional scales to aid analysis (table 2.3). A unified scale, often referred to as Likert self-rating scale was often used to capture the experience of momentary fatigue or fatigue over a given period. The Fatigue Severity Scale (FSS) was the most frequently used unified scale. The FSS "clinical cut off" score varied across the studies from ≥4 [34, 35, 38, 71, 88, 90], ≥4.6 [72] and ≥5 [89]. One study did not indicate this score [17]. A multi-dimensional (MD) fatigue scale aims to capture various aspects that describe the experience of fatigue such as mental, cognitive, physical, and social aspects.

Table 2.2 Study details and overall findings. *Study[34] association found in subset sample only. Abbreviation: Ax, assessment.

Study	*Cognitive Domain:* Cognitive Assessment	Fatigue Measure	Relationship found	Total Associations Investigated	Positive Associations Found	Test Analysis	Domain - specific neuropsychological assessment batteries	Reaction Time based Ax.	Domain general screen	Timing of fatigue Ax. indicated
	TBI									
16	*Divided Attention*: Go No / Go	VAS	Yes	12	10	ANOVAs / chi - square / Spearman r	No	Yes	No	Yes
84	*Selective Attention*: TMT tasks 1-5: Visual scanning: TMT 1; Number sequencing: TMT 2	VAS-f	No	5	0	ANOVAs/ MANOVAs / spearman correlations	Yes	Yes	No	No
	Letter sequencing: TMT 3; Number-Letter seq: TMT 4; Motor speed: TMT 5			-	-					
	Memory: Auditory Consonant Trigrams (ACT)			3	0					
	Sustained Attention: Continuous Performance Test (CPT-II)			5	0					
	Attention & information processing: Driving simulator			3	0					
17	*Sustained selective attention*: Go/No Go	FSS	Yes	14	6	ANOVAs / Pearson correlations	No	Yes	No	Yes
34	*Sustained attention*: Psychomotor Vigilance Task (PVT)	FSS	Yes*	4	0	t-tests / chi square / Ancova / correlation	No	Yes	No	Yes
	Stroke Studies									
87	*Global domain screen*: MOCA	MFI - 20 (mental domain)	Yes	3	3	Logistic regression with OR	No	No	Yes	Yes

88	*Sustained attention*: Dot cancellation tasks	FSS	No	1	0	Multivariable regression	Yes	No	No	No
	Selective attention: Stroop		No	1	0					
	Information Processing: Adult Memory and Information		No	1	0					
	Processing Battery (AMIPB)			-	-					
90	*Global domain screen*: MOCA	FSS	Yes	1	3	Spearman correlation	Yes	Yes	Yes	Yes
	Information processing speed & attention/ vigilance: Simple choice reaction time SRT			1						
	Information processing speed & attention / vigilance: Choice reaction time CRT			1						
72	*Verbal short -term memory*: SRT - LTS /	Yes FSS 0; MFIS-C 1;FSMC 1		3	2	Bivariate correlations	Yes	Yes	No	Yes
	Verbal short - term memory: SRT - CLTR	FSS 0; MFIS-C 1; FSMC 1		3	2					
	Verbal long - term memory: SRT - DR	FSS 0; MFIS-C 0; FSMC 0		3	0					
	Visual short - term memory: 10/36 Spatial Recall Test	FSS 0; MFIS-C 0; FSMC 0		3	0					
	Visual long - term memory: 10/36 - DR	FSS 0; MFIS-C 0; FSMC 0		3	0					
	Working memory: PASAT	FSS 0; MFIS-C 0; FSMC 1		3	1					
	Information processing & mental speed: SMDT	FSS 0; MFIS-C 1; FSMC 1		3	2					
	Executive Function: Word List Generation	FSS 0; MFIS-C 1; FSMC 0		3	1					
83	*Global domain screen :*MMSE (Korean version)	FSS	No	1	0	Spearman correlation	No	No	Yes	No

36	*Processing speed sum score*: TMT / Stroop / Digit symbol coding	POMS-f	Yes	3	2	Chi-square tests / mann whitney / MANOVAs	Yes	No	No	No
	Processing speed: TMT A			3	0					
	Processing speed Stroop colour naming			3	0					
	Processing speed: Digit symbol coding			3	2					
	Memory sum score			3	1					
	Memory: Logical Memory Test I			3	0					
	Memory: 10 - word list learning task			3	1					
	Memory: Benton Visual Retention Test			3	0					
	Executive Function sum score			3	0					
	Executive Function: TMT B & A			3	0					
	Executive Function: Stroop			3	0					
	Executive Function: phonemic fluency task			3	0					
	Reasoning sum score			3	0					
	Reasoning: Similarities			3	0					
	Reasoning: Block Design			3	0					
89	*Global cognitive functioning and visuospatial test*: MMSE & Clock drawing task	FSS	No	2	0	Correlations / linear regressions	Yes	No	Yes	No
	Memory: 10 -word list learning task; 10 - word learning task delayed			2	0					
	Executive Function: TMT forms A & B, Verbal - Fluency: Colour word interference tests			11	0					
	naming / reading); Colour word reading (inhibition / switching); Error tests (naming errors,									
	reading errors, inhibition errors, inhibition / switching errors).									
20	*Attention*: TEA (phasic alert & divided attention)	FAI	Yes	4	3	Logistic regression	Yes	No	No	No

	Attention: D2 (sustained attention)			2	2					
	Long term memory: Rey Auditory verbal memory task			2	1					
	Short - term memory: Digit span			2	0					
	Short - term memory: Corsi Blocks test			2	0					
	Language: Boston Naming test			2	1					
	Language: Boston Diagnostic Aphasia			2	1					
	Executive Function: Stroop			2	1					
	Executive Function: Category & Fluency tasks			2	1					
	Global cognitive score			2	2					
86	*Global domain screen*: MOCA	Likert scale	No	1	0	Binary logistic regression	No	No	Yes	No
35	*Attention:* ANT	FSS	Yes	25	7	ANOVA / t- tests / beta / linear regression	Yes	Yes	No	Yes
	SAH Studies									
71	*Attention and concentration:* D2 concentration performance	FSS	Yes	2	1	t-test / chi-square / correlation	Yes	No	No	Yes
	Attention and concentration: Digit span forwards			3	3					
	Speed of Information Processing: D2 total performance			2	1					
	Speed of Information Processing: TMT A			2	1					
	Speed of Information Processin: symbol substitution (total good)			2	2					
	Memory: 15 Words Task (WT) total score			2	0					
	Memory: 15 WT Total recognition			2	0					
	Memory: 15 WT Total recall			2	0					
	Memory: Rey Complex Figure, recall score			2	0					

	Memory: Word Fluency, semantic			1	1					
	Memory: Digit span, backwards			2	0					
	Memory: Digit span, total score			2	0					
	Executive Function: Tower Test, Total performance			2	0					
	Executive Function: Word Fluency phonological			3	2					
	Executive Function: TMT -B			1	0					
	Visuoconstruction: Rey Complex Figure, copy score			1	0					
	Subjective cognitive functioning: Cognitive Failure Questionnaire total score			1	0					
38	Sum score of: *Verbal memory:* Digit Span backward; Semantic memory: category fluency	FSS	Yes	1	1	ANOVAs / t tests / RR	Yes	No	No	Yes
	Verbal learning: Rey Auditory Verbal Learning Task (RAVLT)									
	Non - verbal learning: Osterrieth Complex Figure Test									
	Executive Function: Brixton Spatial Anticipation Test									
	Attention: Digit span forward, Stroop									
	Visuoconstruction: Rey Complex Figure, copy score									

2.4.4 Overview and meta-analysis of associations between cognitive impairment and fatigue

In total, 221 associations were investigated between cognitive impairment and fatigue across 16 studies (table 2.2). Eleven studies found a 30% rate of positive association (67/221 comparisons analysed) between a cognitive impairment and fatigue across ABI populations [16, 17, 20, 34-36, 38, 71, 72, 87, 90]. The remaining five studies did not find an association across 40 comparisons [83, 84, 86, 89, 90], two of these studies [83, 84] were underpowered (tables 2.2 and 2.4). In terms of domain-specific investigations, the highest rate of positive association was with the domain of information processing with 48% of all specific associations reported found to be significant. The domain of attention had a 40% rate of positive association with fatigue levels, memory had 16% and executive functioning had 14% (table 4). A unified fatigue scale was used in 14 studies [16, 17, 34-36, 38, 71, 72, 83, 84, 86, 88-90] and had an overall 24% rate of positive association with a cognitive impairment (table 2.4). Notably, the two studies [72, 89] that used higher FSS cut-off scores did not find an association. All three studies that used the cognitive dimension of a Multi-Dimensional scale found positive associations with a cognitive domain impairment [20, 72, 87], an overall 56% rate of positive association (table 2.4).

Table 2.3 Fatigue scales and dimensions assessed.

Measure	Number of studies	Dimension of fatigue assessed
Unified Scales		
Fatigue Severity Scale - FSS	11	General experience of fatigue
Visual Analog Scale - VAS / VAS-f	1	General experience of fatigue
Profile of Mood States fatigue subscale - POM-f	1	General experience of fatigue
Fatigue Likert scale, unspecified*	1	General experience of fatigue
Subtotal : 4		
Multi – Dimensional Scales		
Modified Fatigue Inventory - MFI - 20	1	Five domains: general fatigue, physical fatigue, reduced motivation, reduced activity, mental fatigue
Modified Fatigue Impact Scale - MFIS	1	Four domains: Cognitive, physical, psychosocial functioning.
Fatigue Assessment Inventory - FAI	1	Four domains: Severity; pervasiveness associated consequences; response to sleep.
Fatigue Scale of Motor and Cognitive Functions - FMSC	1	Two domains: Cognitive & Motor subscales.
Subtotal: 4		
Total: 8 measures of fatigue		

*Unspecified: Study's own non-standardized unified Likert scale used [86].

In terms of measuring cognition and fatigue, the majority of studies used standardised cognitive screening and/or neuropsychological batteries to determine cognitive changes, though more complex experimental tasks aimed at picking up more subtle changes were also used by some.

1. Cognitive screening measures & fatigue

Global dementia screens were utilised across five studies to investigate for a relationship [83, 86, 87, 89, 90], with two finding positive associations [87, 90]. Delva et al [87] formed a positive association with fatigue using the Montreal Cognitive Assessment (MoCA) and a multi-dimensional fatigue measure (MFI-20, mental dimension) at 3 times points (6months: OR 3,23; CI, 1.12-5.80; p=0.03; 9 months: OR 2,77; CI 1,12-6,88; p=0.03; 12 months OR, 5,95: CI 2,18 – 16,28; p=0.005). Goh & Stewart [90] formed a positive association with the MOCA and the FSS, alongside two reaction time based assessments (SRT, CRT). Holmberg et al. [86] did not find an association with the MOCA and a Likert scale, 3 months post stroke. The other two studies [83, 89] failed to make an association with fatigue using another global dementia screen, the Mini-Mental State Examination (MMSE). Of these, one study was underpowered [83].

2. Domain-specific standardised neuropsychological assessment batteries & fatigue

A total of 9 studies utilised detailed neuropsychological batteries targeting specific cognitive domains when investigating a relationship across lengthy testing procedures [20, 36, 38, 71, 72, 84, 88-90]. Of these, six studies found a 23% rate of positive association (table 2.4). Three studies did not find an association [84, 88, 89]. One study [88] reported that the failure to make an association could be due to participants having relatively minimal cognitive deficits. One study was underpowered [84]. Two studies [20, 38] used the sum score across a battery of cognitive assessments to investigate a relationship with fatigue levels, and 3/3 associations were established.

Nine studies that considered fatigue during testing procedures [16, 17, 34, 35, 38, 71, 72, 87, 90] found a positive association with cognitive impairment. Of the remaining seven studies [20, 36, 83, 84, 86, 88, 89] that did not consider a break (not explicitly mentioned), a relationship was not found in five studies [83, 84, 86, 88, 89]. Fatigue levels were examined pre or post testing of the cognitive task trial within six studies [16, 17, 34, 71, 72, 84]. Of these, five studies found an association with a cognitive impairment [16, 17, 34, 71, 72] and the FSS [16, 71], the

Visual Analogue Scale (VAS) [17], the Fatigue Scale for Motor and Cognitive Functions (FSMC)[72] and Modified Fatigue Impact Scale (MFIS)[72] .

3. Complex Task Approaches and Reaction Time based Assessments

Analytical approaches based on mean Reaction Times (RTs) was used to investigate a relationship with fatigue in seven studies [16, 17, 34, 35, 72, 84, 90]. This approach required participants to sustain attention on challenging reaction time based assessments (RT). Shorter RTs suggest faster information processing speed [84]. Longer RTs were an indication of difficulty with sustaining attention [17, 34], mental fatigue [35] or mental effort [16]. In all, six studies [16, 17, 34, 35, 72, 90] found a 39% positive association (Table 2). The one study that did not find a relationship was underpowered [84].

2.4.5 Meta-analysis

Only the studies employing RT-based measures had sufficient comparable data to conduct a meta-analysis on the correlations found between fatigue levels and processing speed performance on cognitive tasks. The meta-analysis found a significant but low overall effect size ($r = 0.234$) between higher fatigue levels and mean RTs [17, 34, 35, 72, 84, 90] (fig. 2.2, fig. 2.3).

This evidence was of moderate quality (table 1, Risk of bias). There was insufficient reporting of results in one study [16], correlation values were not shown and described as 'low'. Another study [35] used a mixed models approach when making comparisons. Therefore, these results [16, 35] could not be included in meta-analysis. Duration of the specific assessment lasted more than 10 minutes in most studies [16, 17, 34, 35, 72, 84, 90]. Although certain studies did not detail the duration of each session, this can be inferred from the testing procedures used [16, 72, 90].

One study [90] found a significant relationship between baseline fatigue (FSS) and increased RTs (SRT $r = 0.29$, $p = 0.03$, CRT $r = 0.29$, $p = 0.03$), and reports the findings may be due to a manifestation of cognitive deficits particularly information processing and vigilance/attention: correlation coefficients were reported as fair in strength. Another study [72] did not find a significant correlation with baseline FSS scores and RT measures: SDMT (0.23, $p<0.0$); PASAT (0.21, $p<0.01$) although it did find a correlation when cognitive subscales of two multidimensional fatigue scales were applied: MFIS-C (SMDT: $r = 0.45$, $p<0.05$) and FSMC-

C (SMDT: r = 0.54, p< 0.01; PASAT: r = 0.49, p<0.05). FSS clinical cut-off values were higher at > 4.6 in this study in comparison to another study [90] which did find an association using a cut-off of >4. One study [17] that completed two RT sessions on the Go/No Go with TBI participants (2 x 30-minute sessions, T1 & T2) also found baseline fatigue (FSS) was significantly correlated with deterioration in RTs during the second session only (r = 0.41, p ≤0.5). Accuracy was associated with fatigue (FSS) in the first session only, but stayed steady during the second half. These findings may be an indication of fatigability with time on task accounting for effects seen during T2. However significant associations were also reported with higher mental effort and increased RTs across both sessions.

Another study [16] reported 'low' correlations between higher levels of momentary subjective and mental effort (VAS) to perform tasks, even during relatively simple tasks (Go/No Go) in comparison to healthy controls, and described as resulting in higher sensations of fatigue. As mentioned, data was not shown in the study [16].

Figure 2.2 Forest plot displaying Reaction Time scores in Pearson's r and relationship between cognitive measures/fatigue scales.

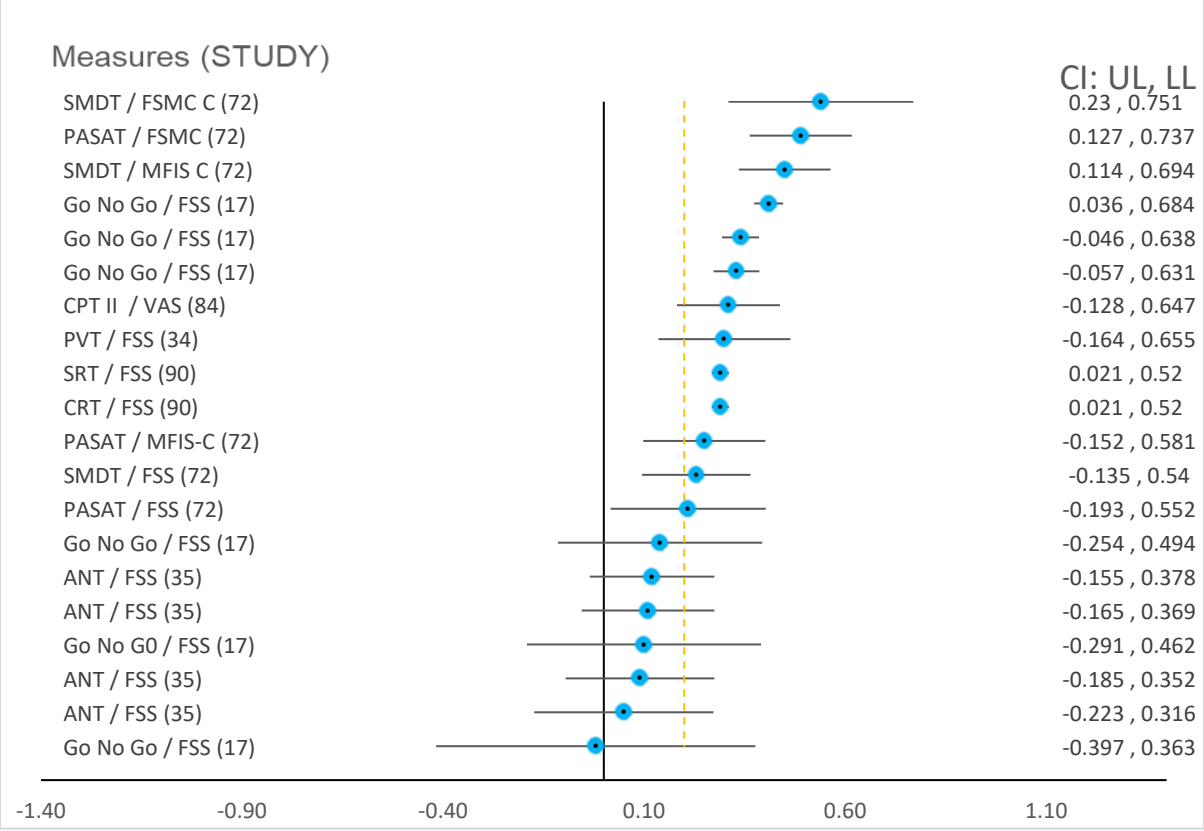


Figure 2.2: Scores based on speed of RT were included in meta-analysis (as opposed to accuracy). Positive threshold target (yellow vertical line), 0.2. All studies that used the cognitive dimension of a multi-dimensional scale found positive associations with a cognitive domain [20, 72, 87]. One study [90] found a positive association the FSS and underlined cognitive deficits of information processing and attention within their sample.

Figure 2.3 Meta-analysis effect size in Pearson's r.

Measures / (Study)	n's	Effect size	CI: LL, UL
SMDT / FSMC C (72)	31	0.54	0.23 , 0.751
PASAT / FSMC (72)	26	0.49	0.127 , 0.737
SMDT / MFIS C (72)	31	0.45	0.114 , 0.694
Go / No Go / FSS (17)	27	0.41	0.036 , 0.684
Go / No Go / FSS (17)	27	0.34	-0.046 , 0.638
Go / No Go / FSS (17)	27	0.33	-0.057 , 0.631
CPT II / VAS (84)	22	0.31	-0.128 , 0.647
PVT / FSS (34)	20	0.3	-0.164 , 0.655
SRT / FSS (90)	53	0.29	0.021 , 0.52
CRT / FSS (90)	53	0.29	0.021 , 0.52
PASAT / MFIS-C (72)	26	0.25	-0.152 , 0.581
SMDT / FSS (72)	31	0.23	-0.135 , 0.54
PASAT / FSS (72)	26	0.21	-0.193 , 0.552
Go No Go / FSS (17)	27	0.14	-0.254 , 0.494
ANT / FSS (35)	53	0.12	-0.155 , 0.378
ANT / FSS (35)	53	0.11	-0.165 , 0.369
Go / No G0 / FSS (17)	27	0.1	-0.291 , 0.462
ANT / FSS (35)	53	0.09	-0.185 , 0.352
ANT / FSS (35)	53	0.05	-0.223 , 0.316
Go / No Go / FSS (17)	27	-0.02	-0.397 , 0.363
	Random effect:	0.234	

Figure 2.2 & 2.3, Abbreviations of cognitive assessments: SMDT, Symbol Digit Modalities Test; PASAT, Paced Auditory Serial Addition Test; CPT II, Continuous Performance Test II; PVT, Psychomotor Vigilance Task; SRT, Simple Reaction Time, CRT, Choice Reaction Time; ANT, Attention Network Test. Abbreviations of fatigue measures: FSMC-C, Fatigue Scale of Motor and Cognition-Cognitive subscale; MFIS-C, Modified Fatigue Impact Scale, cognitive subscale; VAS, Visual Analog Scale; FSS, Fatigue Severity Scale.

Complexity of task was heightened in two studies [35, 84]. The first study [84] did not find a relationship across 4 reaction time conditions on the CPT II ($r = <0.31$, $p \geq 0.16$) and fatigue (VAS-f). There was a significant relationship between RT scores and 'sleepiness' (VAS-s)

before and after testing (r = 0.55, p < .01) with a noted progressive slowing in RT over time in the TBI group, compared to healthy controls possibly due to 'accumulated fatigue' while sustaining attentional tasks. We explored the consequence of adding this trial to the analysis; the overall effect remained positive (r = 0.236).

The other study [35] did not find a significant association between FSS and mean RT across (r = .09, *p* = .48) or within varying complex conditions (incongruent flanker: r = .05, *p* = .67, congruent flanker: r = .11, *p* = .47, neutral flanker: r = .12, *p* = .37). However, results from linear mixed models identified significant associations between FSS score and RT with an observed decrement in sustained performance over time, though this format of analysis could not be included in meta-analysis. The final study [34], identified an overall pattern of cognitive slowing across the attention task (PVT), with delayed RTs seen from the onset (between 1-2 minutes) in comparison to healthy controls. However, statistical significance was not reached (r< .30, p >.14), the authors explain that this is likely due to the large heterogeneity between participants. On a much smaller homogenous sample (n=3), the authors did observe a significant relationship with fatigue (FSS), speed of information processing and attention deficits (PVT). Values were not provided in a suitable format (in r) to include in meta-analysis [34].

2.4.6 Domain specific cognitive impairment, assessments used and their relation to fatigue measures: overall findings

1) Information Processing

The relationship between the domain of information processing and fatigue was investigated across five studies [36, 71, 72, 88, 90]. Four studies established a 48% rate of positive association with fatigue [36, 71, 72, 90] (table 4). All five studies were adequately powered. There were nine different cognitive assessments used when completing the investigations. Six cognitive assessments were paper-based, with four assessments (TMT A, Digit span, D2 and symbol substitution) finding 8/19 positive associations [36, 71], and all were formed with unified fatigue scales: the FSS (4) and POMS-f (4). Two assessments were reaction time based assessments (SRT, SMDT), with both assessments finding 3/4 positive associations [72, 90] using a variety of fatigue scales, namely the FSS (1), the MFIS (1) and the FSMC (1).

2) Attention

The domain of attention was the most frequently investigated domain across ten studies [16, 17, 20, 34, 35, 38, 71, 84, 88, 90]. Eight studies found a 40% rate of positive association with fatigue [16, 17, 20, 34, 35, 38, 71, 90] (table 4). One study that did not find an association was underpowered [84]. In all, 13 different cognitive assessments were used to investigate various domain specific aspects of attention including sustained, divided, and selective attention. Seven cognitive assessments were paper-based tasks, with 3 assessments (TEA, D2, Digit span) finding 9/18 associations [20, 71]. Two fatigue measures were used in these instances, the FAI (5) [20], and the FSS (4) [71]. Seven assessments were reaction time (RT) based assessments, with three (RT) assessments (Go/No Go, CRT, ANT) finding 24/64 positive associations with fatigue levels [16, 17, 35, 90]. Two unified fatigue measures were used when forming these associations: the VAS (10) [16] and the FSS (14) [17, 35, 90]. As noted (see Meta-analysis), the PVT also found positive associations with fatigue levels [34].

3) Memory

The relationship between the domain of memory and fatigue levels was explored across seven studies [20, 36, 38, 71, 72, 84, 89]. Four studies found a 16% rate of association with fatigue [20, 36, 71, 72], (table 4). One study that did not find an association was underpowered [84]. In all, 19 paper-based assessments and one RT based assessment of memory were used to assess either short-term or long-term memory. Two studies found weak associations (3) when using unified fatigue scales (1/13 with FSS; 2/12 with POMS-f) [20, 71]. Two studies found the remaining six associations using the cognitive dimensions from three multi-dimensional fatigue scales were applied: the MFIS-C (2), FSMC (3), and FAI (1) [20, 72].

4) Executive Function

The domain of executive function was assessed in six studies [20, 36, 38, 71, 72, 89]. Three studies [20, 71, 72] found a 14% rate of positivity (table 4). All studies that did not find an association were adequately powered [36, 38, 89]. Eight different paper-based cognitive measures were used. One study found weak associations (2) with a Word Fluency Task and the FSS fatigue scale [71]. Two studies used three cognitive assessments (Word list generation, Stroop, Category and Letter Fluency task) and two multi-dimensional fatigue scales to find three positive associations: the MFIS-C (1) and the FAI (2) [20, 72].

Language was investigated in one study with 2/4 positive associations found with a multi-dimensional fatigue measure (FAI) [20] (table 4). There was no association between reasoning [36], or visuoconstruction [71] and fatigue levels, nor between subjective cognitive assessment and fatigue [71]. Two studies utilised the sum score across a battery of assessments to find the three remaining associations with fatigue [20, 38].

Table 2.4 Summary of domain specific comparisons made, associations found, rate of positivity (%).

	No. of studies	Study making investigations	No. of studies with significant associations	Positive associations found/total associations investigated	Rate of positivity %	Studies finding positive associations
Relationship of domain specific						
cognitive impairments to fatigue						
Information Processing	5	88,90,16,36,71	4	11/23	48%	47,13,46,11
Attention	10	71,16,17,88,84,20,90,38,34,35	7	33/82	40%	11,18,16,14,47,52,51
Memory	7	84,16,36,89,20,71,38	4	9/55	16%	13,46,14,11
Executive Function	6	16,20,71,38,36,89	3	6/35	17%	13,14, 11
Language	1	20	1	2/4	50%	14
Reasoning	1	36	0	0/9	0	
Visuoconstuction	1	71	0	0/1	0	
Subjective cognition	1	71	0	0/1	0	
Relationship of Fatigue Scales						
Unified fatigue scales						
Overall scores	13	16,17,34,84,89,83,88,90,38,71,36,35,86	7	44/180	24%	47,52,11,51,16,46,18
VAS /VAS-f	2	16,84	1	10/28	36%	18
FSS	10	17,34,88,90,72,83,89,35,71,38	5	28/106	26%	47,52,11,51,16
Fatigue Likert scale	1	86	0	0/1	0	0
POMS - f	1	36	1	6/45	13%	46
Multi - dimensional fatigue scales						
Overall scores	3	16,20,87	3	23/41	56%	13,14,33
FSMC	1	16	1	4/8	50%	13
MFIS - C	1	16	1	4/8	50%	13
FAI	1	20	1	12/22	55%	14
MFI - 20*	1	87	1	3/3	100%	33

Overall associations	15		10	67/220	30%	16, 33, 47, 13, 46, 51, 11, 14, 18, 52
Study Designs:						
Design 1: Domain specific assessment	7	84,16,36,20,89,71,88	4	32/141	23%	16,47,13,46,14,51,11,18,35,52
Design 2 : RTs	7	17,16,84,34,90,35,72	6	28/71	39%	16, 18, 13, 47, 52
Domain General	5	87,83,90,89,86	2	4/8	50%	33,47
Global cognition abilities	3	38,20	2	4/5	80%	51,14

2.5 Discussion

To the researchers' knowledge, this is the first systematic review to explore the complex relationship between cognitive impairment and fatigue after Acquired Brain Injury (ABI). We found overall that the association between cognitive impairment and fatigue across the included ABI populations was weak (67/221). However, in-depth analysis of domain-specific cognitive impairment revealed more robust relationships with fatigue levels. The domains of information processing and attention were the most frequently investigated cognitive domains and consistently associated with fatigue post-ABI, reaching statistical significance. Furthermore, studies that challenged attentional resources (i.e. via Reaction time based assessments) were positively associated with fatigue (7/7 studies), although some results were dependent on the method of data analysis performed [35, 84] and population sample assessed [34].

Our results showed an overall weak association between cognitive impairment and fatigue. This review contributes new insights that may explain why we managed to find a relationship in comparison to other studies which found none [8, 93]. First, the broad scope of this review lends itself to extensive investigations of this literature (as opposed to stroke alone [8, 93] and underlines the plethora of measures and methodologies used across the included ABI studies. Next, our results provide insights on the use of two domain-general screens, the MMSE and the MOCA. While the lack of association with the MMSE [83, 89] aligns with previous study findings [8, 93], we found associations with fatigue and the MOCA in two studies [87, 90]. Delva et al. [87] formed an association with fatigue using the MOCA and a multi-dimensional fatigue measure (MFI-20, mental dimension) however wide confidence intervals were applied to make these associations. Goh & Stewart [90] formed a positive association with the MOCA and the FSS, alongside two RT assessments (SRT, CRT). The authors [90] explained that the MOCA may be a more sensitive assessment to investigate this relationship, as executive function and attention are included in this screen and not the MMSE. Although one study [86] noted that lack of association in their research was due to the use of the MOCA. They state [86] it is a global dementia screen known to be insensitive in detecting cognitive change after stroke, which aligns with previous studies [8, 94]. Indeed, the measurement strategy used [90] could have placed demands on other cognitive processes, such as sustained performance, given the use of two RT testing measures [90]. It is therefore unclear if the associations formed in these studies [87, 90] were due to the measures used, a domain-specific function required to complete the test or indeed the measurement strategy.

In addition, while there is sufficient evidence for the use of domain-specific cognitive batteries of assessment when investigating this relationship (32/141), the observed associations are also weak overall. This may be due to either of the following factors: (1) the subtests have been used interchangeably to assess several cognitive domains across some studies. For example, the D2 was used to find associations with fatigue and sustained attention in one study [20], and with speed of information processing and concentration performance in another [71]; or (2) while the research has shown how batteries of assessment offer valid standalone subtests that reliably detect cognitive dysfunction within core domains, arguably each subtest involves several cognitive processes alongside the domain under review. For example, the TMT was utilised in studies to assess speed of information processing [36, 71], selective attention, scanning, sequencing, motor speed [84], and executive function (obtained by using both TMT forms A and B) [84, 89]. These findings are also unclear and likely account for the weak associations overall (See table 2.2 for further examples and results). 3) The approaches used may well exacerbate fatigue for participants. The experience of fatigue may be triggered by the lengthy duration of the testing procedure, rather than a dysfunction in a cognitive domain *per se*. For example, five [83, 84, 86, 88, 89] of the seven studies that did not consider a break (that is, not explicitly stated), did not find an association. Conversely, all nine studies that made attempts to minimise fatiguing situations (such as offering alternative testing days [90] or splitting sessions [17], found positive associations (9/9 studies). The findings indicate that attentional load (i.e., sustained attentional performance) may be related to fatigue rather than fatigue elicited through the testing method [16, 17, 34, 35, 38, 71, 72, 87, 90].

An in-depth analysis of cognitive domain investigations revealed positive associations with information processing and attention, and to some extent memory and executive function and higher fatigue levels after an ABI. The domains of information processing and attention were most frequently investigated and consistently associated with fatigue. A possible theoretical explanation is that information processing and attention are core domains within a hierarchy of cognition and any changes to these may affect appropriate functioning of higher-level cognitive abilities, such as executive function, and possibly new learning [3, 35]. This theory supports the observed interaction between increasing RTs and higher fatigue levels as participants failed to benefit from any learning effect as they progressed through the task, a finding previously noted in one study [35]. An array of techniques are emerging to objectively measure the cognitive manifestations of fatigue within the literature, with typical measurements of deterioration of performance during sustained activity. RT testing (finding 28/71 positive

comparisons) may have exposed subtle cognitive deficits that give rise to the manifestations of fatigue, namely information processing and attention. The results from meta-analysis found fatigue was significantly associated with an overall pattern of slowing in RT over time and this was irrespective of complexity of the task. The findings indicate that sustaining an optimal performance on a task of attention over a prolonged period (>10min) requires greater mental effort [16] which may come at a cost of feeling increasingly fatigued. These findings support the theoretical framework of the "coping hypothesis" [95], where the experience of fatigue could arise from the constant compensatory effort required by individuals with an ABI to maintain performance on tasks in the absence of internal attentional resources, resulting in a response perceived as mental fatigue. However, the complex aetiology involved in each domain, for example the domain of attention, were not entirely accounted for in studies, so results are not entirely conclusive. Further targeted research is needed to establish the strength of associations between cognitive changes after ABI and fatigue.

Half of the studies that used the FSS did not find an association with cognitive impairment. As the FSS has no validated "cut-off" score to define clinically significant fatigue [88], the variability of this could account for the results. As seen, studies that used a higher FSS clinical cut off score [72, 89] did not find an association in comparison to others who used a lower (<4) cut off point [38, 71, 90]. One study [72], using a higher FSS cut off score did not find an association with fatigue but did using two MD fatigue scales (FSMC, FMIS-C). The use of multi-dimensional scales in studies may have minimised confounders known to be associated with response rates (e.g., difficulty with recall) and assisted with the sub-domains under review (e.g., cognitive aspects), increasing the rate of positive association. One study [84] found an association between a cognitive impairment and "sleepiness" (VAS-s) describing the observations as "accumulated fatigue." These results [71, 72, 89, 90] highlight the lack of a universally accepted definition and measurement of fatigue.

This present review has limitations. The broad scope was both a strength and a limitation. First, all categories of ABI were included where rehabilitation was usually provided. This, however, does not include other forms of ABI including mild TBI, a sub-group shown to experience severe fatigue post-ABI [96]. Second, all types of studies were included, irrespective of analysis performed. The heterogeneity of assessments and analysis methods used across these studies, meant that a meta-analysis was limited to reaction time-based assessments (RT speed) only. This study was operationalised to address the complex question of the relationship between cognitive impairment and fatigue. However, this methodology may favour a reporting

bias, as for example certain eligible studies could not be included in the meta-analyses due to the data not being in a suitable format [34, 35]. Results from the included studies (Stroke, TBI and SAH) and meta-analyses in this review should be interpreted with this in mind. Indeed, the findings in this review may favour significant outcomes, as in certain instances the associations formed are not only non-specific, and the findings overall are weak. It must also be noted that not all confounding factors of fatigue such as diurnal changes and comorbidities were documented in all studies, factors known to be associated to the experience of fatigue. In addition, primary data was not provided in two studies, Radman et al. [20] and Azouvi et al. [16], while contact was made however no response has been received to date. While most studies found an association, results should be interpreted with caution, as a number of studies have a fair risk of bias (table 2.1).

2.6 Conclusion

Overall, this review provides positive, though relatively weak, evidence for a relationship within the core domains of information processing and attention as well as, to a lesser extent, memory and executive function, and higher fatigue levels after ABI. To identify more robust relationships, we suggest the use of purer measures targeting domain specific functions could reveal stronger associations. Attention is a core domain within a hierarchy of cognition and any changes to attention may affect appropriate functioning of higher-level cognitive abilities, such as executive function, and possibly new learning [21-23]. Contemporary neuropsychologists detail the dynamic temporal aspects involved sustaining attention over time [26]. However, difficulties with engaging these attentional processes may result in previously effortless activities of daily living that require sustained attention becoming exhausting. Within this review, it would appear that sustained attentional tasks demand greater mental effort for optimal performance, but this comes with a cost of feeling very fatigued. As attention is a potentially modifiable factor post-stroke (chapter 1) [46, 47, 49], an investigation of this association early after stroke would be worthwhile. Given the negative impact of mental fatigue on participation, an understanding of underlying mechanisms mediating mental fatigue is of clinical importance.

Chapter 3 Attention and fatigue: measuring the relationship

3.1 Overview of Chapter 3

Attentional deficits are seen post-stroke. As sustaining attention is crucial for every aspect of adaptive behaviour, it is of interest to understand how stroke survivors actually sustain their attention in real-world situations. However, difficulties with engaging these attentional processes may result in previously effortless activities of daily living that require sustained attention becoming exhausting. Chapter 2 has shown evidence for a relationship between attention and fatigue in 90% of adequately powered studies. However, uncertainties remain in these findings to make any firm conclusions. It is unclear as to what aspect of attention is related to fatigue, and the disparity across measurements strategies used when investigating for a relationship make it difficult to fully synthesise the evidence. Nonetheless, the suggestion that sustained attentional performance is associated with higher PSF levels seems promising and measuring this association merits further exploration. This chapter will address these disparities in more detail, will provide deeper insights into the theoretical base of existing research, and will propose an alternative measurement approach that could potentially provide a more accurate method of determining the relationship between attention and fatigue.

3.2 Attention

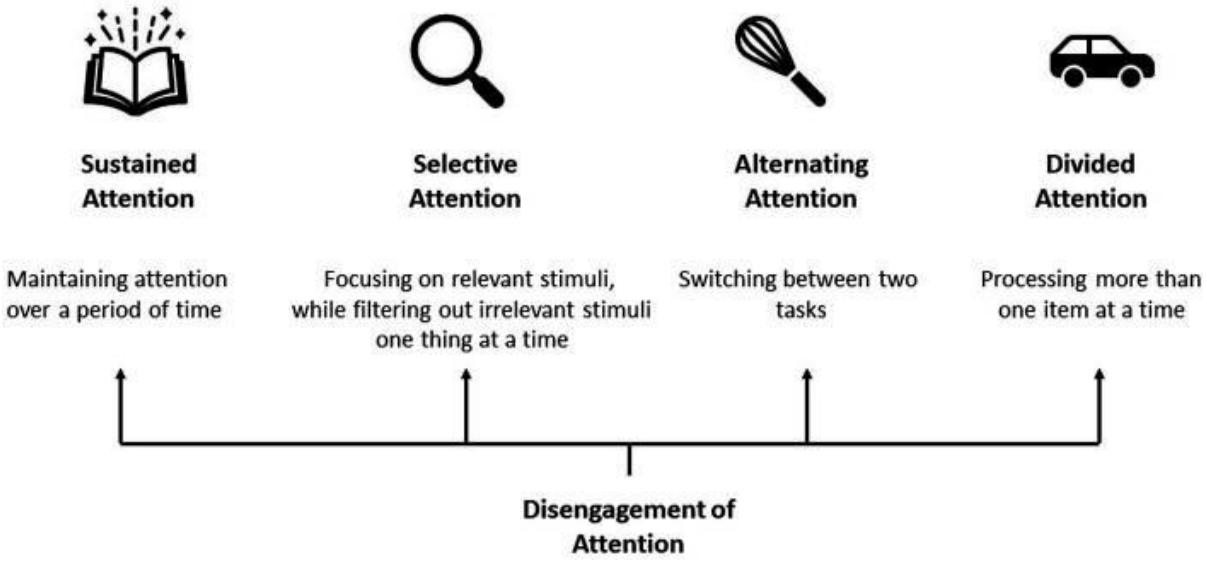
Attention is one of the most studied cognitive functions of the human mind. As our environment is constantly changing over time, it is essential to remain vigilant, or sustain attention, to detect these changes, and be ready to react accordingly [22]. Contemporary neuropsychologists detail the dynamic temporal aspects involved sustaining attention over time. However, difficulties with engaging these attentional processes may result in tasks that require sustained attentional performance to become fatiguing. Our research has shown how the domain of attention was the most frequently investigated cognitive domain and the most consistently associated with fatigue. However, measurement strategies used have been inconsistent, making it difficult to synthesise the evidence due to several factors including 1) conceptualising attention, 2) internal 'top down' demands, and 3) external 'bottom-up' demands, on attentional processes.

3.2.1 Attentional Processes

1) Conceptualisation of attention

Within existing research, it is unclear as to what aspect of attention is being investigated. The complex aetiology involved in the domain of attention were not entirely accounted for in studies, so results are not entirely conclusive. In some studies, attention is described as a unified construct (i.e. the domain of attention) [38, 71, 90] and the other likely attentional processes involved in completion of the given task (or assessment) are unclear, and thus the type of attention relating to fatigue remains vague. For example, within the literature, neuropsychologists describe different types of attention that differ in complexity: sustained attention, selective attention, alternating attention, divided attention, and disengagement of attention (fig. 3.1). Chung-Fat-Yim et al. (2022), provide a general summary where "sustained and selective attention are needed to focus attention on one task at a time, while alternating and divided attention are required for concentration on more than one task [97]. The difference between selective attention and sustained attention is that the former involves focusing on one task while avoiding distractions and the latter refers to a person's ability to focus on an activity continuously" [97].

Figure 3.1 Chung-Fat-Yim description of the sub-types of attention [97].



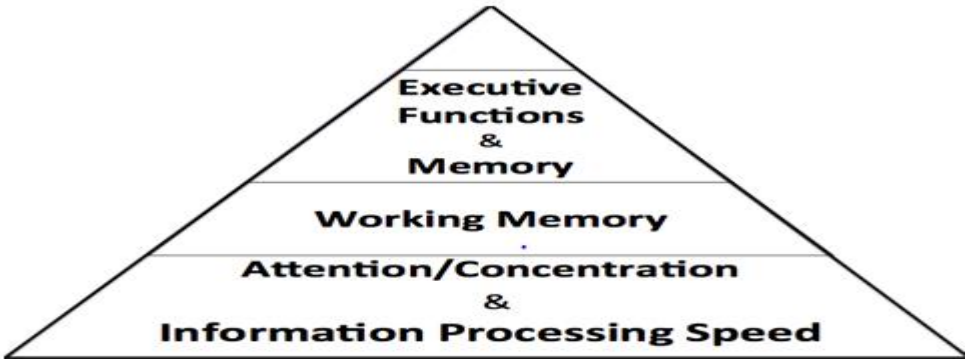
2) Internal 'Top-down' demands

Shipstead et al.[98] describe how higher-order cognitive measures such as measures for working memory place differential demands in an 'internal top-down manner' on executive

attention systems. As shown, many studies in the review used subtests from detailed neuropsychological batteries of assessment [20, 38, 71], the assessments were often not well defined [17, 20] or were used interchangeably to assess several cognitive domains (see review table for description). As noted across research (and in the review), it is theorised that attention is a core domain within a hierarchy of cognition and any deficits to this domain may affect higher-order cognitive abilities, such as executive function [99-101] (fig. 3.2). Arguably the subtests involve several executive cognitive functions alongside attention [20, 38, 98] and unrelated 'top down' demands are placed on other cognitive constructs such as memory, language and executive function which make it difficult to interpret results. Indeed, the central role of controlling attention has been demonstrated in several recent large scales studies [99, 101-103] where relationships between two higher-order cognitive processes (e.g. working memory capacity and fluid intelligence [99]; sensory discrimination and working memory [102] were no longer statistically significant when controlled attention was accounted for. Specifically, Draheim et al (2022) [99] defines the executive attention system as a general ability to engage in a task, and the interplay between sustaining attention in the face of distraction on the one hand, and filtering or inhibiting irrelevant and inappropriate information and behaviour on the other. The authors state that this interplay of attentional control (sustained attention v's inhibition) is a core mechanism used to manage top-down demands and *"Knowledge of an individual's ability to control their attention should explain more variation in higher-order cognitive behaviours and performance than either working memory capacity or fluid intelligence." [99]*

The authors argue that researchers would therefore "*generally be better suited to studying the role of attention control rather than memory-based abilities in explaining real-world behaviour and performance in humans" [99]*. The need for a more focused assessment of attentional processes that minimises top-down demands is now required.

Figure 3.2 Hierarchy of cognition. Image adapted from Lindsey H.M, and Voelbel, G.T (2014) [48].



3) Attentional Processes: External 'Bottom-Up' demands

Competing external demands on attentional resources, such as background noise, could place high burden on the ability to sustain attention in the face of distraction or interference, particularly over a prolonged period [99]. Shalev et al explain how a mere distraction from the environment may act as an exogenous cue, causing attentional capturing in a 'bottom-up manner' [104, 105]. The interaction between contextual factors and attentional mechanisms whilst measuring for a relationship of attention to fatigue in studies is vague. Importantly, Shinoda et al (2001) [105] describe how in everyday life, domain specific operations (i.e. attentional control) are embedded in the context of continuous behaviour, and this is critically dependent on our immediate context [105]. It is therefore unclear in studies if it was the cognitive (attentional) demands from inhibiting responses triggered from abrupt cues from the testing environment, or whether sustaining attention in the face of distraction, was fatiguing.

3.3 Sustained attention

Sustaining attention is essential when responding to our ever-changing environment and remaining vigilant is a prerequisite to detect these changes and being able to react accordingly [22]. Sustained attentional difficulties are a common and troublesome post-stroke sequelae and existing research details correlates across our life span including learning, returning to work, and driving [48, 84]. Sustained attention is unique to other types of attention (e.g. divided attention) in that it involves a period of fixed time required to perform an activity [106, 107]. If we consider everyday activities such as reading a book, cooking, dressing, sustained attention is crucial to cognitive function (as outlined in hierarchy above) and any momentary lapse could

result in delays, repeated activity, or failure to complete a task [97]. Indeed, this thesis proposes that difficulties with engaging in sustained attentional process after stroke could result in previously effortless sustained attentional tasks to become very fatiguing.

Esterman and Rothlein (2019) outline five different neurocognitive models of sustained attention, based on physiological and cognitive functions: arousal, attentional allocation, cognitive control, opportunity costs, and information processing [97, 108]. The term arousal is used interchangeably with sustained attention and described as 'the baseline amount of attentional resources available to perform a task' [97].

3.3.1 Neurophysiological aspects of sustained attention, brief outline

In chapter one (section 1.2), the increased activity in the prefrontal cortex and subsequent higher cognitive effort to maintain an optimal level of task performance was outlined (albeit briefly as this is not necessarily the remit of this thesis). We suggested that higher cognitive effort is required to sustain attention and perform voluntary intentional movement which could be perceived as fatigue to maintain task performance. Nonetheless, Esterman and Rothlein (2019) details the optimal level of arousal required for task performance and the major role of locus-coeruleus (LC) noradranergic system [108]. In general, they state how low LC activity is associated with low task engagement, while high LC activity results in low task engagement due to hyper-arousal and distractibility. Some aspects of attention are quite intuitive: for instance, the threat of shock would enhance sustained attention [109] and 'fight and flight' sympathetic modalities [110]. While suboptimal arousal, such as lack of motivation, could account for a lapse in attention [109]. For optimal engagement, Esterman and Rothlein (2019)[108] found "activity in the locus-coeruleus (LC) noradrenergic system would reduce background noise and enhance neural (phasic) response to salient stimuli, thus enhancing task-related information processing capacity and reducing signal-to-noise-ratios".

3.3.2 Attentional timeframes: approach

One way to reconcile for the various approaches (top-down v's bottom-up) to measuring attention is by describing different timeframes of interest [104]. In neuropsychology literature the complex and multi-dimensional constructs of the temporal processes involved in attention over time is described in terms of two distinct timeframes: 1) 'phasic alertness', described as momentary alertness to the attentional network following an abrupt external cue, 2) and 'tonic alertness' or more commonly referred to in the literature as 'sustained attention', is measured

by the decrement of attentional performance over time. Indeed, sustained attention is an important factor in the recovery of other cognitive syndromes after stroke including motor deficits [26]. The research has shown that sustained attentional performance demands greater mental effort for optimal performance, which comes with a cost of feeling very fatigued. As sustaining attention is a necessity for nearly every adaptive behaviour, it is of interest to us to understand if sustaining attention over time (rather than phasic alertness for example) is mentally fatiguing.

3.3.3 Attentional load: sustaining attention over a prolonged period

The type of attention used changes depending on the demands of the task and the contextual factors [97]. The findings of the review indicate that attentional load (i.e. sustained attentional performance) may relate to fatigue [16, 17, 71, 72]. However, as stated a plethora of assessments were utilised across these studies. As before, it is unclear whether associations found were owing to the interaction of several cognitive processes alongside sustained attentional performance, or were due to a relationship to the domain of attention *per se* [17, 38, 71, 73]. Nevertheless, in all studies (9/9 studies) that made attempts to minimise fatiguing situations (such as offering rest breaks between testing sessions), correlates were found between higher fatigue levels and testing procedures that required participants to sustain attentional performance (>10minutes) in a given testing session. This approach (attentional loading) seems a promising strategy towards the better understanding of the potential attentional mechanisms relating to fatigue and aligns with the Johansson & Ronnback (2012) definition of mental fatigability as 'an inability to repeatedly sustain cognitive performance and the need for a long recovery time after exertion'[15].

3.3.4 Targeted assessment of sustained attention

Chapter 2 and other studies have demonstrated the use of variations of computerised continuous performance tasks (CPTs) [16, 17, 35] to measure temporal aspects of attention. Participants are required to maintain their concentration levels on a computer screen and press a response button to a pre-determined target within a continuous stream of distractors over a prolonged period (approx. 10-20 minutes). This strategy seems suitable to measure attention and of sufficient duration to illicit a fatiguing response [16, 17, 35], as the review of the literature has shown that attention relates to fatigue levels with all studies (7/7 studies) sufficiently powered that used this strategy.

3.3.5 Measuring sustained attention: important considerations and proposed solution

Within the literature, attentional performance on a CPT is usually measured in two ways: 1) In terms of accuracy levels: Omissions (missed targets) and commissions (false alarms); 2) mean reaction time (RT) scores across the task. However, certain considerations with this strategy are needed if measuring sustained attention, as this too can place demands on other confounding cognitive processes, particularly in this clinical population. As seen in the review, various aspects of attention were assessed (divided attention, alternating, etc.). Trade-offs were observed between memory (recalling which target to respond to) [16, 17] inhibitory mechanisms (and not respond to) [17], visual perception (target identification) [16, 17], orienting mechanisms (abrupt external cues such as background noise that attracts attention) [16, 17, 35] and motor control (reaction time speed) [22, 35]. Indeed, measuring sustained attentional performance in relation to reaction time alone after stroke is problematic due to issues with motor control, normal aging processes, and fluctuations in (phasic) alertness [22].

A recent solution that minimises the more top-down confounds when measuring sustained attention in stroke survivors has been successfully demonstrated by Shalev and colleagues [22]. That research presents a purer measure of sustained attention using a Masked Conjunctive Continuous Performance Task (MCCPT) behavioural paradigm lasting 10 minutes (approximately). The research has shown how the use of a constant visual stimuli on the screen (i.e., mask), the demand to sustain attention greatly increases. This way there is no abrupt onset, and therefore less involvement of orienting mechanisms of any kind. In this way, it enables a more focused measure based on accuracy in comparison to other studies [16, 17, 20, 35, 73, 90].

3.4 Measuring fatigue

Fatigue is increasingly being conceptualised as a multi-dimensional post-stroke symptom, and assessment strategies are beginning to reflect this dimensionality. Making distinctions between the dimensions of fatigue is emphasised by Stulemeijer et al (2007) who state that physical factors alone cannot account for the persistence of fatigue, and this should preferably be reflected in assessing PSF [111]. Studies are beginning to differentiate between components of fatigue including 1) 'experienced fatigue' described as increased feelings of mental and physical effort required to complete daily activities [12]; and 2) the 'physiological factors of fatigue' which includes 'central fatigue' (limited ability with sustaining physical activities

and/or concentration, resulting in mental and physical fatigability) and 'peripheral fatigue' (failure to sustain the force of muscle contraction over time resulting in muscle fatigability) [12, 13]. Associations are emerging between components of fatigue and several factors including mental fatigue and cognitive (namely the domain of attention) [16, 17, 20, 35], physical and psychosocial domains [6, 7, 11, 32, 76]. However, these associations are dependent on the measurement strategies used [34, 35, 84]. In addition, the measurement strategies used for fatigue have been also inconsistent, making it difficult to synthesise the evidence. To reconcile for these inconsistencies, the evidence thus far has shown support for assessing two factors regarding fatigue: 1) the multi-dimensional traits of fatigue, 2) for diurnal/temporal variations involved in fatigue (in a similar manner to attention!).

1) Measuring the multi-dimensional aspects of fatigue: Trait fatigue

The primary approach to measuring fatigue is through subjective self-reporting, and a plethora of instruments have been developed to provide separate indices of the multi-dimensional 'traits' of fatigue, such as physical and mental components of fatigue. The results of the review (chapter 2) have shown how in all instances where a multi-dimensional fatigue scale was used (e.g., the FSMC), an association was found. However, Lagogianni et al (2018) state that such multi-dimensional scales are more likely to correlate significantly with the traits of fatigue, such as cognitive impairment, as they were developed with this aim and may reflect subjective cognitive complaints rather than fatigue [8]. The authors argue that a general fatigue scale (e.g., the FSS) would be more appropriate when assessing for a relationship with cognitive impairment. However, the use of a general fatigue measure (e.g. the FSS) did not find such associations in their research [8]. The authors acknowledge that this is likely due to the cognitive measure used (mostly the MMSE, a measure of general cognitive ability), rather than an investigation with specific cognitive domains. This is evident, as our review revealed significant associations between fatigue (using general fatigue scales, the FSS and VAS) and domain-specific cognitive processes without measuring the cognitive aspects of fatigue in seven studies that used this strategy (7/11 studies).

The Fatigue Severity Scale was the most frequently used fatigue scale in our review and others [8, 112, 113] when measuring for a relationship to cognition. As shown, results have been mixed and likely due either to the cognitive measures used (complex attentional paradigms versus the MMSE) or varying 'cut-off' values for the FSS (lower scores found associated only in our review). Furthermore, the FSS measures the degree to which fatigue impacts on

everyday life [114] rather than any multi-dimensional aspects. This may contribute to further ambiguity. Evidently, associations are present between fatigue and domain-specific cognitive processes irrespective of the fatigue scale applied. Moreover, in most instances where attention was assessed (in 9/9 studies), a relationship was found with fatigue. As it stands, using general fatigue scales (such as the FSS), it is therefore unclear as to what dimension of fatigue is relating to attention. The use of a multi-dimensional fatigue scale, such as the FSMC, may provide a more focused assessment of the subcomponents of fatigue under review, namely mental and physical fatigue in comparison to the FSS.

To identify the traits of the post-stroke experience of fatigue, many studies use a Likert self-rating scale for fatigue over a given period. However, self-reporting in measuring fatigue to date has correlated poorly with actual performance [8, 15, 20]. Using a multi-dimensional scale has shown to better capture various traits that describe the experience of fatigue such as the cognitive aspects [72, 115], minimising confounders known to be associated with response rates (e.g. difficulty with recall). Therefore, this thesis will assess various aspects of trait fatigue and how they relate to attention. The Fatigue Scale for Motor and Cognition (FSMC) will be utilised to do so, a multi-dimensional fatigue instrument dedicated to differentiating between motor and cognitive fatigue profiles. Other neurological studies [72, 115] revealed that sensitivity (the percentage of patients correctly diagnosed with stroke) and specificity (compared to the percentage of controls correctly classified as not having stroke) were highest for the FSMC in making these differentiations in comparison to other fatigue measures (e.g. the FSS).

2) Time frames, measuring the momentary experience of fatigue: State fatigue

Whilst multi-dimensional fatigue scales may assist with the dimensions of fatigue under review, it is well established that questionnaires are subject to mood and recall, especially as respondents recall their fatigue experiences over an extended period (often >1 week, as required on questionnaires). To reconcile for these confounds, an adjunct strategy is used to capture the momentary or 'state' experience of fatigue: using a VAS scale could greatly reduce demands on mood and indeed, cognitive processes (i.e. recall) [16, 17]. Repeated measurement of state fatigue during testing (such as pre/post activity) could be beneficial for describing the variability of fatigue, particularly within the context of the activity and the associated impact of the task on fatigue levels, as seen in other studies [16, 17, 34, 71, 72].

3.5 Proposed novel paradigm: Attention to fatigue

The relationship of sustained attention to fatigue levels after stroke has not been systematically assessed, and this may contribute to a better understanding of the mechanisms of mental fatigue. As such, a novel approach to investigate a relationship specifically between sustained attention and fatigue is proposed. Utilising the developed MCCPT paradigm (as detailed below) [104], to the thesis sets out to explore how the processes of sustaining attention over time, within the context of the activity, relates to fatigue as a state and trait. The following measures will be used.

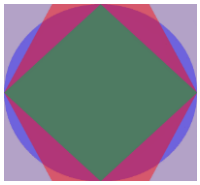
3.5.1 Measuring Sustained Attention: The Masked Conjunctive Continuous Performance Task

The Masked Conjunctive Continuous Performance Task (MCCPT) is a computerised behavioural paradigm which presents a purer measure of sustained attention in comparison to other studies [16, 20, 35]. There are three key features to this paradigm: 1) the use of a continuous presentation of a mask which is comprised of four superimposed shapes of different colours and is presented in the centre of the screen. The mask acts as a sensitive marker of alertness as it remains in a constant position and disappears only when a target or conjunctive distractor appears. This decreases the influence of a sudden alerting visual cue to draw in attention (e.g. a target appearing on a blank screen), delay on target discrimination and confound on memory; 2) the use of a conjunctive distractor that matches a feature of the target either by colour or shape, which will increase the demand on sustained attention to identify the target (as opposed to other distractors that don't match) and thus reduce the confounds on memory or inhibition response demands; 3) the use of this pre- and post-masking system between presentations of a target or distractor, which has the effect of increasing the variability on accuracy and thus, need to sustain attention [22, 104].

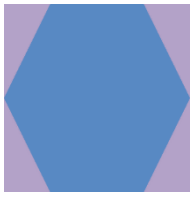
The MCCPT comprises four overlapping figures in different colours (square, triangle, circle and hexagon) which appear at the centre of the screen (fig. 3.3). Participants are asked to react as fast as possible by pressing the space bar on the laptop each time the target appeared. The target is a blue hexagon. The participants are instructed to do nothing when any other shape appeared. The target appeared randomly every 1000-5000ms to avoid habituation. To begin a short practice block (15 trials) was trialled, and the investigator observed subjects' response at this stage to ensure the instructions were clear. Next, the participants performed the whole session without any break until the task terminated after approximately 12 minutes. The task

was comprised of 200 trials (or 4 blocks). The target appeared on 60 trials. The task was generated using NBS presentation software (Neurobehavioral systems, Albany, CA), pre-loaded to guarantee minimal temporal noise. For a full description see Shalev et al, 2016 [22] and Shalev et al, 2018 [104].

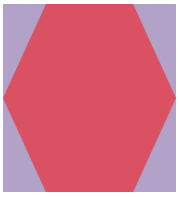
Figure 3.3 The three phases of the Masked Conjunctive Continuous Performance Task for sustained attention.



The MCCPT, constant mask



The MCCPT target



The MCCPT conjunctive distractor

3.5.2 Baseline measure of cognition

Post-stroke general baseline attentional abilities were assessed with the two subtests of executive attention from the Oxford Cognitive Screen (OCS): the Hearts Test, and the Trail Making Task (TMT) (see appendices 1 & 2 respectively). The OCS is a stroke-specific and domain-specific screen, and has demonstrated to be a more sensitive and inclusive cognitive screen for stroke [8, 94], in comparison to other short form cognitive screens, that are more designed to screen for dementia (e.g. the Montreal Cognitive Assessment, the MoCA) [37]. The OCS screening tool was designed to be inclusive for patients with aphasia, hemiplegia and neglect [94]. It is a paper-based task, which takes approximately 10 minutes to administer the full test (the subtest tasks each take approximately 3 minutes to administer).

3.5.3 Measuring fatigue: Trait and state fatigue

In an attempt to further understanding of the possible multi-dimensional facets of fatigue, the everyday 'traits' of fatigue were assessed at baseline (using the FSMC), and then the momentary or 'state' levels of fatigue pre/post the attentional task (using a VAS-f) and association with sustained attentional performance (see appendices 3 & 4 respectively).

3.5.4 Baseline measure of 'trait' fatigue

The FSMC comprises 20 statements (10 cognitive and 10 motor aspects) and participants were asked to rate their fatigue on a Likert scale ranging from 1 (Does not apply) to 5 (Applies

completely). Cut-off values are provided for mild, moderate and severe fatigue for both domains (cognitive and motor aspects), as well as a composite fatigue score.

3.5.5 Measure of momentary or 'State' fatigue

The VAS-f is a widely used measure used to capture momentary or 'state' fatigue [17, 73] in a given moment: Participants were asked to rate their experience of fatigue pre/post the attentional task on a 10 point Likert scale that ranged from 0 (not at all fatigued) to 10 (worst possible fatigue).

3.6 Discussion

Within the literature, the domain of attention is characterised as a multifaceted system [99], consisting of different types of attention that vary in complexity, and this is dependent on the demands of the task [97, 105]. The present chapter provides deeper insights into the competing demands on attentional processes: Attention exists along a continuum depending on internal top-down factors (such as higher-order cognitive processes/intrinsic motivation) and external bottom-up factors (such as environmental demands/testing conditions) and these processes work in tandem to facilitate goal-directed behaviour [97, 99]. Arguably, this interplay has not been fully considered within research when investigating for relationship to fatigue, particularly with all testing conducted within the laboratory setting. Evidently, sustaining attention over time is fatiguing (see chapter 2), it is of interest to understand how stroke survivors actually sustain their attention in real-world situations.

As such, an alternative approach to measuring the relationship between sustained attention and fatigue is now offered in comparison to other studies. First, a computerised behavioural paradigm proven to be more sensitive in measuring sustained attention over time in this population compared to other studies is used [16, 17, 34]. This is important as meta-analysis has shown (chapter 2) that participants experience fatigue irrespective of task complexity. Essentially, this paradigm minimises top-down demands on higher-order cognitive processes (e.g., memory and problem solving) and on motor control, which are likely encountered when using lengthy batteries of neuropsychological batteries of assessment, RT-based assessments or more generalised tests of cognition (e.g. MMSE). Indeed, the highly sensitive nature of the MCCPT, means the potential influence of the attentional load (i.e. sustained attentional performance) on mental and motor fatigability can be assessed in a relatively shorter timeframe (within 12 minutes) in comparison to other studies. Furthermore, this may provide useful

insights into the potential contextual factors that could trigger higher fatigue levels. Taken together, this paradigm reduces the testing session from being an overall fatiguing situation and may provide a better understanding of the attentional mechanisms relating to fatigue experienced in real-world settings. This measurement approach could potentially better determine the relationship of attention to fatigue and will be explored in the proceeding chapters.

Chapter 4 Understanding the relationship between sustained attention to mental and physical fatigue at the early phase (> 2 months) post stroke

4.1. Overview of Chapter 4

Up to this point, this thesis has undertaken a systematic and critical review of the evidence and theory base which extended across Acquired Brain Injury literature. Whilst previous literature [20, 35, 38] suggests that general attentional ability is associated with fatigue, chapter 3 provided compelling evidence to suggest that sustained attentional performance is associated with higher fatigue levels. However, to date this has not been performed using a focused task of sustained attention, without relying on measure reaction time. Using these insights, a measurement approach was proposed that potentially could be a more focused strategy to determine the extent of the relationship of sustained attention alongside established measures of attention to post-stroke mental fatigue and physical fatigue.

This chapter reports on a cross-sectional study investigating the relationship between sustained attention and fatigue early post-stroke. This study set out to determine the extent of the association between sustained attention and mental and physical fatigue in a sample of stroke survivors using a behavioural paradigm to measure sustained attention, as detailed in the previous chapter (chapter 3). Thirty-two adults (18 men) at the early phase (>2 months) post-stroke performed a continuous task of sustained attention (the MCCPT) where demands on memory, inhibition and motor control were minimised. Mutli-dimensional traits of fatigue were assessed before testing of motor and cognitive fatigue (using the FSMC) along with the momentary or 'state' level fatigue pre and post the attentional task (using a VAS-f). Testing was conducted with participants in their own homes. Linear regression was performed to examine the extent of relationships of attention to fatigue. Sustained attentional performance was found to be associated with both state and trait levels of fatigue, whereas no association was observed of inhibition or motor control to either fatigue constructs.

This study evidences the specific role played by sustained attention in relation to mental and physical fatigue post-stroke.

4.1.1 Research aims

We hypothesised that early after a stroke (> 2months), sustained attention would have a stronger relationship to trait or state fatigue than general attentional abilities. As such, the

current study had two main goals. First, to establish, at > 2 months post stroke, the extent to which sustained attention as compared to general attentional ability was associated with higher levels of mental and physical fatigue. The second goal was to determine if the domain specific function of sustaining attention measured throughout an attentional task was associated with higher mental and/or physical fatigue. Finally, to plan for a potential future trial to train attention in people with fatigue, this study set out to determine feasibility issues of recruitment rate and completion of measures within the community.

4.2 Methods

4.2.1 Study design

This study was a cross-sectional design and reported considering the Observational Studies in Epidemiology (STROBE) Statement [116] and was sponsored by Oxford Brookes University. This study was approved by the University Research Ethics Committee at Oxford Brookes University (see appendices 8 & 9, Participant Information Sheets). All testing was completed with participants in their own homes to reduce burden of travel on fatigue levels. Also, testing was completed between the hours of 10.00 – 14.00 to minimise diurnal variation in fatigue levels which can occur across the day. Demographic data was collected prior to baseline assessment of cognition and assessment procedures. The primary investigator (AD) led each session.

4.2.2 Participants and setting

Recruitment: Stroke survivors were identified at the early phase (> 2 months) post-stroke at the time of testing, and had joined an existing pool of stroke survivor research volunteers (OxRecovery Trial) at the Oxford Cognitive Neuropsychology Centre who had consented to be informed of future research opportunities (see appendices 8 & 9, Participant Information Sheets). *Ethics:* Consecutive individuals having consented to being contacted for research were screened by the lead researcher (AD) and recruited on completion of their rehabilitation in the Oxford University Hospital Early Supported Discharge Team (ESD). Participants were consented to this research study by research staff (AD) (see appendix 8, Participant Information Sheet). Given that this was a non-interventional study which carried minimal risk and allows the participant to withdraw at any time during the study, it was not envisaged that this study would raise significant issues. However, due to the intrusive nature of testing participants in their own homes, risk and risk management procedures were put in place for 1) the participant,

including adverse/unexpected outcomes, and 2) the researcher including adhering to lone working procedures.

4.2.3 Eligibility

Inclusion criteria: 1) Adults who were greater than two months post-stroke, 2) any stroke lesion, 3) any level of stroke severity, 4) sufficient functional ability to engage with the jigsaw task, and 5) had the capacity to complete the task. *Exclusion criteria:* 1) couldn't speak sufficient English to follow instructions, 2) insufficient capacity to provide informed consent were excluded. Participants were recruited between April-June 2021. Written informed consent was obtained from all the participants.

4.2.4 Testing order

Participants first completed all baseline measures: the Heart and Trails subtests from the Oxford Cognitive Screen [OCS], and the Fatigue Scale for Motor and Cognition FSMC fatigue questionnaire. Next, participants were invited to rank their fatigue levels on the VAS-f, and then complete the task of sustained attention on the Masked Conjunctive Continuous Performance Task (MCCPT). On completion, the participants were once again invited to rank their fatigue on the VAS-f. The participants were not informed of the experimental aim of the study.

4.2.5 Clinical outcome measures

Outcome measures found sensitive to detect change in previous post-stroke trials and validated in this population were utilised and included the following measures:

Functional ability: post-stroke functional ability was assessed using the modified Rankin scale (mRS) and the Barthel scale (see appendices 6 & 7).

*Baseline measure of cognition**:*** post-stroke general baseline attentional abilities were assessed with the two subtests of executive attention from the Oxford Cognitive Screen (OCS): the Hearts Test and the Trail Making Task (TMT). The OCS is a stroke-specific and domain-specific screen, and has been demonstrated to be a more sensitive and inclusive cognitive screen for stroke [94], in comparison to other short form cognitive screens that are designed more with a view to screening for dementia (e.g. the MOCA) [8, 37]. The OCS is a paper-based task, which takes approximately 10 minutes to administer the full test (the subtest tasks each take approximately 3 minutes to administer).

Task of Sustained Attention: The Masked Conjunctive Continuous Performance Task

The Masked Conjunctive Continuous Performance Task (MCCPT) is a computerised behavioural paradigm which presents a focused measure of sustained attention in comparison to other studies [16, 35, 84].

Baseline measure of 'trait' fatigue: Trait fatigue was assessed with the Fatigue Scale for Motor and Cognition (FSMC), a multi-dimensional fatigue instrument which has shown to better capture various cognitive or physical traits that describe the experience of fatigue [115].

Measure of momentary or 'state' fatigue: The Visual Analog Scale for fatigue (VAS-f) is a frequently used measure used to capture momentary or 'state' fatigue [17, 73] in a given moment: Participants were asked to rate their experience of fatigue pre/post the attentional task on a 10-point Likert scale that ranged from 0 (not at all fatigued) to 10 (worst possible fatigue).

4.2.6 Feasibility of recruitment and completion

Feasibility of recruiting participants from the ESD service was assessed from the numbers referred to this service, characteristics from medical records (obtained from the OxRecovery data set) and eligibility according to the inclusion/exclusion criteria outlined above.

Completion rates were determined by observing the ability to participate and complete of outcome measures throughout the assessment period.

4.2.7 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics software version 28.0 for Windows. Data completion was reported in full. Descriptive statistics were performed for demographics, fatigue and baseline cognitive scores and expressed as mean, standard deviation, while nominal data were described in frequencies (table 4.1). Linear regression statistics explored the unadjusted relationships between tests of attention (OCS Heart Test, OCS TMT), accuracy rates on the sustained attentional task (change in rate of omissions between first and last quarters of the CPT task) and fatigue (FSMC & VAS-f). Also, linear regression statistics were used to investigate the potential confounding variables of demand on inhibition (change in rate of commissions) and reaction time speed, between first and last quarters of the task. Regression (R^2) estimates of effect size were determined as: Minimum.04, Moderate.25, Strong .64 with 95% CI. For potential trends, we determined whether the study was adequately powered. To detect a medium effect of association an αlpha = 0.05 (2 tailed), and power of 0.9 was used. Scatter plots were initially used to identify extreme outliers or non-linear associations.

4.3 Results

4.3.1 Descriptive data

A total of 34 stroke survivors were initially recruited between April-June 2021, on completion of a home-based rehabilitation programme with the Oxford University Hospital Early Supportive Discharge Team. After losses (1 x stroke reoccurrence, 1 x withdrawn consent) 32 participated in this study (18 men and 14 women). Table 4.1 summarises relevant demographic and clinical information of the participants. The mean age was 67.2 years (SD 15; range 22-89 years) and most had had an infarction (97%). Available NIHSS scores (n=22) revealed mild/moderate stroke severity scores (mean 3.15, SD 1.5), 4 participants had received thrombolysis. All participants had either normal or corrected to normal eyesight. Functional ability was assessed using the modified Rankin scale (mRS) and the Barthel scale. Baseline cognitive scores and fatigue ratings are detailed in Table 4.2. (see appendices for indices of cognitive measures and fatigue scales).

Table 4.1 Demographics and clinical information.

Gender	Education	Ethnicity	Stroke type	Hemisphere	Stroke Classification	Duration since stroke	Functional ability
Male 18 Female 14	11.9 years (S.D 1.5)	White 32 Other 0	Ischaemic 31 Haemorrhagic 1 Missing 0	Left 12 Right 17 Bilateral 3 Missing 0	TACS 0 PACS 16 POCS 6 LACS 1 Missing 1	78 days (SD 26.4; range 61-118)	Barthel mean score: 18.31 (SD 3.1) mRS 2.24 (SD 0.75)

4.3.2 Feasibility for a future definitive trial

Recruitment rates: From initial recruitment, out of 150 people meeting inclusion criteria 34 agreed to participate in research over the period (23%). Of these, (n = 32/34, 94%) participated with only two cases of withdrawal, one due to stroke reoccurrence and one returned to work.

Completion rates: Completion rates for the four primary measures was high (OCS Hearts and TMT tests; Fatigue scales, the FSMC and VAS-f; MCCPT) (n=31/32, 97%), except for one participant (in the OCS Hearts subtest due to missing data). Most demographic variables were available with the exception of NIHSS scores from ten participants. Stroke classification was

not listed in one instance. Medical data was obtained from the OxRecovery data set as per consent.

Table 4.2 Baseline scores for executive attention, the OCS Heart and TMT task; Baseline trait fatigue scores, the Fatigue Scale for Motor and Cognition (FSMC); Pre and post momentary state fatigue scores, the VAS-f.

Baseline Cognition	OCS Hearts Test Executive Attention	%	Trail Making Executive Task			
	n = 31		n = 32			
Mean	47.4		0.4			
SD	5.7		2.5			
Impaired	n = 31	%	n = 32	%		
	2	6	3	9		
Trait Fatigue, FSMC scores	FSMC-C		FSMC-M		FSMC-S	
	n = 32		n = 32		n = 32	
Mean	24.4		27.4		51.3	
SD	9.5		11.7		20.9	
Impaired	n = 32	%	n = 32	%	n = 32	%
No fatigue	12	37	11	34.5	13	41
Mild fatigue	7	22	7	22	4	13
Moderate fatigue	8	25	3	9	3	9
Severe fatigue	5	16	11	34.5	12	37
State Fatigue, VAS-f scores	VAS-f Pre-Test		VAS-f Post-Test			
	n = 32		n = 32			
Mean	3.5		3.6			
SD	2.6		2.8			
Impaired	n = 32	%	n = 32	%		
No fatigue	7	22	8	25		
Mild fatigue	9	28	7	22		
Moderate fatigue	13	41	11	34		
Severe fatigue	3	9	6	19		

Abbreviations: n = number of participants completing each assessment; SD = standard deviation; FSMC = Fatigue scale for motor and cognition: FSMC –C (cognitive aspects), FSMC –M (motor aspects), FSMC-S (sum score).

4.3.3 Relationship between sustaining attention on an attentional task and higher mental fatigue

Table 4.3 shows linear regressions (R^2) used to determine the strength of the relationship between accuracy rates (number of omissions) on the MCCPT task and trait and state levels of fatigue. The results revealed a statistically significant relationship between sustaining attention on the MCCPT and trait fatigue: Accuracy & FSMC sum score (R^2=.141), Accuracy & FSMC cognitive score (R^2=.153), Accuracy & FSMC motor score (R^2=.152) (table 4.3). There was no relationship between accuracy rates and state fatigue as measured on the VAS-f before (R^2=.095) and after (R^2= .086) the task of sustained attention (table 4.3).

Table 4.3 Linear regression for analysis of relationship between Accuracy Rates (omissions) and variables of fatigue.

Variable – Trait fatigue	R^2	β co-efficient (95% CI)	*p*
FSMC – sum score	0.141	.640 (.113, 2.727)	0.034
FSMC – cognitive score	0.153	.392 (.083, 1.258)	0.027
FSMC – motor score	0.152	.390 (.100, 1.554)	0.027
Variable – State fatigue			
VAS pre-test scores	0.095	.307 (-.022, .312)	0.087
VAS post-test scores	0.086	.293 (-.032, .330)	0.103

Table 4.4 and 4.5 show an relationship remained present in respect of two possible confounding variables: 1) demands on inhibitory responses (commissions), as there was no relationship found between commissions & FSMC sum score (R^2=.007), commissions & FSMC cognitive score (R^2= .003), commissions & FSMC motor score (R^2= .007); and 2) Mean reaction time (RT) scores across the task: There was no relationship found between mean reaction time (RT) scores as calculated across the task (mean RT across 4 blocks): RT & FSMC sum score (R^2 = .035), RT & FSMC cognitive score (R^2 =.037), RT & FSMC motor score (R^2=.020). See tables 4.4 and 4.5 respectively.

However, a small trend is observed with reaction time speed and experience of state fatigue (R^2 0.107; p=0.068) as measured on the VAS-f on completion of the task of sustained attention (table 4.5).

Table 4.4 Linear regression for analysis of Inhibition (commissions) and variables of fatigue.			
Variable – Trait fatigue	R^2	β co-efficient (95% CI)	*p*
FSMC – sum score	0.007	.086 (-1.021, 1.637)	0.64
FSMC – cognitive score	0.003	.053 (-.517, .688)	0.774
FSMC – motor score	0.007	.081 (-.583, .907)	0.66
Variable – State fatigue			
VAS pre - test scores	0.003	.056 (-.141, .191)	0.76
VAS post - test scores	0.001	.033 (-.163, .195)	0.859

Table 4.5 Linear regression for analysis of Reaction time (mean RT across 4 blocks) and variables of fatigue.			
Variables- Trait fatigue	R^2	β co-efficient (95% CI)	*p*
FSMC – sum score	0.035	.187 (-.014, .043)	0.306
FSMC – cognitive score	0.037	.192 (-.006, .020)	0.293
FSMC – motor score	0.02	.142 (-.010, 0.22)	0.439
Variable – State fatigue			
VAS pre - test scores	0.085	.292 (-.001, .006)	0.105
VAS post - test scores	0.107	.327 (.000, .007)	0.068

4.3.4 Analysis of baseline factors and relationship to fatigue

1) Relationship between baseline cognitive abilities and higher levels of fatigue: OCS Heart test and fatigue measures

Table 4.6 shows there was no relationship between the OCS Heart Test of executive attention and trait fatigue (FSMC): OCS Heart Test & FSMC sum score (R^2=.001), OCS Heart Test & FSMC Cognitive score (R^2= 0.000), OCS Heart Test & FSMC motor score (R^2=0.001). There was no relationship with the OCS Heart test and state fatigue as measured on the VAS-f before (R^2= 0.023) testing (table 4.6).

Table 4.6 Linear regression for analysis of relationship between OCS Heart test and variables of fatigue.			
Variable – Trait fatigue	R^2	β co-efficient (95% CI)	*p*
FSMC – sum score	0.001	.023 (-1.317, 1.486)	0.903
FSMC – cognitive score	0.000	.001 (-.633, .636)	0.997
FSMC – motor score	0.001	.037 (-.707, .861)	0.842
Variable – State fatigue			
VAS pre – test scores	0.023	-.153 (-.244, .102)	0.41

2) OCS TMT test and fatigue measures

There was no relationship found with the OCS TMT test of executive attention and trait fatigue levels: OCS TMT & FSMC sum score (R^2=.001), OCS TMT & FSMC Cognitive score (R^2= .000), OCS TMT & FSMC motor score (R^2=.000). There was no statistical significance with the OCS TMT test and state fatigue as measured on the VAS-f before (R^2= .013) (table 4.7).

Table 4.7 Linear regression for analysis of relationship between OCS TMT test and variables of fatigue.			
Variable – Trait fatigue	R^2	β co-efficient (95% CI)	*p*
FSMC – sum score	0.001	.031 (-2.889, 3.404)	0.868
FSMC – cognitive score	0.000	.013 (-1.374, 1.476)	0.942
FSMC – motor score	0.000	.016 (-1.686, 1.841)	0.929
Variable – State fatigue			
VAS pre - test scores	0.013	-.113 (-.508, .271)	0.539

4.4 Discussion

The findings of this chapter are consistent with our study prediction that sustained attention would be most strongly associated with higher fatigue levels, whereas general attention such as executive would not be, and supports the need for further exploration of the hypothesis that sustained attention impacts on both mental and physical fatigue levels. Furthermore, the lack of a relationship with the other attentional processes of inhibition and motor control underlines the possible role played by this domain-specific function in both mental and physical fatigue.

Our measurement strategy proved to be sensitive enough to capture the potential contextual factors that trigger fatigue and simple enough to be carried out with stroke survivors in the sub-acute phase of recovery. These findings open the door for a number of novel approaches for management of post-stroke fatigue.

Our results highlight a significant relationship between sustained attention and higher fatigue levels. While these findings align somewhat with previous research [16, 17, 35], our results may be more robust and provide a clearer understanding of the attentional factors that do (and do not) trigger post-stroke fatigue in comparison to other studies [20, 35] [84], for a number of reasons. First, our study utilised a more specific measurement of sustained attention, which was found to be directly related to higher fatigue levels (as opposed to general attentional abilities). We found an relationship between sustained attention and higher fatigue levels using a novel behavioural paradigm approach to investigate this relationship. This paradigm included the use of the MCCPT, a measure shown to be a sensitive assessment tool of sustained attention in this population [104], as it minimises the top-down demands on sustained attention (see chapter 3 for a detailed explanation). Within neuropsychology literature, it is well established that the domain of attention is a complex and multifaceted system and measures used in previous trials [20, 35] often incur trade-offs between the sub-types of attention. As shown in chapter 2, Radman et al reported associations between specific aspects of attention (divided and sustained attention, phasic alertness) and fatigue, using measures involving several subtests across a battery of cognitive assessment (the TEA) [20]. We described how the relationships reported are non-specific (with correlation values not shown) as the subtests used assess several cognitive/attentional processes alongside sustained attention [20]. While the use of the domain-general subtests of attention in our study, the OCS Hearts and TMT, may be considered to be more focused assessments of attention [94], these assessments also require several cognitive processes such as memory and problem-solving ability (and may assist?) to complete them in addition to attention. The lack of a relationship in this instance, potentially, provides further support for the hypothesis and for the necessity to use domain-specific measures.

Next, we succeeded in investigating the relationship between sustained attention and fatigue without using a measure that relies on reaction time and inhibition. We operationalised sustained attention as a change in accuracy rates (omissions) over time, and minimised the demands on these confounding cognitive processes, considerations particularly pertinent in this population (see chapter 3 for a detailed explanation). Within the literature, Draheim et al (2022) describes the constant interplay between sustaining attention on the one hand, while inhibiting

inappropriate information or behaviour on the other [99]. Our task minimised demands on motor control and inhibition (with just 30% of stimuli being targets) and placed a greater demand on sustained attention. Potentially then, the lack of trade-off between these processes do not taint our results, though may account for interesting findings from other studies [17]. For example, Belmont et al (2009) reported an association using a similar strategy which included two factors: a continuous performance task (the Go/No Go) and the measurement of state fatigue pre- and post-testing [17]. However, this assessment (Go/No Go) requires several overlapping more general cognitive processing demands on the domain of attention, namely memory, inhibition, and motor control, together with a lengthy testing procedure (30 minutes). Conversely, Ashman et al (2008) noted that failure to find an association in their study using a similar assessment strategy was likely due to the use of an attentional subtest (the RVP subtest from the CANTAB) that overloaded the general cognitive processes of memory, inhibition and motor control and therefore less likely to be related to subjective fatigue [73].

This current study also contributes new insights into the feasibility of testing in a home environment. Within the context of this study which was conducted with participants in their own homes, a distraction from the environment could have acted as a cue to alert attentional networks causing attentional capturing in a 'bottom-up manner' [22]. Importantly, extensive research [99, 105] underscores the competing demands on attention that can stem from the context of the activity. In this instance, sustaining attention in the face of potential distraction was shown to be fatiguing. Furthermore, contextual factors such as noise cues could further explain the trend to make a relationship between reaction time and momentary fatigue on completion of the task. A further theoretical explanation of this trend could be that it is attributable to a potential overlap of the cognitive processes required for motor control, as poor sustained attention abilities has been associated with poor motor control in the literature [26]. In this environment, reacting or moreover inhibiting reaction, in the sense of inhibiting voluntary intentional movement may have placed a further burden on executive attentional processes, attributing to the higher fatigue experienced.

The relatively simple (and inherently mundane) design of the behavioural paradigm detected changes in sustained attentional performance in a considerably shorter duration of testing (12 minutes) in comparison to other studies with longer sessions [17, 73]. As shown in chapter 2, timeframe may not have been considered in certain studies: the higher fatigue levels found in other studies [73] may be owing to the lengthy duration of the testing procedure (Belmont et al: 30 mins) or diurnal variation (Ashman et al: 4.5 hours), rather than the domain specific

function *per se*. Within the short timeframe of this study, having to sustain attention was found to be significantly fatiguing and this finding supports the theoretical explanation offered by Mayo et al (2015), whereby PSF is characterized as an 'inability to sustain concentration and endure mental tasks' [13]. Contemporary theories characterise the dynamic fluctuations in both attention [22] and fatigue [7, 92] across the day. Potentially then, the lack of a relationship between the generalised assessments (OCS Hearts/TMT) and fatigue in this study also may be attributed to the short assessment involved in completion of these tests, i.e., 2 x 3-minute sessions, as these tests are not only non-domain-specific assessments (as described above), they also did not involve a fatiguing situation.

Our measurement paradigm also contributes further insights into the multi-dimensional facets of fatigue. First, when confounds of fatigue, such as recall and potentially mood, were minimised, (via use of a VAS-f scale) sustaining attention was found to be approaching significant fatigue levels in the moments following the completion of the task. This finding aligns with findings in a previous study which utilised a similar measurement strategy [16] and supports a theoretical explanation offered by Chadhuri and Behan (2004) of post-stroke fatigue as 'a failure to initiate and/or sustain attentional tasks and is experienced as mental fatigue'[14]. The elusive nature of fatigue is well documented across the literature, as the quest to clarify the meaning and experience of fatigue continues to challenge not only researchers and clinicians but also the individual [7]. The pre/post measurement design of fatigue used in this study (on the VAS-f scale) potentially then offers a promising strategy to capture a clearer understanding of the factors contributing to the experience of higher fatigue levels in a given moment. A second insight found, using the FSMC, was that significant associations exist between the multi-dimensional traits of fatigue under review, namely both cognitive and physical aspects of fatigue, and sustained attention. Hubacher et al (2012) also found associations using the FSMC, although given the use of a lengthy battery of assessments, again, these results arguably are also unclear [72]. Lagogianni et al (2018) suggested that the use of fatigue scales that consider traits of fatigue may reflect a relationship with a subjective domain complaint, and not with domain ability *per se* [8]. As our study revealed positive associations across both assessments of fatigue, our measurement strategy potentially reconciles the different approaches used across research for assessing fatigue, and in this way strengthens our findings.

This study was completed with good recruitment rates (94%) and outcome measure completion rates were high (97%), though full support with tablet set-up was required. Overall, these

findings provide support for this study design of testing within the community and could be replicated in future investigations. If we are to understand how stroke survivors actually sustain attention in real-world situations, the potential impact of the environment on fatigue levels needs exploration, for example by looking into phasic attention and its relationship to fatigue. Our results support the need for conducting further research in this area, and this study design could be replicated in a larger definitive trial.

The current research has its own limitations. We acknowledge that the participant sample was relatively small and unselected to make any specific subgroup analysis. We did not investigate nor compare any particular type or classification of stroke. For example, patients with total anterior infarcts (TACS) may have greater attentional deficit profiles compared to other stroke subtypes such as lacunar syndromes subtypes [119]. Also, just over half (53%) had right hemisphere damage, of which only four had either frontal or parietal lesions. This is important due to the established connection between this area of the brain and attentional processes [26]. A larger study may enable this. This study was operationalised to address the complex question of the relationship between attention and fatigue. While the results showed a relationship between sustained attention and fatigue, comparisons were not investigated, and the findings overall are weak. While this methodology may favour a reporting bias, this research underlines the complexity involved in fatigue and attention and could never explain all variance. In addition, this study was not statistically powered, and the perceived trend (or absence of a trend) should not be interpreted as an indication of an effect (or absence of an effect). However, we explored a sample size calculation for a future study; the overall effect remained positive (pre-test n= 94/post n=65). Generally, this participant cohort were relatively cognitively unimpaired. Admittedly, a larger sample would further enhance validation for this assessment strategy as not all stroke survivors would be able to endure a computerised task lasting 12 minutes.

The testing environment was both a strength and a limitation. Potential interference or distraction caused from the home environment (e.g. noise) may have affected attentional processes and skewed results and findings should be interpreted with caution. However, findings from this context offer promising insights into the demands on sustained attention in everyday situations and the potential subsequent impact on fatigue levels. Previous chapters have shown evidence for the potential to train attention immediately after stroke (see chapters 1 and 3). The potential effect of altering attentional focus on fatigue in the home environment, by using earphones during attentional tasks for example, warrants further investigation.

4.5 Conclusion

This study observed novel insights into the role played by sustained attention in the development of fatigue at the early phase post-stroke. Within a very short timeframe, participants found that having to sustain attention, was both mentally and physically fatiguing. Furthermore, having to sustain attentional performance may have placed a further burden on executive attentional processes, with an increase in the experience of fatigue in the given moment. The findings indicate the potential for early rehabilitation with a strategy targeting sustained attention post-stroke, and the potential impact of the environment on fatigue levels needs serious consideration. The findings support the case for a further investigation of the mechanisms of attention, and illustrate how novel intervention strategies for attention, such as altering attention (e.g. by use of earphones) have the potential to improve management of this distressing post-stroke symptom.

Chapter 5 Jigsaws and Earphones. Among people with stroke engaging in a task requiring sustained attention, to what extent does the use of noise-cancelling earphones impact on mental fatigue?

5.1 Overview of Chapter 5

Chapter 4 has provided evidence for a relationship between sustained attention and fatigue amongst 32 participants early after stroke when completing a task of sustained attention in the home environment (chapter 4). These results highlight important aspects to consider. First, it demonstrated the potential role played by sustained attention specifically in the development of both mental and physical fatigue. Next, the results offer insights into the development of mental fatigue in a given moment, as participants experienced higher fatigue levels on completion of the attentional task. These findings highlight the complex and multi-faceted systems involved in the domain of attention, as the overlapping cognitive processes required for motor control were potentially burdened as sustaining attentional performance within a short timeframe was experienced as fatiguing. Furthermore, the relationships found may have been triggered from this testing environment (i.e. participants' own homes). Within this context the research has shown how 1) it is feasible to investigate the domain of attention within the home, and 2) sustaining attention on a task, resulted in higher fatigue for the stroke survivor.

As our environment is constantly changing over time, it is essential to remain vigilant, or sustain attention, to detect these changes and react accordingly [104]. Neuropsychology literature outlines two distinct temporal processes involved in remaining vigilant over time, namely 'sustained attention', which is defined as the ability to focus on an activity or stimulus over a long period of time (e.g. 1hr); and 'phasic alertness', which relates to a momentary capturing of the attentional network following an abrupt external cue (e.g. a sudden noise). The impact of contextual factors on these processes, such as background noise is unclear and further research is now warranted.

The recommended provision of ICSS therapy is usually within the home environment and consists of sessions lasting up to 45 minutes as tolerated [39]. Difficulties engaging attentional processes over a prolonged period (such as 45 minutes) may result in previously effortless activities of daily living that require sustained attention to become fatiguing, and subsequently, may result in sub-optimal task performance. However, specific knowledge of the influence of background noise (such as in the home) on attentional abilities after stroke is lacking.

The literature has shown the potential for immediate effects of training attention post-stroke [46, 47, 49]. As such, early identification of risk factors is crucial for recovery, so targeting

participants at the early phase post-stroke (>2 months) is essential. Indeed, the domain of attention has been demonstrated to be related to mental fatigue in part [16, 17, 20, 35] and could offer an intervention strategy that could assist with managing PSF.

To this end, we propose a novel approach to investigate how domain-specific functions of attention (i.e., phasic versus sustained attention) may be related to the experience of fatigue early after stroke. In addition, we will argue for the potential effect of the impact of altering attentional focus early after stroke on fatigue and task performance in the community and home environment, by use of a simple general attention altering strategy – noise-cancelling earphones.

This chapter presents a novel intervention feasibility study that investigated the extent of the impact of altering attentional focus on both fatigue levels and subsequent task performance at the early phase post-stroke. This study set out to determine whether either abrupt cues (i.e. background noise to alerting attentional mechanisms) or sustaining attention with minimal cues (i.e. reduced noise input with noise-cancelling earphones) while doing an attentional task impacted on fatigue levels and performance. A sample of 29 stroke survivors (15 men) at the early phase (>2 months) post-stroke performed two continuous tasks of sustained attention.

The feasibility trial demonstrated how investigating the impact of altering attentional focus (with noise-cancelling earphones) is feasible, acceptable and safe. Overall, the predetermined trial parameters were met: the trial design, a cross-over repeated exposure randomised evaluation, was found to be feasible and safe to deliver within the community, and the intervention was delivered according to pre-specified markers of fidelity.

The findings of this research confirm that when background noise is reduced, sustaining attention without noise cues to alert the attentional network system, is fatiguing. Altering attention over a shorter period of time by use of noise-cancelling earphones placed greater demands on sustained attentional processes. Indeed, the lack of (abrupt) noise cues over a prolonged period, 45 minutes in this instance, resulted in improved performance and higher experiences of fatigue. Performance in meaningful tasks that require sustained attention can be improved when wearing earphones, but at a cost of feeling more fatigued.

5.1.1 Research aims

This study hypothesised that early after a stroke (>2 months), sustaining attention with background noise over a prolonged period of time would not be associated with higher fatigue

and general attentional capabilities, whereas sustaining attention with minimal noise cues would impact fatigue and performance.

This study had three goals: To estimate at >2 months post stroke, to what impact of the use of noise-cancelling earphones during tasks of sustained attention, on 1) on mental and physical fatigue, and 2) performance of the attentional tasks. Two attentional tasks were used, 1) a jigsaw puzzle, used to represent a meaningful everyday attentional task, and 2) a continuous performance task (as described in chapter 3). Finally, this study aimed to inform the feasibility for the design and delivery of the evidence base for conducting a larger definitive trial that could potentially determine the effectiveness of noise cancelling earphones to manage fatigue in the community setting. We aimed to evaluate key trial parameters of recruitment and completion rates of outcome measures. Acceptability of the intervention to participants, which included markers of fidelity and utility, was evaluated. Feasibility of scheduling and costs accrued were outlined.

5.2 Methods

5.2.1 Study design

A cross-over repeated exposure randomised design was used. For this, a simple 1 of 2 exposure sequence crossover design was utilised, and participants were randomly allocated according to their sequential entry into the study. In this way, each participant acted as his or her own control. In addition, some of the known disadvantages of the crossover design (e.g. a potential learning effect) were not expected in this study: Study participants were randomised to do an everyday task of sustained attention, followed by a reaction time-based assessment on a tablet, first with and then without earphones or first without and then with earphones. Study duration for each participant was three weeks which entailed two study visits. Each visit typically lasted 1 hour. The two assessment sessions were carried out one week apart to allow for a washout period to minimise the potential for a learning effect. In addition, a different attention task (i.e. a different jigsaw used at each session) at either session.

Study design and reporting was completed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) and extension to randomised crossover trials [117]. The trial protocol was registered in May 2021 on the Clincialtrials.gov Registry (Protocol Record 201376) and no changes were made to the methods after trial commencement. This study was approved by the University Research Ethics Committee at Oxford Brookes University (see appendices 8 & 9, Participant Information Sheets).

5.2.2 Participants and Recruitment

The recruitment procedure and ethical considerations (see section 4.2.2) for this study was the same as the previous study (chapter 4): stroke survivors were identified at the early phase (> 2 months) post-stroke at the time of testing, had joined an existing pool of stroke survivor research volunteers at the Oxford Cognitive Neuropsychology Centre (as part of the OxRecovery Trial), and been referred to the Oxford University Hospital Early Supported Discharge Team (OUH ESD) (see appendices 8 & 9, Participant Information Sheets). Next, the lead researcher (AD) screened consecutive patients referred to this (ESD) service who were part of the volunteer pool and were then recruited on completion of their rehabilitation (approx. 6 weeks post-stroke). Given that the nature of this study which carried minimal risk and allows the participant to withdraw at any time during the study, it was not envisaged that this study would raise significant issues. However, due to the intrusive nature of testing participants in their own homes, risk and risk management procedures were put in place for 1) the participant, including adverse/unexpected outcomes, and 2) the researcher including adhering to lone working procedures. Participants were recruited between April-June 2021 and were deemed eligible for meeting the following criteria.

5.2.3 Eligibility

Inclusion criteria: 1) Adults who were greater than two months post-stroke, 2) any stroke lesion, 3) any level of stroke severity, 4) sufficient functional ability to engage with the jigsaw task, and 5) had the capacity to complete the task. *Exclusion criteria:* 1) could not speak sufficient English to follow instruction, 2) insufficient capacity to provide informed consent were excluded. Written informed consent was obtained from all the participants by research staff (AD).

5.2.4 Randomisation

Following screening, participants were provided with a sequential number at point of entry (AD). The study number was entered into a computer-generated allocation schedule by the Trial Manager (HD) which randomly assigned the intervention schedule to participants. Participants were assigned 1:1 to either of the following test sequences: first with and then without earphones or first without and then with earphones. The Trial Manager informed AD who allocated participants to the sequence. After a 1-week washout, participants crossed over to the other group.

5.2.5 Setting and location

The OUH ESD Team extends its service across Oxfordshire which includes ethnically and socially diverse populations. All data was collected with each participant in their own homes, between the hours of 10.00-14.00 in most cases. The primary investigator (AD) led each session.

5.2.6 Intervention

This trial was designed to understand how stroke survivors sustain attention in real-world situations, particularly how attentional mechanisms and contexts interact at the sub-acute phase of recovery. Post-stroke therapy sessions with ICSS team are usually within the home environment, with sessions lasting 45minutes as tolerated. As such, the testing design is now described.

As allocated, participants completed the attentional tasks first with and then without earphones or first without and then with earphones. Single-use, light weight and easy to fit (using one hand) earphones* were supplied to participants. These self-adjusting foam earplugs expand in the ear upon insertion to create a secure seal for hearing protection in busy environments; single number rating is 35 dB; noise reduction rating is 32. They are ideal for smaller and larger ears, providing optimal fit and ear protection for smaller ears, but low-pressure Polyurethane foam expands to fit virtually any size ear and ear canal. They are vibrant yellow and magenta colour is highly visible from a distance to help ensure safety. To negate for potential motor-control issues, over-head earphones were also made available, and support was offered with fitting as required. Participants were instructed to wear the earphones throughout the testing session, from the first attentional task (the jigsaw puzzle) through to completion of the second task (the MCCPT). The first task required participants to assemble a jigsaw puzzle over a 45-minute period, to resemble a standard post-stroke rehabilitation session (NICE guidelines: 45 minutes or as tolerated) [39]. Rest breaks were offered as required. A different jigsaw was completed in each session to minimise the potential of a learning effect. As each participant acts as their own control, varying experience of jigsaw construction is not focused upon in this study. Rather, the potential effect of altering attention and subsequent change in performance will be observed (see section 5.2.11 for statistical analysis).

The second task was completion of a reaction time-based assessment on a tablet, the Masked Conjunctive Continuous Performance Task (MCCPT), a highly sensitive computerised behavioural paradigm used to measure sustained attention. The participants performed this session without any break until the task terminated at approximately 12 minutes. Overall,

participants were invited to rate their fatigue levels three times on a VAS-f: First at baseline and then again after participation in each attentional task, the jigsaw puzzle (45 minutes completion time allocated) and then the reaction time based MCCPT test (12 minutes approx.). A podcast was played in the background during each round to ensure the same continuous stream of noise for each participant. This podcast** was chosen to represent everyday hum-drum within the home context - background conversation and light music. In general, the podcast consisted of an interview between the host and guest speaker, with a different interview played at either testing session. The podcast was played for the duration of the testing session, at the same consistent low frequency for all and included general conversation and the programmes' music jingle.

* *The Howard Leight Laser Lite* earplugs were used in this study. The non-irritating, non-allergenic self-adjusting foam recovers to fit virtually any ear canal. These ear plugs have a 32 dB Noise Reduction Rating (NRR 32 dB).

** The '*People, just people'* Podcast was utilised in this study.

5.2.7 Outcome Measures

The outcome measures used in this study were found to be sensitive to detect change in previous post-stroke trials and validated in this population (see chapter 3 for a detailed description) and included the following:

Clinical outcome measures

Functional ability: The Barthel scale and modified Rankin Scale (mRS).

Baseline measure of cognition: two subtests of executive attention from the Oxford Cognitive Screen (OCS): the Hearts Test, and the Trail Making Task (TMT).

Baseline 'Trait' fatigue: The Fatigue Scale for Motor and Cognition (FSMC), a multi-dimensional fatigue instrument which describes the various cognitive or physical traits of fatigue post-stroke.

Measure of momentary or 'state' fatigue: The Visual Analogue Scale for fatigue (VAS-f), a 10-point Likert scale that ranged from 0 (not at all fatigued) to 10 (worst possible fatigue), was used to capture fatigue in a given moment.

Measures for sustained attention

Jigsaw puzzles: Performance was measured by counting the number of appropriately fitted puzzle pieces within the allotted timeframe of 45 minutes.

The Masked Conjunctive Continuous Performance Task: The MCCPT is a reaction-time based assessment, set-up on a tablet. It comprises of four overlapping figures in different colours (square, triangle, circle and hexagon) which appeared at the centre of the screen (see chapter 3 for a detailed description). Participants were asked to react as fast as possible by pressing the space bar on the laptop each time the target appeared. The target was a blue hexagon.

The temporal processes involved in attention over time will be measured in terms of two distinct timeframes: 1) sustained attention was assessed based on changes in performance over time (difference in accuracy rates (omissions) between first and last quarters of the MCCPT task); 2) phasic alertness was measured based on ability to inhibit reaction over the course of the trial (commissions), as false alarms are considered to be indices of lapses in inhibitory control over time in CPT tasks. We hypothesized that over the course of the trial, a lack of abrupt noise-cueing (i.e., using earphones) will increase the demand on the inhibitory mechanisms and result in a pattern of increased commissions compared to standard cues. The task will be completed twice (once with, once without earphones) over the two assessment days.

5.2.8 Summary of testing procedure

Participants first completed all baseline measures: the Hearts and the Trail Making Task subtests from the Oxford Cognitive Screen (OCS); functional abilities (The Barthel scale and modified Rankin Scale (mRS); Fatigue Scale for Motor and Cognition (FSMC). Next, participants were invited to rank their fatigue levels on the Visual Analog Scale for fatigue (VAS-f), and then complete the task of sustained attention (a jigsaw puzzle) over 45 minutes. On completion, the participants were once again invited to rank their fatigue on the VAS-f. Next, participants completed the reaction time based MCCPT test (12 minutes approx.). On completion, the participants were once again invited to rank their fatigue on the VAS-f.

5.2.9 Sample size

As this was a feasibility study, a prospective sample size calculation was not conducted. Instead, we aimed to recruit 30 stroke participants from one site (Early Service Discharge Team for Stroke, Oxford) over 3 months, which appeared realistic given the team's referral rates of approximately 50 patients per month, i.e., 150 patients during this recruitment period. Additionally, 30 participants would allow for a central limit theorem (i.e. allowing samples' means to be normally distributed) and, assessment of feasibility factors [118].

5.2.10 Key feasibility parameters

We aimed to evaluate key trial parameters including recruitment, utility, fidelity and completion rates of outcome measures. Feasibility of recruiting participants from this service was assessed from the numbers referred to this service, characteristics from medical records and eligibility according to the inclusion/exclusion criteria as outlined above. The completion of the six clinical outcome measures for this trial were used to determine feasibility for a substantive RCT. Feasibility of scheduling and cost of testing delivery will be evaluated.

5.2.11 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics software version 28.0 for Windows. Analyses were based on the intention-to-treat (ITT) principle with all randomised participants being included according to the sequence they were allocated to.

Primary feasibility outcomes were descriptive and performed for clinical demographics, fatigue and baseline cognitive scores, and markers of feasibility were all expressed as mean, standard deviation, and described in frequencies (see tables 5.1-5.3, figure 5.2).

Statistical testing for secondary outcomes were completed as follows. A one-way repeated measures ANOVA was conducted to explore the unadjusted relationships between the tasks of attention, the jigsaw puzzle and the MCCPT and fatigue (pre/post VAS-f scores). Next, a paired sample *t*-test was conducted to investigate the effect of wearing earphones on performance while doing these attentional tasks. Repeated measures ANOVA were then completed on demand over time on 1) inhibition (change in rate of commissions in the first quarter/ first and fourth quarters of the MCCPT task), 2) motor control (change in reaction time speed in the first/first and fourth quarters of the MCCPT task), and 3) testing order, with and without earphones. Scatter plots were initially used to identify extreme outliers or non-linear associations.

5.3 Results

5.3.1 Primary outcomes: Demographic data

The demographic and clinical characteristics of participants are presented in Table 5.1. The mean age was 67 years (SD 15.6; range 22-89 years) and most had had an infarction (97%). Available NIHSS scores (n=19) revealed mild/moderate stroke severity scores (mean 2.9, SD 1.6), 4 participants had received thrombolysis. All participants had normal/corrected to normal eyesight. Detailed information on fatigue scores and cognitive scores are shown in Table 5.2.

Table 5.1 Demographics and clinical information.

Gender	Education	Ethnicity	Stroke type	Hemisphere	Stroke Classification	Duration since stroke	Functional ability
Male 15 Female 14	11.7 years (SD 1.3)	White 29 Other 0	Ischaemic 28 Haemorrhagic 1 Missing 0	Left 10 Right 15 Bilateral 3 Missing 1	TACS 0 PACS 15 POCS 8 LACS 5 Missing 1	79 days (SD 29.2; range 61-118)	Barthel mean score: 17.90 (SD 3.6) mRS 2.28 (SD 0.75)

Table 5.2 Baseline scores for executive attention (OCS Hearts and TMT) and fatigue.

Abbreviations: n = number of participants completing each assessment; SD = standard deviation; FSMC = Fatigue scale for motor and cognition: FSMC –C (cognitive aspects), FSMC –M (motor aspects), FSMC-S (sum score).

Baseline Cognition	OCS Hearts Test Executive Attention	%	Trail Making Executive Task			
	n = 28		n = 29			
Mean	47.2		0.3			
SD	5.9		2.1			
	n = 29	%	n = 29	%		
Impaired	2	7	2	7		
Trait Fatigue, FSMC scores	FSMC-C		FSMC-M		FSMC-S	
	n = 29		n = 29		n = 29	
Mean	25.2		27.6		52.2	
SD	9.6		11.7		21.1	
	n = 29	%	n = 29	%	n = 32	%
No fatigue	10	34	9	31	11	38
Mild fatigue	7	24	6	21	4	14
Moderate fatigue	6	21	3	10	2	7
Severe fatigue	6	21	11	38	12	41
State Fatigue, VAS-f scores	VAS-f Pre-Test		VAS-f Post-Test			
	n = 29		n = 29			
Mean	3.4		4.3			
SD	2.6		2.5			
	n = 29	%	n = 29	%		
No fatigue	5	17	3	10		
Mild fatigue	9	31	8	28		
Moderate fatigue	12	41	12	41		
Severe fatigue	3	10	6	21		

5.3.2 Primary Feasibility Outcomes

Figure 5.1 shows a relatively even distribution of participants (15/14) and men to women (8/7), between sequences. The 29 participants (15 men) were randomised, with no data missing from initial losses (not tested) and the outcomes were as follows:

Recruitment rates*:* From initial recruitment 32/150 agreed to participate in this trial (21%). Of these, 29/32 agreed to participate giving a 91% retention rate. Three participants withdrew prior randomisation due to 1 x stroke reoccurrence, 2 x withdrawn consent. A study number had been assigned at their point of entry to this study, however sequential ordering remained unchanged.

Utility and fidelity of acceptability of the intervention: The feasibility of utility and fidelity of acceptability are presented in Table 5.3. All participants adhered to the wearing of the noise-cancelling earphones throughout the assessment process with most reporting no issue with fitting (100%) or burden with wearing (97%) the earphones. Two reported that placing anything in their ears as uncomfortable. There were no issues regarding set-up of the jigsaw (97%). Full support with the MCCPT software set-up was required (97%), and the initial trial practice was reported as highly beneficial by most participants (90%). Overall, the assessment process was deemed acceptable: Completion of the jigsaw was reported as enjoyable (97%), with the exception of one participant, and participants tolerated 45minutes of participation in this task. Participants found the twelve-minute computerised test of attention tolerable (59%) (Albeit inherently boring in some instances), with no reports of burden indicated. There were no adverse events reported.

Completion rates*:* Completion rates for all measures was high (Barthel, mRS (100%), OCS Hearts (97%) and TMT tests, (100%) the VAS-f (100%), the Jigsaw puzzle, and the MCCPT (100%)), with the exception of missing data for one participant (in the OCS Hearts subtest only). Most clinical demographic variables were available with the exception of NIHSS scores with missing data for ten participants (66%). Stroke classification was not listed in one instance (97%).

Feasibility of scheduling and cost of testing delivery: All testing was completed with participants in their own homes to reduce burden of travel on fatigue levels. Testing sessions was conducted between the hours of 10.00-14.00 to minimise diurnal variation in fatigue levels which can occur across the day [7]. Costs were minimal and generated with fuel prices accrued by the primary investigator (AD), purchase of the Presentation Software package (platform for the MCCPT) and the jigsaws. Participant flow can be found in fig.5.1.

Figure 5.1 Consolidated Standards of Reporting Trials (CONSORT) Flow Diagram.

CONSORT Flow Diagram

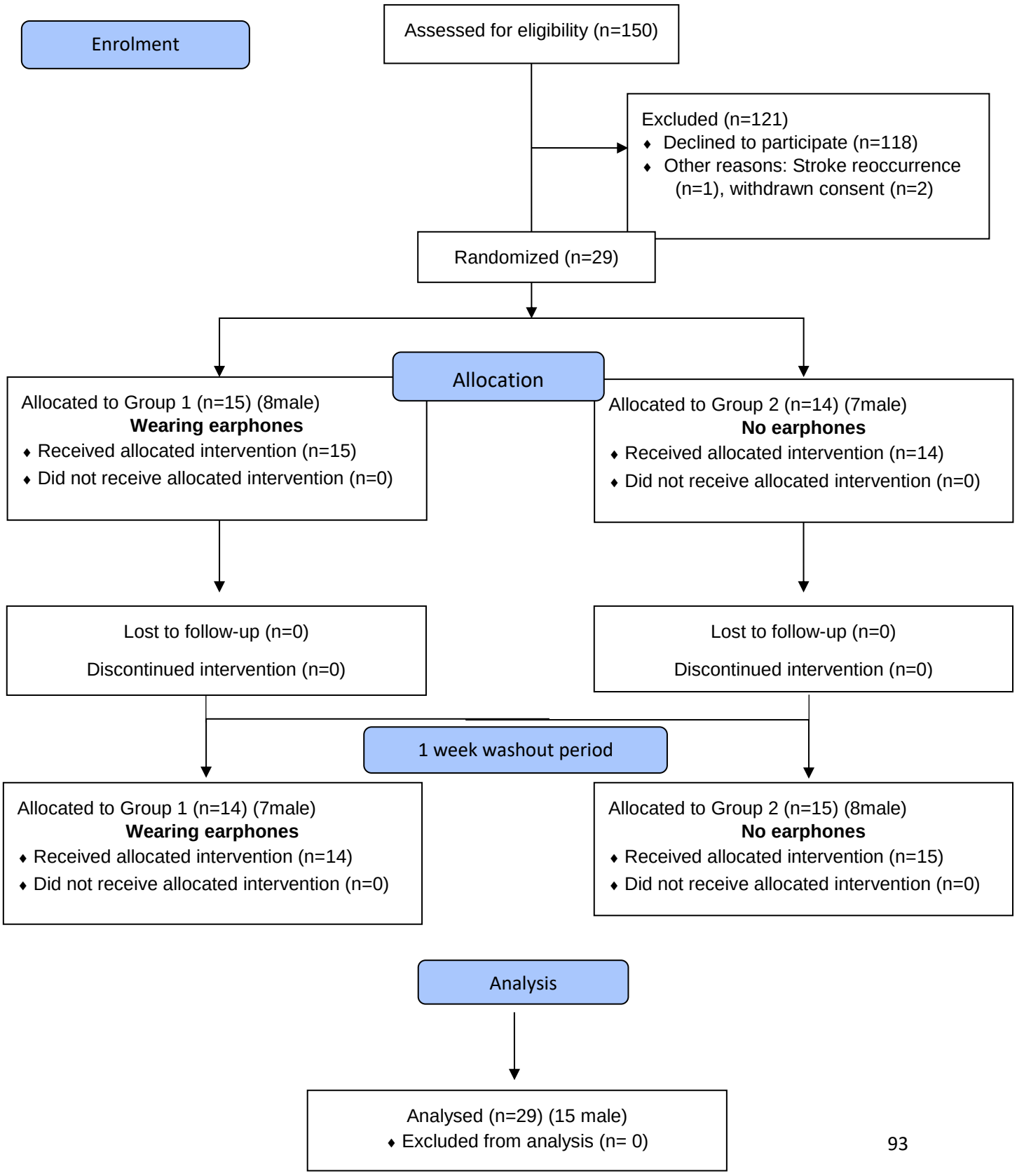


Table 5.3 Feasibility markers of fidelity and utility for the intervention.

Earphones survey results, n = 29	With Earphones	Without Earphones
Feasibility of fidelity:		
1. Do you feel you could concentrate on the jigsaw? Y N	Y - 29 (100 %)	Y – 26 (90%) N – 3 (10%)
2. Do you feel you could concentrate on the MCCPT? Y N	Y – 17 (59%) N – 12 (41%)	Y – 14 (48%) N – 15 (52%)
3. Did you find the background noise (PODCASTS) distracting? Y N	Y - 5 (17%) N – 24 (83%)	Y – 12 (41%) N – 17 (59%)
4. Did you find the background noise irritated you? Y N	Y – 4 (14%) N – 25 (86%)	Y – 9 (31%) N – 20 (69%)
5. Do you feel fatigued? Y N	Y -23 (79%) N – 6 (21%)	Y – 22 (76%) N – 7 (24%)
6. How would you describe your fatigue? Mental Physical Mixture of all Doesn't apply to me (NA)	Mental – 19 (66%) Physical – 3 (10%) Mixture – 4 (18%) NA- 3 (10%)	Mental – 15 (52%) Physical – 6 (21%) Mixture – 6 (21%) NA – 2 (6%)
7. Did you find the earphones comfortable? Y N	Yes – 27 (93%) N - 2	NA
8. Would you rather wear earphones when doing tasks that require your attention? Y N	Y – 19 (66%) N – 10	
Feasibility of utility: task set-up and level of enjoyment		
9. Do you require assistance with fitting of the earphones Y N	Y – 0 N - 29 (100%)	
10. Do you require assistance with set-up of the Jigsaw Y N	Y - 1 N – 28 (97%)	
11. Do you require assistance with set-up of the computer task? Y N	Y – 28 (97%) N - 1	
12. Do you require the trial practice of the computer task? Y N	Y – 26 (90%) N - 3	
13. Did you enjoy making the Jigsaw? Y N Tolerable	Y – 28 (97%) N – 1 Tolerable – 0	
14. Did you enjoy the computer task? Y N Tolerable	Y – 4 (14%) N – 8 (27%) Tolerable – 17 (59%)	

5.3.3 Descriptive results: Fatigue across the testing procedure

Fatigue mean scores, as measured on the VAS-f, are similar between stroke subjects in either group (no earphones M = 3.45, SD 2.6; with earphones M = 3.76, SD 2.2) at the start of testing. On average fatigue levels were higher on completion of the testing period (no earphones M = 4.3, SD 2.5; with earphones M = 5.6, SD 2.7) but this did not reach statistical significance (p=0.1; η^2 0.04).

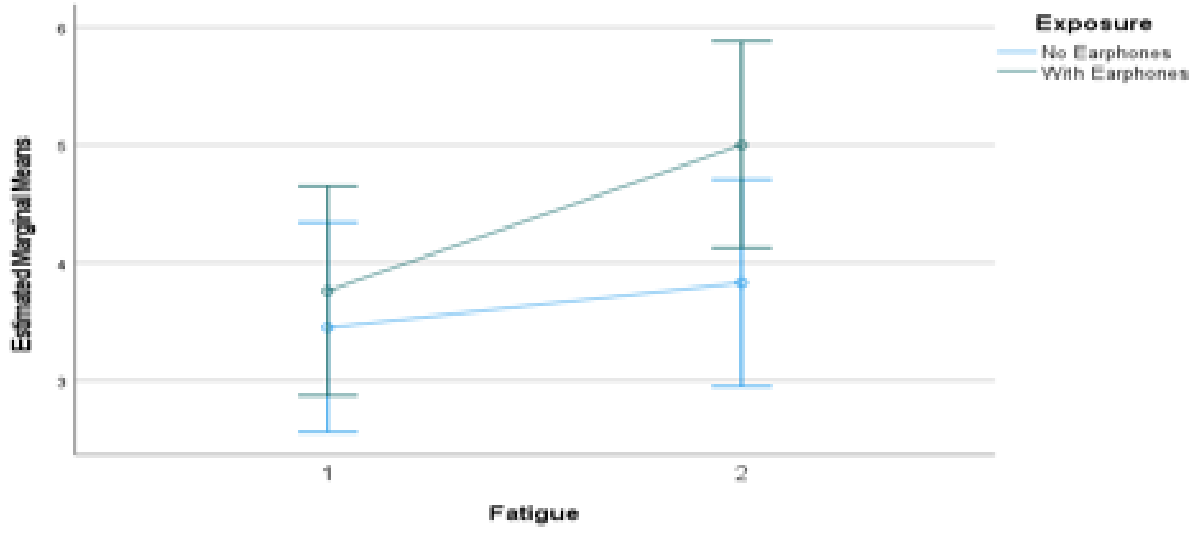
5.3.4 Secondary outcomes

A) An everyday task of sustained attention: A Jigsaw puzzle

- The impact of using noise-cancelling earphones on *fatigue* (pre/post VAS scores) whilst doing a general task of sustained attention (jigsaw)

On completion of the task (45 minutes), participants had statistically significant higher fatigue levels when wearing earphones (M = 5.0, SD 2.4) (F (1, 56) = 7.006, p =.011), than those without earphones (M =3.83, SD 2.331), (p<.001) (fig 5.2).

Figure 5.2 Jigsaw and fatigue levels. Estimated marginal means scores on the VAS-f: Participants using noise-cancelling earphones experienced significant higher fatigue levels (VAS-f scale) on completion of the jigsaw (45 minutes).



Error bars: 95% CI

Dependent Variable: Within-subject Factors Pre-VAS (1) & Post-VAS (2) scores.

- The impact of using noise-cancelling earphones on Jigsaw *performance*

On average, participants performed better with earphones (M = 61.0 jigsaw pieces, SD =35.5) than participants without earphones (M = 48.5 jigsaw pieces, SD = 31.0) (Table 5.4). This improvement, -12.6, 95% CI [-7.1, -4.7] was statistically significant, t (28) = - 4.7, p = <.001 (table 5.5).

Table 5.4 Jigsaw performance, paired sample *t*-tests, between subject factors.

	No earphones	With earphones	Diff	*p*
Jigsaw performance (number of pieces)	48.5 ±31.0	61.0 ±35.5	-12.6 (95% CI -18.0: -7.1)	<.001

Mean ± SD, Diff = mean difference (95% Confidence Intervals).

Table 5.5 Jigsaw performance scores with (R1) and without (R0) earphones, paired sample correlations coefficients.

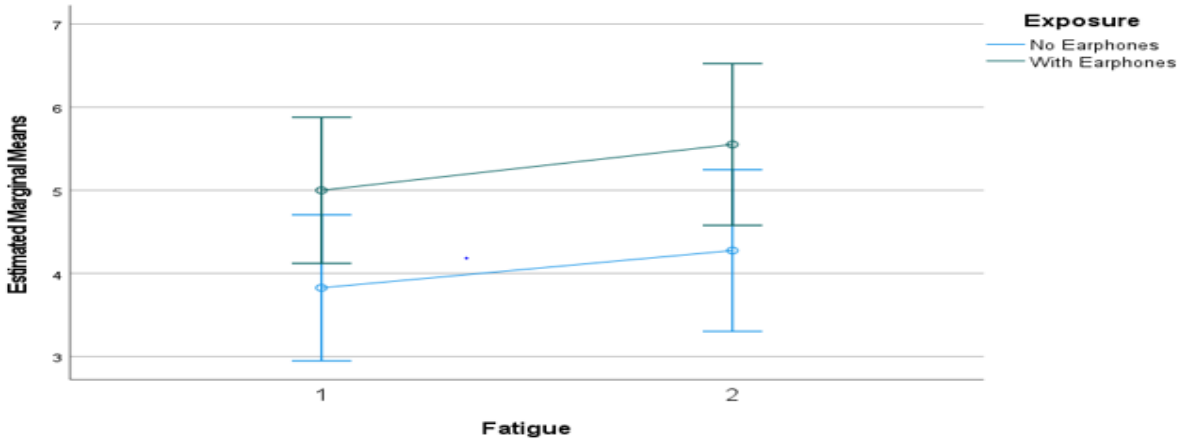
	N	Correlation	*p*
Jigsaw R0 & Jigsaw R1	29	.916	<.001

B) A purer task of sustained attention: The MCCPT

- The impact of using noise-cancelling earphones on *fatigue* (pre/post VAS scores) during the sustained attention task, the MCCPT

Over this sustained attention task (12mins), an increase in fatigue levels was observed in both groups, however there was no significant effect observed at completion of this particular task with high variance observed. (F (1, 56) = .215, p = .644) (fig. 5.3)

Figure 5.3 MCCPT and fatigue. Estimated marginal means scores on the VAS-f: Participants using noise-cancelling earphones did not experience higher fatigue levels (VAS-f scale) whilst doing a shorter task of sustained attention (12 minutes).



Error bars: 95% CI

Dependent Variable: Within-subject Factors Pre-VAS (1) & Post-VAS (2) scores.

- The impact of noise-cancelling earphones on *performance* (omissions) during the MCCPT

On average, participants performed similarly with earphones (1.38, SD = 4.1) to those without earphones (M = 1.59, SD = 4.12) during the MCCPT task (table 5.6) with no .21, 95% CI [-1.57, 1.98] statistically significant difference, *t* (28) = -.24, *p* = .81 (table 5.7).

Table 5.6 MCCPT performance with (R1) and without (R0) earphones, paired sample *t*-tests.

	No earphones	With earphones	Diff	*p*
MCCPT performance (Omissions)	1.59 ±4.12	1.38 ±4.1	0.21 (95% CI -1.57, 1.98)	0.81

Mean ± SD, Diff = mean difference (95% Confidence Intervals).

Table 5.7 MCCPT performance scores with (R1) and without (R0) earphones, paired sample correlation coefficients.

	N	Correlation	*p*
Jigsaw R0 & Jigsaw R1	29	.352	0.061

Abbreviations: R0 = no earphones, R1 = with earphones

C) Post-stroke exploratory factors: Inhibition and motor control during the MCCPT

- *Inhibition: Differences between groups during the **1st quarter** of MCCPT*

There was a small difference in rates of inhibition between subjects with earphones (M = 8.55, SD 7.7) and subjects without earphones (M = 9.8, SD = 7.5) but this did not reach statistical significance: *t* (56) = .62, *p*= .54, (table 5.8).

Table 5.8 MCCPT and demand on inhibition (number of commissions in the first quarter): Independent sample *t*-tests of rate.

	No earphones	With earphones	Diff	*p*
MCCPT Inhibition (number of commissions	9.8 ± 7.5	8.6 ±7.7	1.24 (95% CI -2.77: 5.25)	0.54

Mean ± SD, Diff = mean difference (95% Confidence Intervals).

- *Inhibition: change over time **(1st-4th Quarters)***

Over the duration of the test, subjects made more commissions when using earphones (M = -0.6, SD 2.8) compared to when not using them (M = -2.1, SD = 4.4), but this did not reach statistical significance *t* (56) = -1.61, *p* = .11 (tables 5.9).

Table 5.9 MCCPT and demand on inhibition (number of commissions over the course of the test), Independent sample *t*-tests of rate.

	No earphones	With earphones	Diff	*p*
MCCPT Inhibition (number of commissions)	-2.1 ± 4.4	-0.6 ±2.8	-1.55 (95% CI -3.49: 0.39)	0.11

Mean ± SD, Diff = mean difference (95% Confidence Intervals)

- *Motor control: Differences between groups during the **1st quarter** of MCCPT*

In the short-term, there was no significant difference in motor control between subjects with (M = 462.76, SD 193.370) and without earphones (M = 434.29; SD 194.22); *t* (56) = .559, *p* = .58 (table 5.10).

Table 5.10 MCCPT and demand on motor control (Reaction time in the first quarter), Independent sample t-tests.

	No earphones	With earphones	Diff	*p*
MCCPT Motor Control (Reaction time, Block 1)	434.3 ± 194.2	462.8 ± 193.4	-28.47 (95% CI -130.42: 73.48)	0.58

Mean ± SD, Diff = mean difference (95% Confidence Intervals).

- *Motor control: change over time **(1st-4th Quarters)***

Over the duration of the assessment there was no significant difference in motor control between subjects with (M = 486.98, SD 183.63) or without earphones (M = 452.91; SD 178.44); *t* (56) = -.716, *p* = .5 (table 5.11).

Table 5.11 MCCPT and demand on motor control (change in reaction time over the course of the test): Independent sample *t*-tests of rate.

	No earphones	With earphones	Diff	*p*
MCCPT Motor Control (Reaction time, Block 4-1)	452.9 ± 178.4	487.0 ± 183.6	-34.1 (95% CI -129.3: 61.2)	0.5

Mean ± SD, Diff = mean difference (95% Confidence Intervals).

5.3.5 Testing Order and Effect size

Table 5.12 shows how there was no significant difference regarding testing order in either round.

Table 5.12 Testing order

	Round 1	Round 2	*p*
Testing order	52.8 ± 32.2	56.7 ± 35.4	0.66

5.4 Discussion

This is the first study to test the extent of the impact of altering attentional focus (with noise-cancelling earphones) on both fatigue levels and performance at the early phase post-stroke within the community setting. Overall, the predetermined trial parameters were met: the trial design, a cross-over repeated exposure randomised evaluation, was found to be feasible and safe to deliver within the community. In total, 91% of participants from initial recruitment completed testing with no adverse events. The intervention was delivered according to pre-specified markers of fidelity with high rates of completion across the testing session (100%), the outcome measures (97%) and all participants found this simple everyday device to be useful (100%) when doing tasks that required sustained attention. The study set up also revealed that altering attentional focus had potential to alter fatigue and performance. The results of this investigation contribute novel insights that may help pave the way for prevention strategies towards effective management of post stroke mental (and physical) fatigue.

This study has demonstrated how, through wearing noise-cancelling earphones, known competing external demands on attentional resources [97, 99, 105] (see chapter 3) can be altered to assist attentional focus. In doing so however, the highly sensitive MCCPT test has shown that this increased focus appears to place greater demands on attentional processes involved in executive motor functioning processes i.e. inhibition [26] within a short timeframe (> 12 minutes). This finding aligns with previous research [28]. As discussed in chapter 1, Parr et al (2019) describe how voluntary intentional movement requires executive motor functioning to anticipate, predict, produce and correct actions [28]. In response to cerebral damage, the authors highlight the critical importance of the Prefrontal Cortex (PFC) in motor regulation during tasks requiring executive control, visual guidance, and sustained attention [28, 31]. Furthermore, emerging evidence suggests that increased PFC activity is a likely compensatory mechanism and enables task performance to be maintained [28]. Potentially then, subtle sustained attentional deficits may have been camouflaged when cues were not received from orientating mechanisms of any kind. Hence, this may have begun to manifest in the form of increased demand on executive motor processes within a short timeframe.

Over the longer term (45 minutes), altering attention paid dividends with significant improvement shown in performance on the jigsaw. However, when demands on sustained attentional processes were increased through wearing earphones, the lack of noise cues to alert the attentional network over this period came at a cost as participants had significantly higher experiences of fatigue. The cognitive processes involved in the construction of a jigsaw (or

attentional tasks in general) are quite intuitive: for instance, problem solving and memory, amongst others. Within a noisy context, these cognitive processes (and possibly heightened PFC activity), may have assisted in a 'top down' manner to ease attentional load on this domain [98, 99, 102], though overtime resulted in sub-optimal performance.

Potentially then, these findings underline specific interactions between contextual factors and attentional mechanisms on fatigue, as the lack of attentional capturing in a 'bottom-up manner' [104, 105] in this instance was fatiguing. Additionally, these results may contribute novel insights into the multi-dimensional facets of fatigue and present a clearer link between attentional mechanisms and the manifestations of both mental and physical fatigue post-stroke. Distinctions as previously noted by Chadhuri and Behan (2004) (in chapter 1) "as a failure to…sustain attentional tasks (mental fatigue) and physical activities (physical fatigue)…and is experienced without any peripheral motor impairment" [14].

Overall recruitment rates were greater than 20% and the rate of retention (< 10% attrition) exceeded expectations. The high adherence across trial parameters also reflects the fidelity of acceptability of the intervention to participants. This willingness to participate is likely owing to the trial design, with all testing conducted within the home so minimising the burden of travel and likely associated fatigue for the participant. In addition, participants were not unduly burdened by the study requirements: they found no issue in all instances with fitting (100%) or wearing the earphones (97%) for the duration of the testing session or issue with set-up and construction of the jigsaw (97%). The requirement for repeated instruction on the use of the tablet-based task may be owing to the novelty of the task and general motivation, or lack of, to complete this assessment. It also highlights the lack of a learning effect, which can occur in this type of study design.

The trial was designed to understand real-world behaviour and performance. As such, the design set out to investigate how attentional mechanisms and contexts interact within the home environment and employed a number of strategies to do so. First, the relatively short assessment procedure (> 1hour all in, conducted between 10am-2pm) reduced the testing procedure from being a fatiguing situation compared to longer-duration testing procedures used in other studies which typically include the use of full neuropsychological testing batteries of assessments or longer testing days [38, 73, 84]. The jigsaw puzzle, used to represent an everyday attentional task, allows for an understanding of competing demands on attentional resources over the longer term. Second, the use of more focused attentional measures and

measurement strategy allows for the analysis of attention sub-types (e.g., sustained attention) and changes over time. The shorter task, the MCCPT, was designed to enable specific analysis of sustained attention which compares favourably to other measures that involve trade-offs between other cognitive processes to complete the task (e.g., memory) [20, 38]. Importantly, this trial demonstrated the feasibility of capturing the demands on attentional resources that occur in the face of real-world distraction (i.e., home setting) over various timeframes. The ability to participate and focus on attentional tasks throughout the allocated time of <45 minutes is promising for rehabilitation and research, and insights into which certain conditions are fatiguing could enhance intervention options.

A limitation of this study is that our sample of post-stroke survivors were relatively high-functioning and cognitively unimpaired which may account for the relative ease of delivering this intervention. We must be mindful that post-stroke survivors, particularly at the early phase, may not be able to perform a CPT task lasting 12 minutes [22]. A larger, more heterogeneous sample across multiple sites would produce more generalizable outcomes. Another limitation is that this study is underpowered to make firm conclusions and findings should be interpreted with this in mind. Nevertheless, a sufficiently powered sample size would determine a medium effect size (the power calculation specified n-32: an αlpha = 0.05, effect size 0.34, power 0.95) and further strengthen these findings. The potential for a learning effect was avoided, as no difference was observed with regard to testing order. To this end, initial findings of this trial have the potential to advance a theory that could inform future research design towards the understanding of how attentional mechanisms and context interact in this group of patients. Preliminary findings provide the following insights which have promising implications for both research and clinical purposes:

- Altering attention by increasing focus through wearing headphones appears to place greater demands on sustained attentional processes in the short term, >12 minutes in this instance, by potentially increasing commissions but without increasing other factors.
- Sustaining attention without prompts (i.e., background noise to help alert attentional network systems), results in higher experiences of fatigue over a prolonged period such as the duration of a standard rehabilitation session (45 minutes) although performance was greater.
- Consideration of context is most important when conducting research and rehabilitation.

- A simple, easy to use and affordable device, such as noise-cancelling earphones, could be used as a potential strategy for self-management of fatigue and improve attentional performance for stroke survivors once discharged.

5.5 Conclusion

This feasibility trial has demonstrated how investigating the impact of altering attentional focus (with noise-cancelling earphones) is feasible, acceptable, and safe within the community. Whilst cognitive tasks led to increased fatigue, altering contextual noise led to better performance but at a higher cost in terms of fatigue. The findings indicate that a future, multicentre study could be replicated with this trial design, which would add to the generalisability of the findings in this population. The initial findings are promising for both research and clinical practice with potential implications for furthering knowledge of who is at risk of developing symptoms of mental fatigue. Additionally, it may shed a light on possible prevention strategies, and provide guidance to those affected by mental fatigue post-stroke. A larger definitive trial is now warranted.

Chapter 6 General discussion and conclusion

6.1 Thesis summary

The primary aim of this thesis is to provide a better understanding of the relationship between attention and fatigue, in order to inform the development of a complex occupation-focused intervention support system as a strategy to manage post-stroke mental fatigue. Health-related interventions are complex. As such, a pragmatic approach was required in order to understand the extent of the inter-relationship between the individual, the activity and environmental factors. To this end, this thesis used a multi-dimensional framework approach drawn from empirical research [12, 58, 60] and MRC guidelines [52, 56] to conceptualise this inter-relationship and assist with the development of a complex intervention. Within these frameworks, the following objectives of this investigation were identified.

Objective 1: To gain insights into the extent of the relationship between any cognitive impairment and fatigue after Acquired Brain Injury (ABI), including stroke.
Objective 2: To develop an in-depth understanding of the existing theory base within the field of attention research, and subsequently develop a measurement strategy based on all insights gained.
Objective 3: To gain insights into the use of a novel measurement strategy to investigate a relationship between sustained attention, mental fatigue and physical fatigue within the context of daily living.
Objective 4: To develop an in-depth understanding of the potential effectiveness of a complex occupation-focused support system, as a strategy for managing post-stroke mental fatigue within the community.

All four objectives were achieved, and the results of this research represent an original contribution to the post-stroke fatigue (PSF) knowledge base. Novel insights were arrived at into the relationship between sustained attention, the traits of fatigue (mental fatigue and physical fatigue) and the factors contributing to higher experiences of fatigue in a given moment. This chapter now presents a summary of the main findings of this research including the limitations of this research and of the potential implications for clinical practice and proposes a direction for future research.

6.2 Summary of main findings

6.2.1 Findings from the existing literature: the theory base

An initial scope of the literature has shown how post-stroke fatigue (PSF) is a highly distressing and persistent symptom for the stroke survivor. It is a complex and multi-dimensional symptom [7] with little consensus on how to define it within research or clinical practice. This complexity has likely led to inconsistencies in how PSF is measured, and to the lack of intervention strategies to manage it. What is promising is how PSF research is rapidly developing with a growing potential for the understanding and measurement of fatigue, and for the development of targeted post-stroke mental fatigue interventions. Emerging evidence supports the contention that certain domains of cognition (i.e. attention), which is a potential modifiable factor, may be related to mental fatigue as well as physical performance and physical fatigue. Furthermore, theoretical frameworks highlight the inter-relationship between the individual and the activity and underline the importance of relevant contextual dimensions when developing a complex intervention.

The systematic review underlined the disparity across measurement strategies and highlighted significant gaps within this field of research. Increasingly, studies have been dedicated to quantifying and understanding, in a more precise way, the mental and physical dimensions of fatigue. Promising results stemmed from meta-analysis, which has shown how studies that challenged attentional resources (via RT-based assessment), had more robust relationships with higher fatigue levels [17, 34, 35, 72, 90]. An in-depth review of the existing theory base suggested further important considerations when measuring this relationship and provides the basis for arguing that the domain of attention is a key factor in the development of fatigue. Those considerations are set out below.

First, the theory base underlines how attention is a complex and multi-faceted system [22, 97, 99-102, 105]. There are several sub-types of attention and the type used is dependent on the demands of the activity [97]. The theory has shown how attention is a core domain within a hierarchy of cognition [98] (see chapter 3), and any changes at this level may affect overall higher-level cognitive abilities, such as memory, executive function and learning [99-101]. The use of neuropsychological assessment batteries and complex behavioural paradigms (reaction time-based assessments) require several cognitive processes alongside attentional processes and this may place demands on attention to complete the assessment and result in trade-offs between certain cognitive processes, making it difficult to interpret results. Furthermore, the

involvement of other cognitive processes in a top-down manner may camouflage subtle deficits within this core domain [20, 38, 71, 72, 84, 88-90]. Potentially then, in studies where mainly attentional resources were challenged, the top-down cognitive processes (such as memory) compensate or disguise the challenge on this core domain.

Second, competing external demands on attention stem from the context of the activity, as even a mere sound from the environment provides cues, in a bottom-up manner, to the attentional networking systems keeping us alert [105]. Taking a multi-dimensional view of the theory [52, 58, 60, 78], an understanding of the inter-relationship between the ability to sustain attention in the face of this distraction, and in particular inhibit inappropriate behaviour, may better describe how stroke survivors sustain their attention in real-world situations. An investigation from this viewpoint may also describe more precisely the interaction between fatigue levels and subsequent activity performance within this context [58]. Additionally, it is well established within the neuroscience literature that attentional dysfunction significantly overlaps and exacerbates changes in physical ability [26]. Without specification or indeed appropriate measurement, the potential impact of sustained attentional effort on executive attentional, motor control, and self-perceived state and traits of fatigue remains vague. Despite these insights, the impact of contextual factors, such as background noise, on attentional control has not been fully considered within research.

Third, attention has its own dynamic fluctuations over time [74, 92], which in turn are influenced by the interplay between the demands of the activity and contextual factors (i.e. noise). The evidence suggests that sustaining attention over a certain period of time (>12 minutes) is fatiguing and it occurs irrespective of task complexity (see meta-analysis). If we are to understand the extent of the role played by these competing demands on the ability to sustain attention, an investigation of the temporal aspects involved in the domain of attention is required.

6.2.2 Findings following Investigation: the evidence base

This research offers novel insights into the role played by sustained attention in the development of fatigue at the early phase post-stroke. The results confirm that when the top down demands from higher-order cognitive processes are minimised, the specific attentional process of sustained attention resulted in significantly higher fatigue experiences in a relatively short time-frame (<12 minutes). This initial finding supports the theory that a hierarchical

process [98] is involved in cognition: as the core domain of attention was challenged (or exposed?), the extra burden on sustained attentional effort resulted in significantly higher levels of fatigue. This hypothesis is further strengthened by the finding that general attentional ability did not result in higher fatigue levels.

The findings also support previous research wherein attentional dysfunction has been shown to overlap with motor ability post-stroke [26]. The results provide insights into the potential attentional processes involved in executive motor control, which otherwise may have remained undetected by less sensitive measurement strategies [17, 35]. That is, the finding that motor control was trending towards a relationship with fatigue may have been due to the burden on the attentional control process of inhibition, which is more exposed in this testing environment. There are two speculative explanations for this. The first lies with the design of the measurement strategy which intentionally reduced the element of fatigue from the task in that the task was completed in one sitting, the MCCPT was configured to have a limited number of targets requiring physically reactions (compared to other measures such as the Go/No Go where targets can be at least double that) and it had a relatively shorter testing session of 12 minutes in comparison to other studies (e.g. 2 x 30 minutes [17]). The second possible explanation is that the assessment was completed in the home environment where domain-specific operations (i.e., attentional control) may have been more challenged, as opposed to a quiet laboratory setting used in other studies. That is, within this context, the humdrum sounds from each home such as a ringing doorbell or mobile phone may have provided sufficient noise cues to keep the attentional networks alert. As noted in chapter 4, reacting or inhibiting reaction, in the sense of inhibiting voluntary intentional movement, may have placed a further burden on executive attentional processes, attributing to the higher levels of fatigue experienced.

Engaging sustained attentional resources over a longer period is required for most everyday activities. One can imagine how important it is to sustain attention after a stroke for tasks such as organising a dossett box or preparing a meal. The results have shown how sustained attentional effort and focus is challenging in this population and demands greater mental effort for optimal performance. Within a short time, demands on inhibitory mechanisms were evident. Over a prolonged period, 45 minutes in this instance, the benefits of sustained focus (assisted by use of the earphones) had pay-offs, with significant improvement in the overall performance in the task, but at a cost of feeling more fatigued.

In summary, an initial broad scope approach was undertaken for this research which lends itself to extensive investigations of the literature (as opposed to stroke alone) [20, 36, 72, 83, 87, 89, 90] to support the evidence for the development of a novel measurement strategy that is more focused on measuring the sub-types of attention compared to other studies [20, 38, 71, 90]. Furthermore, the use of two fatigue measures (for state and trait fatigue) reconciled for confounds known to affect the measurement of fatigue, including memory and mood [7, 33]. This enabled a better understanding of the variability of fatigue, particularly within the context of the activity. The findings of this thesis underline specific interactions between contextual factors and attentional mechanisms on fatigue, as the lack of attention capturing in a 'bottom-up manner' [104, 105] in this instance was fatiguing. Defining the experience of fatigue continues to challenge not only researchers and clinicians but also the individual [7]. These results contribute additional insights into the multi-dimensional facets of fatigue and present a clearer link between attentional mechanisms and the manifestations of both mental and physical fatigue post-stroke. The pre/post measurement design of fatigue used in this study (on the VAS-f scale) offers a promising strategy to capture a clearer understanding of the factors contributing to the experience of higher fatigue levels in a given moment.

6.3 Key limitations of this thesis

The specific limitations of each study have been reported in individual chapters. However, there are some overall key limitations of this thesis that should be considered in addition to those and are now presented.

This research was operationalised to understand how certain mechanisms of attention were related to fatigue post-stroke. This methodology may favour a reporting bias, as for example the systematic review has shown how other cognitive processes were also associated with fatigue. However, this research has proven that attention is a core domain within a hierarchy of cognition and underlines the importance of its function in real-world settings. The results underline the importance of including contextual factors (i.e. noise in this instance), particularly when addressing fatigue and exploring optimal performance. It must also be noted that causality cannot be determined on the basis of these findings, as all studies were cross-sectional. RCTs with a more heterogeneous cohort (e.g. greater variability regarding fatigue levels/cognitive abilities) would allow for more generalisability. Indeed, for more generalisability, this should include a sample of participants with greater heterogeneity, such

as greater variability in fatigue levels or cognitive ability. A multi-site design could facilitate this.

Capturing the role of domain-specific functions in real-world settings is challenging, particularly given the constant distraction within the context of a task and the demands on other cognitive processes. Nevertheless, this research has shown how it is feasible and safe to assess attentional mechanisms within the context of an activity, and the study designs could be replicated in the community.

6.4 Potential implications for research, practice and the direction of future research

This thesis makes important contributions towards the greater understanding of the mechanisms mediating mental fatigue at the early phase post-stroke. This research underlines the complex aetiology involved in the domain of attention, with evidence for the specific role played by sustained attention in the development of both mental and physical fatigue post-stroke. Whilst the findings of this Thesis are provisional, preliminary results provide evidence that could be the used as the stepping-stones towards measurement and managing this distressing post-stroke symptom. The potential implications for the direction of future research, and for clinical practice include:

- Management of cognitive (attentional) dysfunction may improve fatigue and participation in meaningful activities after stroke, traumatic brain injury or subarachnoid haemorrhage.
- An intervention for attention could potentially improve the efficiency of performing everyday physical and mental activities and so reduce fatigue early after stroke.
- Reducing the cognitive load during everyday activities (e.g., grading the burden on attentional resources) may potentially be effective in managing post-ABI fatigue.
- Assessing the competing demands stem from the cognitive demands of the task on the one hand, and the impact of a noisy environment on the other. Consideration of the inter-relationship between the individual, activity and environmental factors when working with participants is required.
- An intervention to improve attention, a modifiable factor early after stroke, as a potential therapeutic approach for reducing post-stroke fatigue has been demonstrated. Participants found 45 minutes of participation in a meaningful activity tolerable, albeit fatiguing in certain conditions.

- A support system (such as noise-cancelling earphones) could be a simple and effective strategy for self-management of PSF.
- Agreement on core measures could facilitate integration of findings into clinical practice. This could be achieved by using a multi-dimensional approach that captures the traits of fatigue, and fatigue within the context of the activity. More robust (cognitive) domain-specific investigations that include the assessment of core cognitive domains may provide a clearer understanding of the cognitive aspects challenging participants.

6.5 Conclusion

This research has demonstrated how investigating the impact of altering attentional focus (with noise-cancelling earphones) is feasible and the design of these studies as described in chapter 4 and 5 could be replicated within the community. A central consideration when working with participants is the inter-relationship between the individual, the activity and environmental factors. This could potentially provide a greater understanding of how mechanisms and context interact, along with further evidence that could be applied in other contexts. As such we propose a larger definitive trial to investigate the impact of attentional training early after stroke, and of the feasibility of providing this training in the community and home environment and of the feasibility of implementing a support system within the ICSS.

This research represents an original contribution to the evidence base for post-stroke mental fatigue. In addition, the findings of this feasibility trial could shed a light on possible prevention strategies and provide self-management guidelines to those affected by mental fatigue.

References

1. National Institute for Health and Care Excellence. *NICE Impact Stroke*. 2019 2 December 2022]; Available from: https://www.nhsresearchscotland.org.uk/uploads/tinymce/NICE-Impact-stroke.pdf.
2. Lakshminarayan, K., et al., *Trends in 10-year survival of patients with stroke hospitalized between 1980 and 2000: the Minnesota stroke survey.* Stroke, 2014. **45**(9): p. 2575-81.
3. Kutlubaev, M.A., F.H. Duncan, and G.E. Mead, *Biological correlates of post-stroke fatigue: a systematic review.* Acta Neurol Scand, 2012. **125**(4): p. 219-27.
4. Stroke Association. *Fatigue and tiredness*. 2022 2 December 2022]; Available from: https://www.stroke.org.uk/effects-of-stroke/tiredness-and-fatigue.
5. Crichton, S.L., et al., *Patient outcomes up to 15 years after stroke: survival, disability, quality of life, cognition and mental health.* J Neurol Neurosurg Psychiatry, 2016. **87**(10): p. 1091-8.
6. Hinkle, J.L., et al., *Poststroke Fatigue: Emerging Evidence and Approaches to Management: A Scientific Statement for Healthcare Professionals From the American Heart Association.* Stroke, 2017. **48**(7): p. e159-e170.
7. DeLuca, J., *Fatigue as a window to the brain*. Issues in clinical and cognitive neuropsychology. 2005, Cambridge, Mass.: MIT Press. xx, 336 p.
8. Lagogianni, C., S. Thomas, and N. Lincoln, *Examining the relationship between fatigue and cognition after stroke: A systematic review.* Neuropsychological Rehabilitation, 2018. **28**(1): p. 57-116.
9. Glader, E.L., B. Stegmayr, and K. Asplund, *Poststroke fatigue: a 2-year follow-up study of stroke patients in Sweden.* Stroke, 2002. **33**(5): p. 1327-33.
10. Alliance, J.L. *Stroke Rehabilitation and long-term Care. Top 10 Priorities.* . 2022 11th November 2022]; Available from: https://www.jla.nihr.ac.uk/priority-setting-partnerships/stroke/stroke-rehabilitation-and-long-term-care-top-10-priorities.htm.
11. Kuppuswamy, A., et al., *Post-stroke fatigue: a deficit in corticomotor excitability?* 2015. **138**(1): p. 136-148.
12. De Vries, J., et al., *Fatigue in neuromuscular disorders: focus on Guillain–Barré syndrome and Pompe disease.* 2010. **67**: p. 701-713.
13. Mayo, N.E. and R. International Society for Quality of Life, *Dictionary of quality of life and health outcomes measurement*. First edition. ed. 2015, Milwaukee, WI: International Society for Quality of Life Research (ISOQOL).
14. Chaudhuri, A. and P.O. Behan, *Fatigue in neurological disorders.* Lancet, 2004. **363**(9413): p. 978-88.
15. Johansson, B., H. Bjuhr, and L. Rönnbäck, *Mindfulness-based stress reduction (MBSR) improves long-term mental fatigue after stroke or traumatic brain injury.* Brain Injury, 2012. **26**(13/14): p. 1621-1628.
16. Azouvi, P., et al., *Divided attention and mental effort after severe traumatic brain injury.* Neuropsychologia, 2004. **42**(9): p. 1260-8.
17. Belmont, A., N. Agar, and P. Azouvi, *Subjective fatigue, mental effort, and attention deficits after severe traumatic brain injury.* Neurorehabilitation & Neural Repair, 2009. **23**(9): p. 939-944.
18. Jonasson, A., et al., *Mental fatigue and impaired cognitive function after an acquired brain injury.* Brain and behavior, 2018. **8**(8): p. e01056.

19. Maaijwee, N.A., et al., *Post-stroke fatigue and its association with poor functional outcome after stroke in young adults.* Journal of neurology, neurosurgery, and psychiatry, 2015. **86**(10): p. 1120-6.
20. Radman, N., et al., *Poststroke fatigue following minor infarcts: a prospective study.* Neurology, 2012. **79**(14): p. 1422-1427.
21. Harvey, P.D., *Domains of cognition and their assessment.* Dialogues in clinical neuroscience, 2019. **21**(3): p. 227-237.
22. Shalev, N., G. Humphreys, and N.J.N. Demeyere, *Assessing the temporal aspects of attention and its correlates in aging and chronic stroke patients.* 2016. **92**: p. 59-68.
23. Glisky, E.L., *Frontiers in Neuroscience. Changes in Cognitive Function in Human Aging*, in *Brain Aging: Models, Methods, and Mechanisms*, D.R. Riddle, Editor. 2007, CRC Press/Taylor & Francis. Copyright © 2007, Taylor & Francis Group, LLC.: Boca Raton (FL).
24. Holtzer, R., et al., *Cognitive fatigue defined in the context of attention networks.* Neuropsychology, development, and cognition. Section B, Aging, neuropsychology and cognition, 2011. **18**(1): p. 108-128.
25. Pearce, S.C., et al., *Sleep disturbance and deficits of sustained attention following stroke.* 2016. **38**(1): p. 1-11.
26. Robertson, I.H., et al., *Motor recovery after stroke depends on intact sustained attention: a 2-year follow-up study.* Neuropsychology, 1997. **11**(2): p. 290-5.
27. Staub, F. and J. Bogousslavsky, *Fatigue after stroke: a major but neglected issue.* Cerebrovasc Dis, 2001. **12**(2): p. 75-81.
28. Parr, J.V.V., et al., *Visual attention, EEG alpha power and T7-Fz connectivity are implicated in prosthetic hand control and can be optimized through gaze training.* J Neuroeng Rehabil, 2019. **16**(1): p. 52.
29. Landahl, K.S., et al., *Comparison of attention process training and activity-based attention training after acquired brain injury: A randomized controlled study.* 2021. **53**(10).
30. De Doncker, W., S. Ondobaka, and A. Kuppuswamy, *Effect of transcranial direct current stimulation on post-stroke fatigue.* J Neurol, 2021. **268**(8): p. 2831-2842.
31. Holmqvist, A., et al., *Does Intensive Training of Attention Influence Cognitive Fatigability in Patients With Acquired Brain Injury?* Front Neurosci, 2021. **15**: p. 656876.
32. Eilertsen, G., H. Ormstad, and M. Kirkevold, *Experiences of poststroke fatigue: qualitative meta-synthesis.* J Adv Nurs, 2013. **69**(3): p. 514-25.
33. Stull, D.E., et al., *Optimal recall periods for patient-reported outcomes: challenges and potential solutions.* 2009. **25**(4): p. 929-942.
34. Sinclair, K.L., et al., *Sustained attention following traumatic brain injury: Use of the Psychomotor Vigilance Task.* Journal of Clinical and Experimental Neuropsychology, 2013. **35**(2): p. 210-224.
35. Ulrichsen, K.M., et al., *Dissecting the cognitive phenotype of post-stroke fatigue using computerized assessment and computational modeling of sustained attention.* 2020. **52**(7): p. 3828-3845.
36. Pihlaja, R., et al., *Post-stroke fatigue is associated with impaired processing speed and memory functions in first-ever stroke patients.* Journal of Psychosomatic Research, 2014. **77**(5): p. 380-384.
37. Demeyere, N., et al., *Domain-specific versus generalized cognitive screening in acute stroke.* 2016. **263**(2): p. 306-315.

38. Passier, P.E., et al., *Predicting fatigue 1 year after aneurysmal subarachnoid hemorrhage.* Journal of neurology, 2011. **258**(6): p. 1091-7.
39. NHS England. *National Stroke Service Model: Integrated Stroke Delivery Networks*. 2021 [cited 2 December 2022]; Available from: https://www.england.nhs.uk/publication/national-stroke-service-model-integrated-stroke-delivery-networks/.
40. Su, Y., M. Yuki, and M. Otsuki, *Non-Pharmacological Interventions for Post-Stroke Fatigue: Systematic Review and Network Meta-Analysis.* J Clin Med, 2020. **9**(3).
41. Clarke, A., S.L. Barker-Collo, and V.L. Feigin, *Poststroke fatigue: does group education make a difference? A randomized pilot trial.* Top Stroke Rehabil, 2012. **19**(1): p. 32-9.
42. Lorig, K.R., et al., *Chronic disease self-management program: 2-year health status and health care utilization outcomes.* 2001: p. 1217-1223.
43. Zedlitz, A.M., et al., *Cognitive and graded activity training can alleviate persistent fatigue after stroke: a randomized, controlled trial.* Stroke, 2012. **43**(4): p. 1046-51.
44. Liu, Y., L. Wang, and X.J.N.R. Dong, *Influence of cognitive behavioral intervention on health behavior and treatment compliance of patients with post stroke fatigue based on problem solving method. Chin.* 2018. **32**: p. 327-329.
45. Nguyen, S., et al., *Cognitive behavioural therapy for post-stroke fatigue and sleep disturbance: a pilot randomised controlled trial with blind assessment.* Neuropsychol Rehabil, 2019. **29**(5): p. 723-738.
46. Winkens, I., et al., *Efficacy of Time Pressure Management in Stroke Patients With Slowed Information Processing: A Randomized Controlled Trial.* Archives of Physical Medicine and Rehabilitation, 2009. **90**(10): p. 1672-1679.
47. Westerberg, H., et al., *Computerized working memory training after stroke–a pilot study.* 2007. **21**(1): p. 21-29.
48. Lindsey, H.M., *Effects of Neuroplasticity-based Auditory Processing Speed Training in Adults with Traumatic Brain Injury.*
49. Barker-Collo, S.L., et al., *Reducing attention deficits after stroke using attention process training: a randomized controlled trial.* 2009. **40**(10): p. 3293-3298.
50. Gupta, J. and S.D.J.S.J.o.O.T. Taff, *The illusion of client-centred practice.* 2015. **22**(4): p. 244-251.
51. Yerxa, E.J.J.O.t.i.h.c., *An introduction to occupational science, a foundation for occupational therapy in the 21st century.* 1990. **6**(4): p. 1-17.
52. Skivington, K., et al., *A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance.* 2021. **374**.
53. Saunders, M., P. Lewis, and A. Thornhill, *Research methods for business students*. 2009: Pearson education.
54. Collis, J. and R. Hussey, *Business research: A practical guide for undergraduate and postgraduate students*. 2013: Macmillan International Higher Education.
55. Wilson, J.J.E.o.B.R., *Essentials of business research: A guide to doing your research project.* 2014: p. 1-376.
56. Craig, P., et al., *Developing and evaluating complex interventions: the new Medical Research Council guidance.* 2008. **337**.
57. Kristensen, H.K. and K.S.J.S.J.o.O.T. Petersen, *Occupational science: An important contributor to occupational therapists' clinical reasoning.* 2016. **23**(3): p. 240-243.
58. World Health Organisation. *International Classification of Functioning, Disability and Health (ICF)*. 2023 [cited 2 December 2022]; Available from: https://www.who.int/standards/classifications/international-classification-of-functioning-disability-and-health.

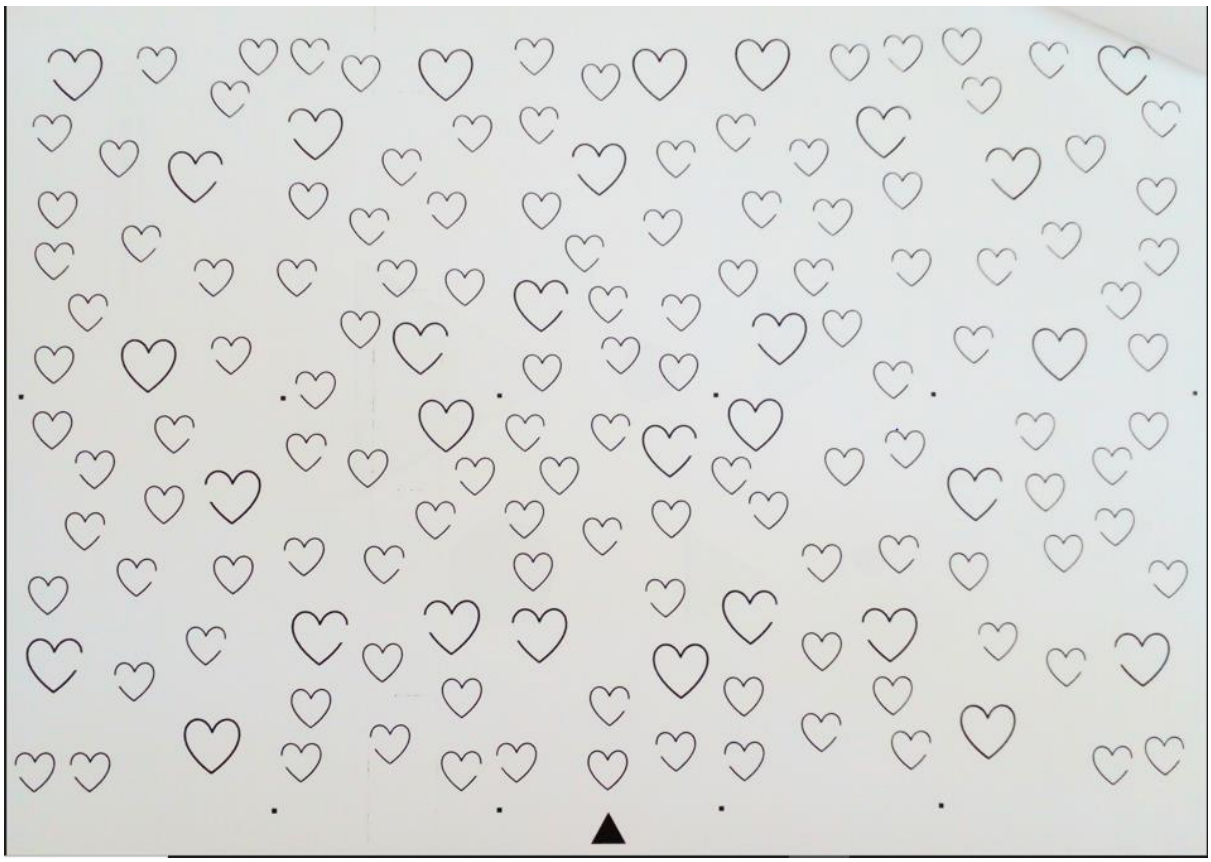
59. Halligan, P.W. and D.T. Wade, *The effectiveness of rehabilitation for cognitive deficits*. 2005: Oxford University Press, USA.
60. Wu, S., et al., *Model of understanding fatigue after stroke.* Stroke (00392499), 2015. **46**(3): p. 893-898.
61. Hoddinott, P.J.P. and f. studies, *A new era for intervention development studies*. 2015, BioMed Central. p. 1-4.
62. Wight, D., et al., *Six steps in quality intervention development (6SQuID).* 2016. **70**(5): p. 520-525.
63. Bleijenberg, N., et al., *Increasing value and reducing waste by optimizing the development of complex interventions: Enriching the development phase of the Medical Research Council (MRC) Framework.* 2018. **79**: p. 86-93.
64. Yvonne Feilzer, M.J.J.o.m.m.r., *Doing mixed methods research pragmatically: Implications for the rediscovery of pragmatism as a research paradigm.* 2010. **4**(1): p. 6-16.
65. Brain Injury Association of America. *Brain Injury Overview*. 2023 11/01/2023]; Available from: https://www.biausa.org/brain-injury/about-%20brain-injury/basics/overview#:%EF%BF%BD:text=An%20acquired%%2020brain%20injury%20(ABI,that%20has%20occurred%%2020after%20birth.
66. Johnson, C.O., et al., *Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016.* The Lancet Neurology, 2019. **18**(5): p. 439-458.
67. Dewan, M.C., et al., *Estimating the global incidence of traumatic brain injury.* 2018. **130**(4): p. 1080.
68. Mollayeva, T., et al., *A systematic review of fatigue in patients with traumatic brain injury: The course, predictors and consequences.* Neuroscience & Biobehavioral Reviews, 2014. **47**: p. 684-716.
69. Ezekiel, L., et al., *Factors Associated With Participation in Life Situations for Adults With Stroke: A Systematic Review.* Archives of physical medicine and rehabilitation, 2019. **100**(5): p. 945-955.
70. Boerboom, W., et al., *Differences in cognitive and emotional outcomes between patients with perimesencephalic and aneurysmal subarachnoid haemorrhage.* Journal of rehabilitation medicine, 2014. **46**(1): p. 28-32.
71. Boerboom, W., et al., *Long-term fatigue after perimesencephalic subarachnoid haemorrhage in relation to cognitive functioning, mood and comorbidity.* Disability and rehabilitation, 2017. **39**(9): p. 928-933.
72. Hubacher, M., et al., *Assessment of post-stroke fatigue: The Fatigue Scale for Motor and Cognitive Functions.* European Neurology, 2012. **67**(6): p. 377-384.
73. Ashman, T.A., et al., *Objective measurement of fatigue following traumatic brain injury.* The Journal of Head Trauma Rehabilitation, 2008. **23**(1): p. 33-40.
74. Colle, F., et al. *Fatigue after stroke*. in *Annales de réadaptation et de médecine physique*. 2006. Elsevier.
75. Lewis, S.J.P., et al., *Is Fatigue After Stroke Associated With Physical Deconditioning? A Cross-Sectional Study in Ambulatory Stroke Survivors.* Archives of Physical Medicine and Rehabilitation, 2011. **92**(2): p. 295-298.
76. Duncan, F., S. Wu, and G.E. Mead, *Frequency and natural history of fatigue after stroke: a systematic review of longitudinal studies.* J Psychosom Res, 2012. **73**(1): p. 18-27.
77. van Markus-Doornbosch, F., et al., *Factors related to fatigue after paediatric acquired brain injury (ABI).* Brain Injury, 2016. **30**(13/14): p. 1533-1541.

78. De Vries, E.A., et al., *Fatigue is Associated with Reduced Participation and Health-Related Quality of Life Five Years After Perimesencephalic Subarachnoid Haemorrhage: A Multicentre Cross-Sectional Study.* 2022.
79. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* 2009. **6**(7): p. e1000097.
80. Payne, T.W., M.A.J.D.r. Schnapp, and treatment, *The relationship between negative affect and reported cognitive failures.* 2014. **2014**.
81. National Heart, L.a.B.I. *Study Quality Assessment Tools*. 2021 2 December 2022]; Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.
82. Exploratory Software for Confidence Intervals. *Introduction to new statistics*. 2021 2 December 2022]; Available from: https://www.esci.thenewstatistics.com/.
83. Park, J.Y., et al., *Functional outcome in poststroke patients with or without fatigue.* American Journal of Physical Medicine & Rehabilitation, 2009. **88**(7): p. 554-558.
84. Beaulieu-Bonneau, S. and M.-C. Ouellet, *Fatigue in the first year after traumatic brain injury: Course, relationship with injury severity, and correlates.* Neuropsychological Rehabilitation, 2017. **27**(7): p. 983-1001.
85. Faul, F., et al., *G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences.* 2007. **39**(2): p. 175-191.
86. Holmberg, J., et al., *Very Early Cognitive Screening and Self-Reported Feeling of Fatigue Three Months After Stroke.* 2021. **15**.
87. Delva, M., N. Lytvynenko, and I. Delva, *Factors Associated with Post-Stroke Fatigue during the Second Half Year after Stroke.* Georgian medical news, 2017(272): p. 59-64.
88. Drummond, A., et al., *The Nottingham Fatigue after Stroke (NotFAST) study: factors associated with severity of fatigue in stroke patients without depression.* Clinical Rehabilitation, 2017. **31**(10): p. 1406-1415.
89. Morsund, Å.H., et al., *The development of cognitive and emotional impairment after a minor stroke: a longitudinal study.* 2019. **140**(4): p. 281-289.
90. Goh, H.-T. and J.C.J.J.o.N.P.T. Stewart, *Poststroke fatigue is related to motor and cognitive performance: a secondary analysis.* 2019. **43**(4): p. 233-239.
91. Morsund Å, H., et al., *Factors influencing employment after minor stroke and NSTEMI.* J Stroke Cerebrovasc Dis, 2020. **29**(9): p. 105036.
92. Claros-Salinas, D., et al., *Fatigue-related diurnal variations of cognitive performance in multiple sclerosis and stroke patients.* Journal of the neurological sciences, 2010. **295**(1-2): p. 75-81.
93. Ponchel, A., et al., *Factors associated with poststroke fatigue: a systematic review.* 2015. **2015**.
94. Demeyere, N., et al., *The Oxford Cognitive Screen (OCS): validation of a stroke-specific short cognitive screening tool.* 2015. **27**(3): p. 883.
95. Van Zomeren, A. and W. Van den Burg, *Residual complaints of patients two years after severe head injury.* Journal of Neurology, Neurosurgery & Psychiatry, 1985. **48**(1): p. 21-28.
96. Allonsius, F., et al., *Fatigue in young patients with acquired brain injury in the rehabilitation setting: Categorizing and interpreting fatigue severity levels.* 2022. **25**(8): p. 542-553.
97. Chung-Fat-Yim, A., et al., *Continuous effects of bilingualism and attention on Flanker task performance.* 2020. **23**(5): p. 1106-1111.
98. Shipstead, Z., T.L. Harrison, and R.W.J.P.o.P.S. Engle, *Working memory capacity and fluid intelligence: Maintenance and disengagement.* 2016. **11**(6): p. 771-799.

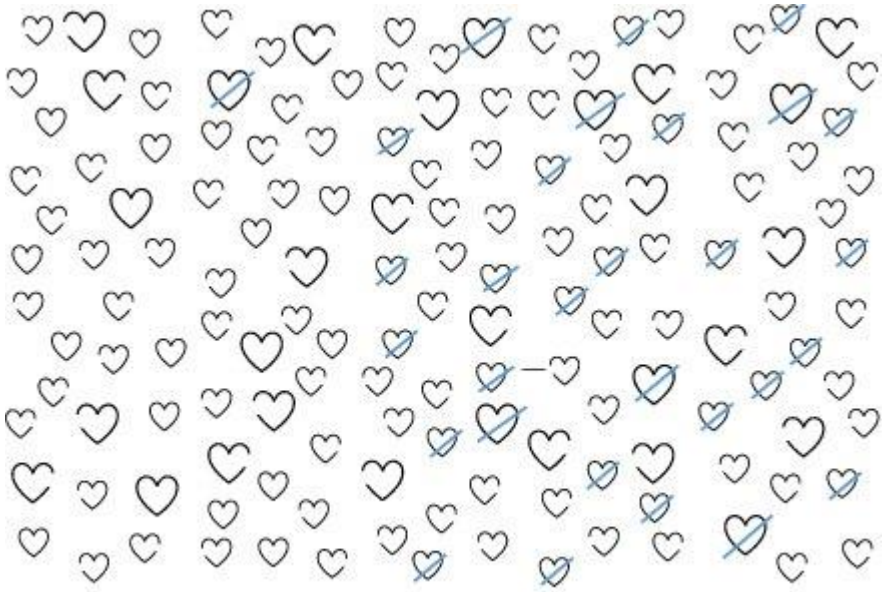
99. Draheim, C., et al., *The role of attention control in complex real-world tasks.* 2022: p. 1-55.
100. Fukuda, K., et al., *Individual differences in visual working memory capacity: Contributions of attentional control to storage.* 2015. **105**.
101. Frith, E., et al., *Keeping creativity under control: Contributions of attention control and fluid intelligence to divergent thinking.* 2021. **33**(2): p. 138-157.
102. Tsukahara, J.S., et al., *Attention control: The missing link between sensory discrimination and intelligence.* 2020. **82**(7): p. 3445-3478.
103. McVay, J.C. and M.J.J.J.o.e.p.g. Kane, *Why does working memory capacity predict variation in reading comprehension? On the influence of mind wandering and executive attention.* 2012. **141**(2): p. 302.
104. Shalev, N., G. Humphreys, and N. Demeyere, *Manipulating perceptual parameters in a continuous performance task.* Behav Res Methods, 2018. **50**(1): p. 380-391.
105. Shinoda, H., M.M. Hayhoe, and A.J.V.r. Shrivastava, *What controls attention in natural environments?* 2001. **41**(25-26): p. 3535-3545.
106. Langner, R. and S.B.J.P.b. Eickhoff, *Sustaining attention to simple tasks: a meta-analytic review of the neural mechanisms of vigilant attention.* 2013. **139**(4): p. 870.
107. Van, Z., et al., *Clinical neuropsychology of attention*. 1994, Oxford University Press.
108. Esterman, M. and D.J.C.o.i.p. Rothlein, *Models of sustained attention.* 2019. **29**: p. 174-180.
109. Grillon, C., et al., *Effect of attention control on sustained attention during induced anxiety.* 2016. **30**(4): p. 700-712.
110. Lang, P.J., et al., *Motivated attention: Affect, activation, and action.* 1997. **97**: p. 135.
111. Stulemeijer, M., et al., *Cognitive performance after mild traumatic brain injury: the impact of poor effort on test results and its relation to distress, personality and litigation.* Brain injury, 2007. **21**(3): p. 309-18.
112. Lerdal, A., et al., *Poststroke fatigue—a review.* 2009. **38**(6): p. 928-949.
113. Cumming, T.B., et al., *Investigating post-stroke fatigue: An individual participant data meta-analysis.* 2018. **113**: p. 107-112.
114. Lerdal, A. and A.J.I.j.o.n.s. Kottorp, *Psychometric properties of the Fatigue Severity Scale—Rasch analyses of individual responses in a Norwegian stroke cohort.* 2011. **48**(10): p. 1258-1265.
115. Penner, I.-K., et al., *The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue.* 2009. **15**(12): p. 1509-1517.
116. Von Elm, E., et al., *The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.* 2007. **370**(9596): p. 1453-1457.
117. Dwan, K., et al., *CONSORT 2010 statement: extension to randomised crossover trials.* 2019. **366**.
118. Lancaster, G.A., S. Dodd, and P.R.J.J.o.e.i.c.p. Williamson, *Design and analysis of pilot studies: recommendations for good practice.* 2004. **10**(2): p. 307-312.
119. Spaccavento, S., Marinelli, C.V., Nardulli, R., Macchitella, L., Bivona, U., Piccardi, L., Zoccolotti, P. and Angelelli, P. *Attention deficits in stroke patients: the role of lesion characteristics, time from stroke, and concomitant neuropsychological deficits.* Behavioural neurology, 2019.
120. De Doncker, W., Dantzer, R., Ormstad, H. and Kuppuswamy, A., 2018. *Mechanisms of post-stroke fatigue*. Journal of Neurology, Neurosurgery & Psychiatry, 89(3), pp.287-293.

Appendices

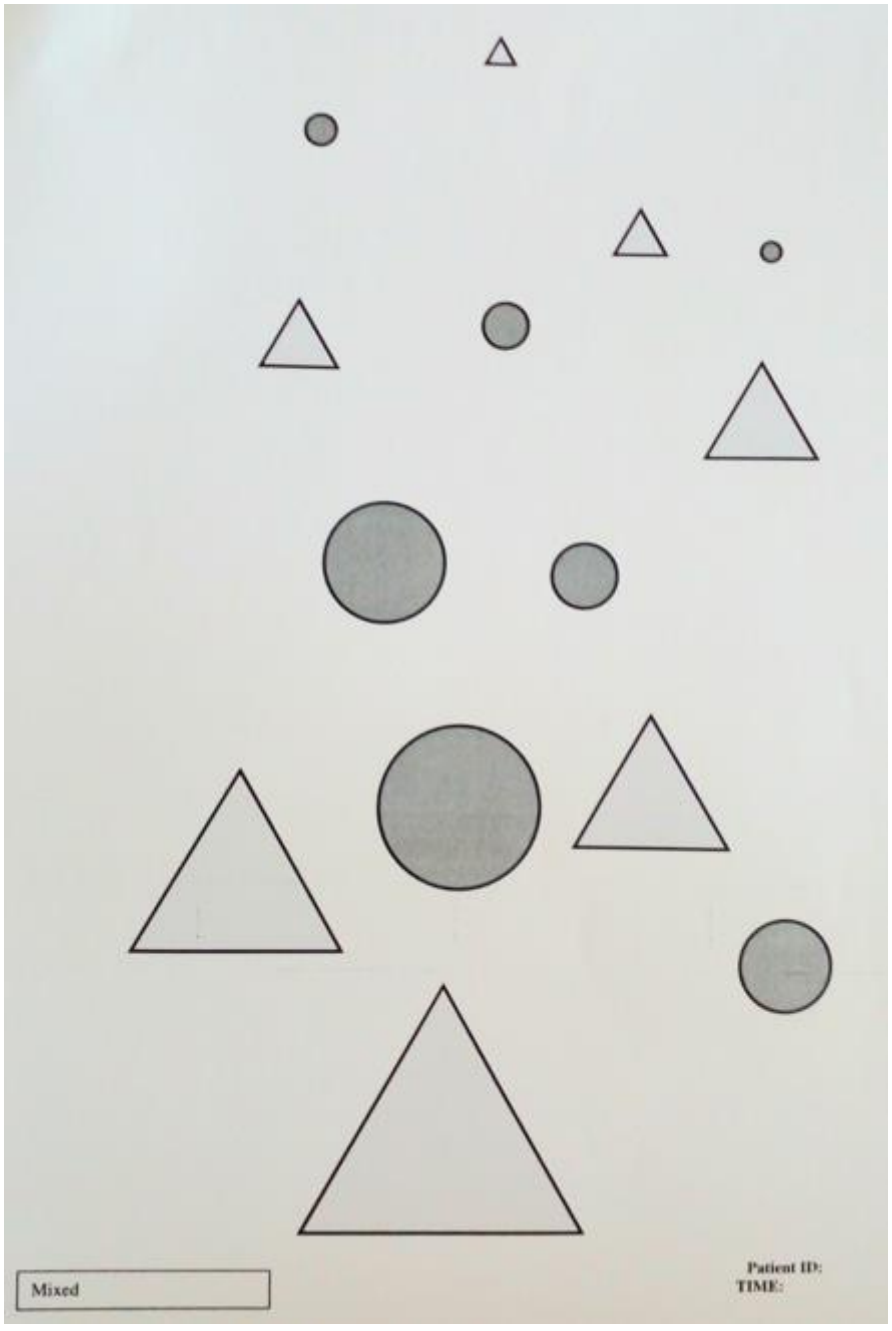
Appendix 1 Baseline sub-test of executive attention: OCS Hearts test of executive attention



An example of a completed version



Appendix 2 Baseline sub-test of executive attention: OCS TMT test of executive attention



Appendix 3 Fatigue Scale for Motor and Cognition (FSMC)

The FSMC, page 1

FSMC

Fatigue Scale for Motor and Cognitive Functions

Date: _____

ID: _____

Initials: _____

Age: _____ Sex: m ○ f ○

Instructions

The following questionnaire is about problems in everyday life which are directly associated with an extreme form of tiredness (fatigue). This extreme form of tiredness refers to an overwhelming state of lethargy, exhaustion and lack of energy which comes on abruptly and is unrelated to any obvious external causes. It does not mean the sort of isolated episodes which everyone might experience in the course of the day, after exertion, or after a sleepless night!

Please read each statement carefully. Then decide to what extent each statement applies to you and your everyday life. Please try not to base your answers on the way you are feeling at the moment; instead try to give us a picture of the way you feel in normal day-to-day life. Please put a cross in the appropriate circle (only one cross per statement please!).

	Does not apply at all	Does not apply much	Slightly applies	Applies a lot	Applies completely
1. When I concentrate for a long time, I get exhausted sooner than other people of my age.	○	○	○	○	○
2. When I am experiencing episodes of exhaustion, my movements become noticeably clumsier and less coordinated.	○	○	○	○	○
3. Because of my episodes of exhaustion, I now need more frequent and/or longer rests during physical activity than I used to.	○	○	○	○	○
4. When I am experiencing episodes of exhaustion, I am incapable of making decisions.	○	○	○	○	○
5. When faced with stressful situations, I now find that I get physically exhausted quicker than I used to.	○	○	○	○	○
6. Because of my episodes of exhaustion, I now have considerably less social contact than I used to.	○	○	○	○	○
7. Because of my episodes of exhaustion, I now find it more difficult to learn new things than I used to.	○	○	○	○	○

Please turn over

FSMC-cog = _____ FSMC-mot = _____ FSMC total = _____

Appendix 3 Fatigue Scale for Motor and Cognition (FSMC)

The FSMC, page 2

FSMC

	Does not apply at all	Does not apply much	Slightly applies	Applies a lot	Applies completely
8. The demands of my work exhaust me mentally more quickly than they used to.	○	○	○	○	○
9. I feel the episodes of exhaustion particularly strongly in my muscles.	○	○	○	○	○
10. I no longer have the stamina for long periods of physical activity that I used to have.	○	○	○	○	○
11. My powers of concentration decrease considerably when I'm under stress.	○	○	○	○	○
12. When I am experiencing episodes of exhaustion, I am less motivated than others to start activities that involve physical effort.	○	○	○	○	○
13. My thinking gets increasingly slow when it is hot.	○	○	○	○	○
14. When I am experiencing an episode of exhaustion, my movements become noticeably slower.	○	○	○	○	○
15. Because of my episodes of exhaustion, I now feel less like doing things which require concentration.	○	○	○	○	○
16. When an episode of exhaustion comes on, I am simply no longer able to react quickly.	○	○	○	○	○
17. When I am experiencing episodes of exhaustion, certain words simply escape me.	○	○	○	○	○
18. When I am experiencing episodes of exhaustion, I lose concentration considerably quicker than I used to.	○	○	○	○	○
19. When it is hot, my main feeling is one of extreme physical weakness and lack of energy.	○	○	○	○	○
20. During episodes of exhaustion, I am noticeably more forgetful.	○	○	○	○	○

Please make sure that you have written down your initials, age and sex on page 1 and have put a cross by each statement. Thank you.

FSMC ranking score sheet

FSMC Sum Score	≥ 43 Mild fatigue	
	≥ 53 Moderate fatigue	
	≥ 63 Severe fatigue	
FSMC Cognitive Score	≥ 22 Mild cognitive fatigue	
	≥ 28 Moderate cognitive fatigue	
	≥ 34 Severe cognitive fatigue	
FSMC Motor Score	≥ 22 Mild motor fatigue	
	≥ 27 Moderate motor fatigue	
	≥ 32 Severe motor fatigue	

Appendix 4 Visual Analog Scale – fatigue (VAS-f)

VAS-f ranking score sheet

VAS -f	1 - 3 ≥ Mild fatigue	
	4 – 6 ≥ Moderate fatigue	
	7 – 10 ≥ Severe fatigue	

Appendix 5 Systematic Review, examples of search strategies

PsycInfo

1 DE "Cerebrovascular Accidents" OR DE "Cerebral Ischemia" OR DE "Cerebral Small Vessel Disease" OR DE "Hemorrhage" OR DE "Cerebral Hemorrhage" OR DE "Hematoma" OR DE "Subarachnoid Hemorrhage" OR DE "Cerebrovascular Disorders" OR DE "Brain Injuries" OR DE "Traumatic Brain Injury"
2 stroke* OR "ischemic stroke*" OR haemorrhagic stroke*
3 brain* or cerebr* or cerebell* or intracran* or intracerebral
4 ischemi* OR ischaemi* or infarct* or thrombo* or emboli* or occlus*
5 S3 AND S4
6 S1 OR S2 OR S5
7 DE "Fatigue" OR DE "Chronic Fatigue Syndrome"
8 tiredness* OR slowness OR weariness* OR exhaustion* OR "mental fatigue"
9 S7 OR S8
10 DE "Cognitive Impairment" OR DE "Cognition" OR DE "Cognitive Processes" OR DE "Cognitive Ability" OR DE "Memory" OR DE "Sustained Attention" OR DE "Attention" OR DE "Reasoning" OR DE "Concentration" OR DE "Executive Function"
11 "information processing" OR "mental concentration" OR "cognitive function*"
12 S10 OR S11
13 S6 AND S9 AND S12
14 limit 13 to human
15 limit 14 to adulthood
16 limit 15 to All Journals

PubMed

1 "Stroke"[Mesh] OR "Brain Ischemia"[Mesh] OR "Cerebral Small Vessel Diseases"[Mesh] OR "Hemorrhage"[Mesh] OR "Cerebral Hemorrhage"[Mesh] OR "Hematoma, Subdural, Intracranial"[Mesh] OR "Hematoma, Subdural, Chronic"[Mesh] OR "Hematoma, Subdural, Acute"[Mesh] OR "Hematoma, Subdural"[Mesh] OR "Hematoma, Epidural, Cranial"[Mesh] OR "Putaminal Hemorrhage"[Mesh] OR "Basal Ganglia Hemorrhage"[Mesh] OR "Subarachnoid Hemorrhage"[Mesh] OR "Cerebrovascular Disorders"[Mesh] OR "Brain Injury, Chronic"[Mesh] OR "Brain Injuries"[Mesh] OR "Brain Infarction"[Mesh] OR "Carotid Artery Diseases"[Mesh] OR "Hypoxia-Ischemia, Brain"[Mesh] OR "Intracranial Aneurysm"[Mesh] OR "Intracranial Embolism and Thrombosis"[Mesh] OR "Intracranial Arteriovenous Malformations"[Mesh] OR "Intracranial Embolism"[Mesh] OR "Vasospasm, Intracranial"[Mesh] OR "Vertebral Artery Dissection"[Mesh] OR "Brain Injuries, Traumatic"[Mesh]
2 stroke* OR "ischemic stroke*" OR haemorrhagic stroke*
3 brain* or cerebr* or cerebell* or intracran* or intracerebral
4 ischemi* OR ischaemi* or infarct* or thrombo* or emboli* or occlus*
5 S3 AND S4
6 S1 OR S2 OR S5
7 "Fatigue"[Mesh] OR "Fatigue Syndrome, Chronic"[Mesh] OR "Mental Fatigue"[Mesh]
8 tiredness* OR slowness OR weariness* OR exhaustion* OR "mental fatigue"
9 S7 OR S8
10 "Cognitive Dysfunction"[Mesh] OR "Cognition"[Mesh] OR DE "Cognitive Processes" OR DE "Cognitive Ability" OR "Memory"[Mesh] OR "Spatial Memory"[Mesh] OR "Memory, Long-Term"[Mesh] OR "Memory, Short-Term"[Mesh] OR "Memory Disorders"[Mesh] OR "Attention"[Mesh] OR "Cognition Disorders"[Mesh] OR "Executive Function"[Mesh]
11 "information processing" OR "mental concentration" OR "cognitive function*"
12 S10 OR S11
13 S6 AND S9 AND S12
14 limit 13 to human
15 limit 14 to adult

Appendix 6 Test of functional abilities: Modified Rankin Scale (mRS)

Modified Rankin Scale (mRS) for measuring the degree of disability or dependence in the daily activities of people who experience a stroke.

Level	Description
0	No symptoms
1	No significant disability, despite symptoms; able to perform all usual duties and activities
2	Slight disability; unable to perform all previous activities but able to look after own affairs without assistance
3	Moderate disability; requires some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requires nursing care and attention

Appendix 7 Test of functional abilities: The Barthel Index

Barthel Index of Activities of Daily Living

Instructions: Choose the scoring point for the statement that most closely corresponds to the patient's current level of ability for each of the following 10 items. Record actual, not potential, functioning. Information can be obtained from the patient's self-report, from a separate party who is familiar with the patient's abilities (such as a relative), or from observation. Refer to the Guidelines section on the following page for detailed information on interpretation.

The Barthel Index

Bowels
0 = incontinent (or needs to be given enemata)
1 = occasional accident (once/week)
2 = continent
Patient's Score:____

Bladder
0 = incontinent, or catheterized and unable to manage
1 = occasional accident (max once per 24 hours)
2 = continent (for over 7 days)
Patient's Score:____

Grooming
0 = needs help with personal care
1 = independent face/hair/teeth/shaving (implements provided)
Patient's Score:____

Toilet Use
0 = dependent
1 = needs some help, but can do something alone
2 = independent (on and off, dressing, wiping)
Patient's Score:____

Feeding
0 = unable
1 = needs help cutting, spreading butter, etc.
2 = independent (food provided within reach)
Patient's Score:____

Transfer
0 = unable – no sitting balance
1 = major help (one or two people, physical), can sit
2 = minor help (verbal or physical)
3 = independent
Patient's Score:____

Mobility
0 = immobile
1 = wheelchair independent, including corners, etc.
2 = walks with help of one person (verbal or physical)
3 = independent (but may use any aid, e.g., stick)
Patient's Score:____

Dressing
0 = dependent
1 = needs help, but can do about half unaided
2 = independent (including buttons, zips, laces, etc.)
Patient's Score:____

Stairs
0 = unable
1 = needs help (verbal, physical, carrying aid)
2 = independent up and down
Patient's Score:____

Bathing
0 = dependent
1 = independent (or in shower)
Patient's Score:____

Total Score:____

Scoring: Sum the patient's scores for each item. Total possible scores range from 0 – 20, with lower scores indicating increased disability. If used to measure improvement after rehabilitation, changes of more than two points in the total score reflect a probable genuine change, and change on one item from fully dependent to independent is also likely to be reliable.

Appendix 8 Participant Information Leaflet and Consent Forms, University of Oxford.

Oxford University Hospitals NHS
NHS Foundation Trust

Department of Experimental Psychology,
Prof Nele Demeyere (Chief Investigator)

PARTICIPANT INFORMATION LEAFLET

Long-term recovery of cognitive deficits in stroke patients

REC name: OCS-Recovery: Investigating the longer term natural history of cognitive domains after stroke.
REC Reference: 18/SC/0550

We would like to invite you to take part in our research study. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information, and discuss it with others if you wish. If there is anything that is not clear, or if you would like more information, please ask us.

What is the purpose of the study?
This project aims to assess the way we measure the kinds of problems in memory, language and attention people can have after a brain injury. The study aims to understand how these kind of cognitive problems change over time. The tasks aim to discover if you have any particular cognitive problems with things like seeing, reading, problem solving etc. We also want to see if you improve in the next few months. The long-term aim being to guide therapy that will attempt to remedy these problems.

Why have I been invited?
You have been invited because you are thought to have had a stroke. We would like to look at any problems in memory, language and attention you may be experiencing. We aim to investigate as many participants as possible during the time-frame (currently funded until 2021).

Do I have to take part?
No. It is up to you whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care that you receive.

What will happen to me if I take part?
The study will involve you going through a short series of tests that will measure your language, memory, sight and the ability to solve problems. The tests will be

given in one or two initial sessions, no more than 5 days apart, each lasting about 30 minutes (or about an hour if a single session), and will be carried out with a trained member of the research team. Some of the tests will be paper based, others will use a touch sensitive tablet computer.

In parts of the computerised tests, you may be voice-recorded in order to facilitate scoring of certain tasks (for example naming and reading tasks, where more detailed scoring can take place if there are some problems with speech).

The results of the standardized cognitive assessments will be summarised in your clinical notes to inform the Multidisciplinary care team.

We will also contact you for a follow up assessment around 6 months from now. We will come out to your home to do this or, if you prefer, you can visit us at the clinic or at the University. At this stage a very similar set of short tests will be done.

Some people are asked if they would like to complete extra follow-up assessments around 1 month and 3 months. This will depend on whether you show particular characteristics with your vision and/or or attention. These extra visits are optional. You can choose to only be contacted after 6 months. Similarly, if you have a close familial relative who cares for you, we may ask them to do a few extra very brief (<5 min) tests with you in the time in between our visits, which is also optional.

In addition to this, we will look at your medical records to check information relevant to the study. With your permission, we would also like to look at any brain scan you have had taken as part of routine care. All records will be kept confidential. Your name will be kept separately from any research data.

Why is the procedure being tested?
In the long term, the study aims to help us choose measures of memory, language and attention that might be given in order to predict recovery of function after brain injury. Therefore the study should be of benefit for future patients to better understand how their cognitive problems are likely to recover over time.

What are the risks or disadvantages of taking part?
There are no risks involved in carrying out the tests. Since the tests are simple paper-and-pencil and touch computer-based measures, there is nothing to go wrong.

What are the possible benefits of taking part?
We cannot promise the study will help you, but it will hopefully aid in identifying problems you may be experiencing as a result of your brain injury. This may then be helpful in guiding the course of treatment you will receive. It may also help to improve the treatment of future patients.

What will happen to the results of the research study?
The results from these tests will be used to try to predict the outcome of brain injuries, and the data will be reported in scientific papers. If useful, the tests can also be incorporated into standard admissions and rehabilitation procedures for

patients who have suffered a brain injury. Some of the research being undertaken will also contribute to the fulfilment of an educational requirement (e.g. a doctoral thesis).

What will happen if I do not want to carry on with the research study?

You are free to withdraw from the study at any time without giving a reason. This will not affect your medical care. Any data collected about you will be destroyed, and will not be used in analysis. If you do not wish to carry on with the research study this will not affect the care you receive.

What if there is a problem?

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. NHS indemnity operates in respect of the clinical treatment which is provided. If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Dr Nele Demeyere (nele.demeyere@psy.ox.ac.uk – 01865 271 340) or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224 or the head of CTRG, email ctrg@admin.ox.ac.uk

Will my data be kept confidential?

Our procedures for handling, processing, storing and destroying your data are all compliant with the General Data Protection Regulations 2018 (GDPR). All information that is collected about you during the course of the research will be kept strictly confidential. Your data will be collected both from your medical records and from the test interviews we will conduct. Research is a task that we perform in the public interest. The University of Oxford, as sponsor, is the data controller. This means that we, as University of Oxford researchers, are responsible for looking after your information and using it properly. We will use the minimum personally-identifiable information possible. We will keep identifiable information about you for 3 months after the study has finished unless you agree to be kept informed about future research opportunities. We will store the anonymised research data and any research documents with personal information, such as consent forms, securely at the University of Oxford for 5 years after the end of the study as part of the research record.

The NHS will collect information from you and/or your medical records for this research study in accordance with our instructions. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it. The data and hard copy paper files will be stored securely at The Cognitive Neuropsychology Centre, in the Department of Experimental Psychology, University of Oxford. The office where it will be stored as well as the Centre can only be accessed by staff with authorised access cards. Access to all computers is password protected. Responsible members of the University of Oxford, or responsible members of the Oxford University Hospitals NHS Trust, may be given access to data for monitoring and/or audit of the study to ensure that we are

complying with the regulations. Anonymised data will be archived and can be shared with other researchers, here and abroad and with commercial companies, for scientific reuse.

Your rights to access, change, or move your personal information may be limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. You can find out more about how we use your information at https://www1.admin.ox.ac.uk/councilsec/compliance/gdpr/university policyondataprotection/.

Participation in future research
If you agree, we would like to retain your contact details to inform you of future research opportunities for which you may be eligible. These details would be held for an indefinite period, separately from the rest of the study data and would not be shared outside of our department. You can opt out any time by contacting the research team using the details on this letter. Agreeing to be contacted does not oblige you to take part.

Who is organising and funding the research?
The research is organised by the University of Oxford (Research Sponsor). It is funded by the Stroke Association, UK.

Who has reviewed the study?
This study was given a favourable ethical opinion for conduct in the NHS by *the South Central – Oxford C* Research Ethics Committee. (Ref: 18/SC/0550)

You will be given a copy of the signed consent form to keep along with this information sheet. Thank you for considering taking part and taking the time to read this sheet.

Contact Details:

Chief investigator:

Prof Nele Demeyere
Cognitive Neuropsychology Centre
Department of Experimental Psychology,
University of Oxford, Oxford OX1 3UD
nele.demeyere@psy.ox.ac.uk
(01865 271 424)
Nele.demeyere@psy.ox.ac.uk
(01865 618 637)

Department of Experimental Psychology,
Prof Nele Demeyere (Chief Investigator)

CONSENT FORM

Centre Number: _ _ _ _ _ _
Participant ID: _ _ _ _ _ _

OCS-Recovery: Investigating the longer term natural history of cognitive domains after stroke. (REC reference: *18/SC/0550*)

Please initial if you agree

1. I confirm that I have **read the participant information sheet** dated 23/11/2018 (version 0.5) for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that **my participation is voluntary** and that I am **free to withdraw at any time** without giving any reason, without my medical care or legal rights being affected.	
3. I understand that **relevant sections of any of my medical notes** and data collected during the study may be looked at by responsible individuals from the University of Oxford or the Oxford University Hospitals NHS Foundation Trust for monitoring and/or audit to ensure we are complying with regulations. I give permission for these individuals to have access to my records.	
4. I understand that **brain scans I have had taken as part of routine care** may be analysed by responsible individuals from the University of Oxford where it is relevant to my taking part in this research. I give permission for these individuals to have access to my scan records.	
5. I agree to **being contacted in ~6 months' time** with regard to having a follow up assessment of language, memory and attention.	
6. I agree to be audio recorded as part of the computerised tablet tests. These recordings will only be used to facilitate the scoring of certain tasks and will be destroyed once the study is completed.	
7. I agree to take part in this study.	

Department of Experimental Psychology,
Prof Nele Demeyere (Chief Investigator)

Optional EXTRAS:		
8. ***OPTIONAL.*** *I agree to being contacted in ~1 months' and ~3 months for in-between follow up assessments around vision and attention.*	YES	NO
9. ***OPTIONAL*** *I agree to be contacted about ethically approved research studies for which I may be suitable. I understand that agreeing to be contacted does not oblige me to participate in any further studies. I understand I can withdraw my contact details at any time.*	YES	NO

Name of Participant	Date	Signature

I verify the above stated person has agreed to the content of this consent form in the manner above, as indicated by the initialled boxes.

----------	----------	----------
Name of Witness	Date	Signature

Name of person taking consent	Date	Signature

(File: 1 for participant, 1 for researcher, 1 for hospital records)

Appendix 9 The MenFAS Study: Participant Invitation Letter, Patient Information Sheets and Consent form.

OXFORD BROOKES UNIVERSITY

Project Title: The MenFAS Study: Understanding mental fatigue after stroke.

Dear .....

We are contacting you about a new research study that we are currently running at Oxford Brookes University. You have previously indicated that you would like to be contacted for future research studies, which is why you are receiving this email/letter. If you no longer wish to be contacted, please do let me know and I will remove your details from the list.

The research is seeking to improve our understanding of how attention problems and fatigue of varying severities impact on people's daily life and participation patterns after having a stroke. I have attached further information regarding the study to this email/letter. Take your time to read through all the information and if you have any questions at all please do not hesitate to get in touch.

If you are interested in getting involved please do let me know and we can arrange a time to discuss the details of the study and your participation further.

Yours sincerely

Prof Helen Dawes
Director, Centre for Movement, Occupational and Rehabilitation Sciences
Oxford Brookes University
Gipsy Lane, Headington
OX3 0BP
Ph. 01865 483 293
Email: hdawes@brookes.ac.uk

PARTICIPANT INFORMATION SHEET

The MenFAS Study:

Understanding mental fatigue after stroke

We would like to invite you to take part in our research study. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take the time to read this information and discuss it with others if you wish. If there is anything that is not clear, or if you would like more information, please ask us.

What is the purpose of the study?

This project aims to determine the relationship of attention to mental fatigue more than 2 months after stroke. We hope to gain an understanding of how attention problems and fatigue of varying severities impact on people's daily life and participation patterns. It will also assist us to recognise what contextual factors are important for participation levels. In general, this study aims to improve how we look for and care for attention and fatigue problems in the long-term stroke survivors by assisting clinical teams, policy-makers, and future treatment research studies. This study will contribute to a doctoral research project towards a MPhil/PhD.

Why have I been invited?

You have been invited because you have had a stroke, and have consented to receive information about future research in relation to stroke. We would like to test your attention and monitor your fatigue levels to see how they affect you after a stroke, and you use an android smart phone. We aim to include 30 participants in this research.

Do I have to take part?

No - it is entirely up to you whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and are not required to provide a reason for doing so. A decision to withdraw at any time, or a decision not to take part, will not affect the opportunity to participate in future research if you so wish. And, it will not affect any clinical care or support you currently receive.

What will happen to me if I take part?

You will be contacted via phone and asked to participate in two in-person visits. Visit 1 and 2 will not be more than two weeks apart. The visits will be at your home or our research centre (whichever you prefer) with one of our trained researchers. The visits will be scheduled during the initial phone call.

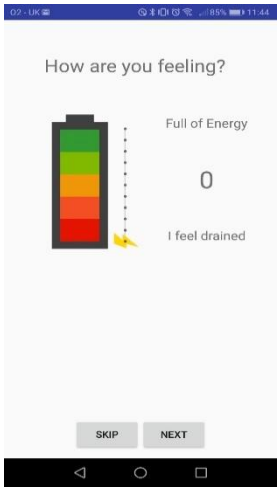
Study Procedure: Visit 1

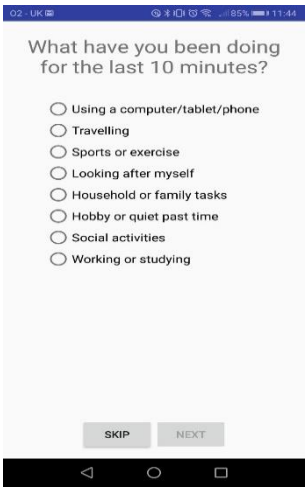
The visit will involve you going through some short questionnaires about your experience of fatigue, followed by a brief interview about how fatigue influences your activity and participation levels in relation to the context of where the activity is happening. This interview will be audio recorded. Also there will be one cognitive test that will assess your attention span. The questionnaires tests will be paper-based, and the cognitive test is be on a tablet computer. Full instruction will be given and a trial practice will be provided. All of the questionnaires and the assessment are relatively short, completed in a matter of minutes with opportunities for breaks at any time, if necessary. The first session will typically last 1 hour and will never be more than 2 hours.

Between Visit 1 & Visit 2 we will also ask you if you are happy to use two participatory measures: 1) A mobile phone app – smart EMA and 2) An activity monitor, for a maximum of 1 week, which is completely optional.

First, the researcher will assist you to set up the app onto your mobile phone or you will be provided with a mobile phone that will have the pre-installed app. This app will collect “in the moment” information by asking you to rate your fatigue, identify what you were doing and to complete a reaction time test. The app will also passively collect information about your sleep and rest patterns by the phone screen turning on and off. Background noise will also be collected, by recording decibel levels only, no background conversations will be captured. If you are happy to use this app, we would ask you to do so for a maximum of 1 week and respond to 5 alerts triggered by time points (10am and 8pm), a change in activity levels (from sedentary to active) and by background noise levels. The alerts will have a minimum of 2 hours between each alert and will only occur between 10am and 8pm. Full instruction on its use will be provided by our researcher.

The smart EMA mobile phone app





Second, we will also ask you if you are happy to wear an activity tracker for a maximum of 1 week. Again this is completely optional. The sensor is the size of a watch and will be worn on

the wrist to monitor physical activity. It records activity level continuously, such as movement/how many steps you take over a 7-day period, but it doesn't track the type of activity. It records the amount of hours you sleep indirectly in the absence of movement for longer periods at night. The sensor does not record your location (No GPS data). You will be asked to remove the monitor after 7 days and we will collect it at the next visit. You will not have to charge the device within that time period.

The wearable activity tracker

Visit 2

The researcher will complete a short follow-up visit at your home, which will typically take less than 1 hour. The study phone will be collected and the activity tracker will be retrieved. We will then summarise the study, offer an opportunity for further questions and summarise key points of your involvement (for example, what happens to your data) and a summary sheet of the outcome of the study will be offered.

We ask you to do nothing different from your daily life activity. Your normal daily routine should remain unaffected when volunteering for this study. The collected data is initially stored on the device, and will be extracted by us once you give the tracker back to the research team. Your data can be shared with you and your care providers (GP, carers etc), if you are interested and agree. The responsibility for the devices lies with the research team. If you discover any problems or discomfort with the device, you can take it off without any worry. We will pick it up on our next visit.

What are the risks or disadvantages of taking part?

There are no evident risks involved in carrying out the tests. Since the tests are simple paper-and-pencil and a touch computer-based measure, there is nothing invasive involved and therefore this research is low risk. If you do experience any anxiety or distress during the assessment, you may stop at any time and/or pause to ask questions.

However, there is a risk that you would find focusing on your fatigue throughout this study upsetting. If you are affected in any way by the topic of this study, the researcher will provide you with information on who to contact for further support. In addition, if we feel that it would be of benefit to inform your GP or relevant person of any distress or concerns arising from this study, we will also your permission prior to doing so. In addition, a list of support services are

listed at the end of this sheet. A mid – week call can be arranged to assist with any queries or issues who may wish to discuss.

What are the possible benefits of taking part?

We cannot promise the study will help you in any specific way, but it may help to improve the diagnosis and management of symptoms experienced by future chronic stroke survivors.

What will happen to the results of the research study?

All information that is collected from you during the course of the research will be kept strictly confidential (subject to legal limitations) according to good clinical guidelines and the general data protection regulation. Data will be stored in line with the University's storage policy, encrypted, stored according to security standard ISO27001 and kept for a minimum of 10 years. Your data will only be accessed by the research team. All data handled outside of the research group (by means of scientific publication or reports) will be anonymised whereby nobody will be able to trace the data back to you as being you.

The activity monitor collects information about your physical activity (number of steps taken) and your sleep patterns.

All data from the app is de-identified, encrypted and streamed to a secure server. The app collects data from the two questions you answer, your reaction times and when your phone turns on and off. When the app alerts you, it will collect the noise level (in decibels only) and your physical activity level (number of steps you have done) as recorded by the phone.

All results will be de-identified and reported in scientific papers and possibly presented at relevant health care conference with the aim of helping clinical teams.
Additionally, de-identified results of the study will be summarized and communicated in lay language to all participants (if requested) at the end of the study through a lay report, which will be sent to each participant in a hardcopy through the post. Some of the research being undertaken will also contribute to the fulfilment of an educational requirement (e.g. a doctoral thesis).

What are we doing to reduce the risk of spreading COVID-19?

The study complies with the most updated government policies in respect of COVID-19, and the following mitigations are put in place to ensure the health and safety of participants and researchers.

Prior to the study visit, you be asked to complete a symptom-screening over the telephone to ensure you (and members of their household) are free from COVID-19 symptoms.

On the day of the study visit, **researchers** will pre -screen to ensure you (and members of their household) are free from COVID-19 symptoms.

On the day of the study visit, **researchers** will maintain social distance at arrival and as far possible, throughout the visit.

In the unlikely event of cardiac arrest, CPR will be administered with chest compressions only – no rescue breaths will be administered in line with government guideline.

How will Personal Protective Equipment (PPE) be used?

Researchers will wear a face mask, apron covering, gloves, visor or goggles. Participants will be encouraged to wear a mask. PPE will be provided by the researcher and will be disposed of in a clinical waste bag.

Computer tablet, wrist monitor and mobile phones

The computer tablet and each wrist monitor and mobile phone will be thoroughly washed and disinfected before and after each use. Disinfectant disposable wipes will also be included in each mailing pack and you will be encouraged to disinfect the wrist accelerometer before wearing it.

Contact tracing:

For the purposes of contact tracing, a record of the research participants (name and visit date), together with researcher's details (name and research group) will be maintained. The log book will be maintained by the researchers performing the assessments and regularly checked by the principle investigator.

Who is organising and funding the research?

Avril Dillon is a research student at Department of Sports and Health Sciences, Oxford Brookes University and is conducting the research as part of studying for her MPhil/PhD.

The research is being funded through the Elizabeth Casson Trust at Oxford Brookes University.

Who has reviewed the study?

The research study been approved by the University Research Ethics Committee, Oxford Brookes University.

Contact for Further Information

Professor Helen Dawes Clinical Research Lead Centre for Movement, Occupation and Rehabilitation Research (MOReS) Headington Campus Oxford OX3 0BP	Avril Dillon PhD Student Centre for Movement, Occupation and Rehabilitation Research (MOReS) Headington Campus Oxford OX3 0BP
hdawes@brookes.ac.uk Telephone: 01865 483630	18091897@brookes.ac.uk Telephone: 07423474926

If you have any concerns about the way in which the study has been conducted, please contact the Chair of the University Research Ethics Committee on ethics@brookes.ac.uk

Thank you for taking the time to read the information sheet.

PARTICIPANT INFORMATION SHEET

The MenFAS Study:

Understanding mental fatigue after stroke

Support Services

Should you wish to seek external support at any point, these service are available to contact:

- The Stroke helpline : 0303 3033 100 or email at info@stroke.org.uk
  The Stroke helpline offers support and information for people who have experienced stroke.

- The Samaritans: providing confidential, emotional support, 24 hours a day, 365 days a year. Call the Samaritans on 08457 90 90 90 or email jo@samaritans.org

Specifically for carers

Carers direct helpline 0300 123 1053 for practical advice and help about caring

Carers UK helpline: 0808 808 7777 for advice and support.

CONSENT FORM – Participants

The MenFAS Study:

Understanding mental fatigue after stroke

Please initial if you agree

1. I confirm that I have **read the participant information sheet** dated 01/07/2020 and version 1.2 for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that **my participation is voluntary** and that I am **free to withdraw at any time** without giving any reason, without my medical care or legal rights being affected.	
3. I understand that data collected during the study may be looked at by responsible individuals from Oxford Brookes University for monitoring and/or audit to ensure we are complying with regulations. I give permission for these individuals to have access to this data.	
4. I agree to take part in this study.	

Additional:	YES	NO
5. ***OPTIONAL*** *I agree to wear a wrist accelerometer (activity monitor worn on the wrist with a sampling rate at 100 hertz) for 1 week in between two assessment visits. I understand that only movement is tracked and not the type of activity or location.*		
6. ***OPTIONAL*** *I agree to use a smart EMA mobile phone app for 1 week in between two assessment visits. I understand that the app will passively collect information about sleep and rest patterns as indicated by inactivity and not location. Also the app will passively collect background noise in decibels only, no background conversations will be captured at any point.*		

7. OPTIONAL *I agree to use noise cancelling single use disposable earbuds while completing the assessments or between visits if find they assist with concentration levels. I understand that these can be removed at any time, and be disposed of in the rubbish bin. I understand that these are single use earbuds.*		

_____	_____	_____
Name of Researcher	Date	Signature

_____	_____	_____
Name of Participant	Date	Signature

Team contact details for any further information

Professor Helen Dawes Clinical Research Lead Centre for Movement, Occupation and Rehabilitation Research (MOReS) Headington Campus Oxford OX3 0BP	Avril Dillon PhD Student Centre for Movement, Occupation and Rehabilitation Research (MOReS) Headington Campus Oxford OX3 0BP
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