

Investigation of the Relationship between Fatigue and Cognition After Stroke

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Academic Outcomes of Thesis

-The preliminary results of studies 1 and 2 have been approved for a bursary and were presented in the Organisation for Psychological Research Into Stroke (OPSYRIS) Conference on Monday 12th of October, 2015.

-Hawkins, L., Birks, E., Clark, E., Drummond, A., Lagogianni, C., Lincoln, N. B., Milligan, H., Mistri, A., Sprigg, N., Tyrrell, P., Ward, N., Worthington, A. & Worthington, E. (2015). An Investigation of post-stroke fatigue: The Nottingham Fatigue After Stroke (NotFAST) study. *International Journal of Therapy And Rehabilitation*, 22(Sup8), p. S7. 1/3p *(Abstract)*

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-Lagogianni, C., Thomas, S., & Lincoln, N. (2016). Examining the relationship between fatigue and cognition after stroke: A systematic review. *Neuropsychological Rehabilitation*

Thesis Abstract

Background:

Stroke is among the most common causes of disability and stroke survivors may experience cognitive impairment, low mood and fatigue. These three are often associated, as mood and fatigue share some common symptoms and fatigue can also be expressed in a cognitive manner. Fatigue is multifaceted and cannot be easily defined which complicates its measurement. There is a lack of understanding regarding the relationship between fatigue and cognition after stroke and the studies suffer methodological limitations.

Objective:

This project examined the above concepts and the relationship between fatigue and cognition, more specifically, speed of information processing, sustained and selective attention.

Methods:

The relationship was examined by: i) systematically reviewing current evidence on this relationship and ii) by conducting three studies that investigated the relationship between fatigue, mood and cognitive impairment in first stroke survivors in the acute phase without depression, in first stroke survivors in the acute phase with depression and in chronic stroke survivors measuring cognitive aspects of fatigue (Fatigue Scale for Motor and Cognitive Functions) as well. We also iii) explored the reliability of and the components assessed by the Fatigue Severity Scale.

Results:

The systematic review identified 11 studies that examined the relationship. Results were inconclusive as some studies confirmed a significant relationship while others did not. Overall, the findings suggested that memory, attention and speed of information processing are associated with fatigue after stroke, with coefficients ranging from r= .36 to .46. Levels of fatigue and cognitive impairment were reported as moderate. Our three studies did not reveal any statistically significant association between fatigue (general, cognitive or motor) and cognitive performance (either selective and sustained attention or speed of information processing). We also confirmed the uni-dimensionality of the Fatigue Severity Scale in our sample with the use of component analysis; the scale also revealed nearly excellent internal consistency (α=0.95).

Conclusion:

The Fatigue Severity Scale is a reliable fatigue scale that is commonly used in stroke research. The Fatigue Scale for Motor and Cognitive Functions is a relatively new fatigue scale with high psychometric properties. The lack of significant relationship between fatigue and cognitive impairment may be attributed to the choice of cognitive components that were examined in this study.

Implication of Project/Findings:

Cognitive impairment after stroke is very common and so is fatigue. If these two are associated in any way, it will be beneficial to explore such a relationship, or even the lack of it, in order to better understand cognitive mechanisms of fatigue

and to potentially incorporate them in future psychological interventions.

Further Suggestions:

Future studies may benefit from incorporating general and cognitive fatigue scales as well as including domain specific and general cognitive test. The findings of this study highlight the complexity of fatigue and speed of information processing as phenomena. Despite not revealing any significant relationship between certain cognitive aspects and fatigue, it may be worth examining the relationship between fatigue and memory components which are less commonly included in similar studies.

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Components Discussed and Assessed in the Thesis

Component	Definition	Test/Scale
Sustained Attention (Vigilance)	The capacity to prioritise certain stimuli over others (Cohen, 2013)	Dot Cancellation
Selective Attention	The ability to switch/move attention across stimuli; process of discrimination of stimulus (Cohen, 2013; Wickens & McCarley, 2007)	Victoria Stroop Test
Interference (Concentration)	High order mental process which regulates inhibitory functions and disregards irrelevant material (Norman & Shallice, 1986)	Dot Cancellation; Victoria Stroop Test
Speed of Information Processing (Mental Speed)	The efficiency of cognitive functions such as reaction time and amount of time taken to complete tasks (Sweet, 2011)	Information Processing (Adult Memory Information Processing Battery)
General Fatigue	Exhaustion and lack of energy during physical and/or mental activities, disproportionate to the exertion caused, that does not ameliorate with average rest (Staub & Bogousslavsky, 2001)	Fatigue Severity Scale
Cognitive Fatigue (Mental Fatigue)	Lack of energy that occur during physical and/or mental activities, deterioration in cognitive domains, such as memory, attention, and information processing (De Groot et al., 2003; Chaudhuri & Behan, 2004)	Fatigue Scale for Motor and Cognitive Functions-Cognitive Sub-scale
Motor Fatigue	Weakness and loss of capacity to generate force (Schwid et al., 1999)	Fatigue Scale for Motor and Cognitive Functions-Motor Sub-scale

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Chapter 1: Literature Review

1.1 Abstract

Fatigue and cognitive impairment are very common after stroke and have an impact on the quality of life of stroke survivors and their carers. There are several factors that may be associated with fatigue, including cognitive impairment and various mechanistic explanations for fatigue. There is no consensus as to whether fatigue and cognitive impairment are associated. In addition, there is a challenge in measuring these two due to the lack of instruments that have been validated in people with stroke. This chapter reviews the prevalence of fatigue, predictors of fatigue, factors associated with cognitive impairment after stroke, and the relationship between fatigue, cognitive impairment and depression, as well as discussing issues with psychometric evaluation and methodological considerations.

1.2 Objectives

The aims of this chapter are to: 1) describe stroke and review common symptoms after stroke; 2) describe fatigue and its prevalence; 3) review the mechanisms of and the factors associated with fatigue; 4) discuss psychometric properties and their relevance to this thesis; 5) present an overview of the most commonly used fatigue scales used in stroke research and the issues associated with assessing fatigue; 6) describe the impact and prevalence of cognitive impairment and discuss the most commonly associated factors of cognitive impairment; 7) present an overview of the most commonly used cognitive impairment tests used in stroke research; 8) discuss the relationship between depression and cognition; 9) discuss cognitive fatigue and 10) discuss

methods for examining the relationship between fatigue and cognitive impairment. The aims of the thesis are also presented at the end of this chapter.

1.3 Stroke

According to the definition provided by the World Health Organisation (Aho et al., 1980) stroke is "a clinical syndrome of presumed vascular origin, typified by rapidly developed clinical signs of focal or global disturbance of cerebral functions, lasting more than 24 hours, with no apparent cause other than vascular origin" (pp. 114). It is among the leading causes of disability in the UK and is the third most common cause of morbidity (Adamson, Beswick, & Ebrahim, 2004). A stroke occurs when the blood supply to the brain is disrupted causing neurological deficits. There are several types of stroke which can either be identified by lesion location, or pathology such as ischaemic and haemorrhagic (Reyzelman, Karamanoukian, Aoukar & Freeman, 2004).

Ischaemic strokes are caused by blood clots in the arteries supplying blood to the brain, and haemorrhagic strokes by the bursting of a blood vessel which results in blood leaking into the brain tissue. The former accounts for about 80% of all strokes while the latter is less common (Lindley, 2008). Current estimates suggest that 152,000 strokes occur annually in the UK, and that each year 1,200,000 people will be living with the consequences of stroke (Stroke Association, 2016).

1.4 Common Symptoms after Stroke

The effects of stroke are known to be devastating and long lasting. A stroke onset may result in motor impairment and sensory impairment, and may cause emotional, cognitive

and social consequences (Lai, Studenski, Duncan, & Perera, 2002) as well as pain and fatigue (Miller et al., 2013).

1.4.1 Motor Impairment after Stroke

Muscle weakness produces a spectrum of symptoms. Spasticity (abnormal involuntary movements) affects as many as 30% of stroke survivors, with elbows, wrists and ankles being the most commonly affected (Thibaut et al., 2013). Hemiparesis (weakness of entire side of the body) occurs in around 60% of patients experience residual motor impairment even beyond the acute phase (≥6 months post stroke) (Lai et al., 2002; Nakayama, Jørgensen, Raaschou, & Olsen, 1994). With regards to upper limb function, it is estimated that while 80% will permanently lose full upper limb functioning (Kwakkel, Kollen, van der Grond, & Prevo, 2003; Nakayama et al., 1994) only 20% of stroke patients regain full functional recovery. Balance may also be affected, causing an inability to maintain position (Niam, Cheung, Sullivan, Kent, & Gu, 1999), which increases the likelihood of falling, particularly in patients with hemiplegia (Geiger, Allen, O'Keefe, & Hicks, 2001). Motor weakness causes difficulties which are reported in the chronic phase of stroke with either severe disability (van de Port, Kwakkel, van Wijk, & Lindeman, 2006) or reduced walking speed (Kollen, van de Port, Lindeman, Twisk, & Kwakkel, 2005), while about 30% of patients are completely unable to walk during the acute phase (Buurke et al., 2008). Both urinary and faecal incontinence are common after stroke due to a lack of muscle control (Brittain, Peet, & Castleden, 1998). Muscle weakness also causes dysphagia (difficulty swallowing). The prevalence ranges from 23% to 50% in the acute phase of stroke and can leave the individual unable to eat normally (Singh & Hamdy, 2006).

1.4.2 Sensory Impairment after Stroke

The prevalence of *visual field deficits* after stroke is not clear as one study reported it to be as low as ≤1% (Gilhotra, Mitchell, Healey, Cumming, & Currie, 2002), whereas other studies provide higher ranges (49%-57%) (Falke et al., 1991; Rowe et al., 2009). Hemianopia is the most common visual field deficit and accounts for around 70% of all visual deficits, compromising the daily activities of stroke survivors (such as walking) (Nelles et al., 2009).

1.4.3 Emotional Consequences of Stroke

Due to the medical nature of stroke, stroke survivors feel that their psychological needs are often neglected and more emphasis is given on their physical problems (Stroke Association, 2013b). Emotional consequences include depression, anxiety, post-traumatic stress disorder and emotionalism. According to systematic reviews, depression is estimated to occur in around 31% to 33% of stroke survivors and anxiety affects around 28% of patients with similar prevalence rates in acute and chronic phase (Hackett & Pickles, 2014; Hackett, Yapa, Parag, & Anderson, 2005). However, another review based on 50 studies by Ayerbe, Ayis, Wolfe, & Rudd (2013), suggested that depression prevalence was 29%, with higher incidence within 5 years after stroke. Post-traumatic stress disorder has been reported to affect somewhere between 5-30% of patients (Lincoln, Kneebone, Macniven, & Morris, 2012) and emotionalism (extreme emotional responses that do not correspond to inner state) somewhere between 20-25% of patients (Calvert, Knapp, & House, 1998).

Depression and anxiety are estimated to be persistent

up to 1 year post-stroke in 36% and 34% of patients respectively (Donnellan, Hickey, Hevey, & O'Neill, 2010). According to a review conducted by Hirschfeld, (2001), around 50% of patients had a comorbidity of depression and anxiety within 12 months post-stroke. The impact of stroke on mood is of clinical significance as it can directly affect medication adherence, rehabilitation and quality of life (Masskulpan, Riewthong, Dajpratham, & Kuptniratsaikul, 2008). Previous studies have shown that stroke patients without post-stroke depression recover better and faster (Williams et al., 2007).

1.4.4 Cognitive Consequences of Stroke

Cognitive effects of stroke affect 50-70% of stroke survivors (Hochstenbach, Mulder, van Limbeek, Donders, & Schoonderwaldt, 1998; Mok et al., 2004; Rasquin, Verhey, Lousberg, Winkens, & Lodder, 2002) and include: impairments of memory (short-term, long-term, verbal, visual, working), attention (divided, sustained, selective, concentration, neglect), executive functioning (cognitive control, planning, inhibition, flexibility, organization), language (expression, reception), visuospatial ability (visual perception, construction) and mental speed (speed of information processing, reaction time) (Cumming, Marshall, & Lazar, 2013). According to a systematic review conducted by West, Bowen, Hesketh & Vail (2008), evidence regarding the prevalence of apraxia (inability to execute a learned skill; Kaya, Unsal-Delialioglu, Kurt, Altinok, & Ozel, 2006) is inconsistent since there are no figures available, however it is estimated that around 50% of patients with right side hemiplegia suffer motor apraxia. This is in accordance with another study that also suggested that 54% of patients with right side hemiplegia and 25% of those with left side

hemiplegia suffer motor apraxia (Kaya et al., 2006). Cognition after stroke is further discussed later in the thesis in more details.

1.4.5 Social Consequences of Stroke

The social consequences of stroke affect leisure, work and financial domains (Birkett, 2008; Sirven & Malamut, 2008; Stein, Harvey, Macko, Winstein, & Zorowitz, 2009). Due to the functional limitations that many stroke patients have, it may take them long to return to work after their stroke (Tanaka, Toyonaga, & Hashimoto, 2011), which impacts on people's financial situation (Stroke Association, 2012; Stroke Association 2013a). It is estimated 44% of patients will fully return to work at some point (Daniel, Wolfe, Busch, & McKevitt, 2009) while studies have shown that the majority of these people will return to work within 6-12 months post-stroke (Glozier, Hackett, Parag, & Anderson, 2008; Saeki, Ogata, Okubo, Takahashi, & Hoshuyama, 1995; Wozniak et al., 1999). Overall, financial difficulties after stroke are estimated to affect 24% to 33% of patients (Daniel et al., 2009).

Leisure and social activities (such as travelling, having hobbies and meeting with friends socially) are significantly reduced after stroke in both younger (Pound, Gompertz, & Ebrahim, 1998) and older stroke patients (Anderson, 1992). The estimated range of stroke survivors who have a decrease in leisure and social activities is between 15% and 79% (Corr & Wilmer, 2003; Kersten, Low, Ashburn, George, & McLellan, 2002). Patients usually report that they have more trouble with their spouses following stroke, including conflicts, separation and deterioration in sexual life (Daniel et al., 2009; Teasell, McRae, & Finestone, 2000). For instance, Teasell et

al., (2000) reported that 15% of the couples went through a divorce within three months after discharge and that psychosocial occurrences such as these had an effect on the patients' rehabilitation and recovery.

Caregivers are also affected by the experience of distress, low mood, the load of several responsibilities and by having trouble adjusting to their new role (Low, Payne, & Roderick, 1999). Finally, troubles in sexual and intimate relationships were also detected in some studies; between 14% and 75% of stroke survivors reduce or cease sexual intercourse (Korpelainen, Kauhanen, Kemola, Malinen, & Myllylä, 1998; Sjögren & Fugl-Meyer, 1982), 38% of couples have frequent conflicts and 15% separate within 3 months of stroke onset (Teasell et al., 2000).

1.4.6 Pain after Stroke

Pain is a very common consequence of stroke. Up to 42% of patients report to feel pain in the acute phase of stroke (van Wijck, Smith, Halliday, & Mead, 2013). There are two main types of stroke related pain: central pain (neurological pain) and musculoskeletal pain (muscle tension; usually affecting the shoulder) (Lincoln et al., 2012). Central pain is estimated to occur in around 8% of stroke survivors (Andersen, Vestergaard, Ingeman-Nielsen, & Jensen, 1995) and shoulder pain is estimated to affect between 22% and 32% of stroke survivors within 4 months post-stroke (Jönsson, Lindgren, Hallström, Norrving, & Lindgren, 2006; Lindgren, Jönsson, Norrving, & Lindgren, 2007). Pain also affects patients in the chronic phase. Kong, Woon, & Yang, (2004) found that 42% of stroke patients self-reported chronic pain at ≤6 months post-stroke. Pain can decrease quality of life and slow down the rehabilitation process (Klit, Finnerup,

Overvad, Andersen, & Jensen, 2011; Miller et al., 2013).

1.4.7 Fatigue after Stroke

Fatigue manifests in both a physical and mental lack of energy, and feelings of weariness, with high prevalence after stroke (30-70%) (Annoni, Staub, Bogousslavsky, & Brioschi, 2008; Schepers, Visser-Meily, Ketalaar & Lindeman, 2006; Naess, Nyland, Thomassen, Aarseth, & Myhr, 2005; Carlsson, Moller, & Blomstrand, 2004; De Groot et al., 2003; Glader et al., 2002; Ingles et al., 1999; Staub & Bogousslavsky, 2001; Winward, Sackley, Metha, & Rothwell, 2009). Fatigue is the least well understood symptom of stroke in terms of its cause, course and treatment (Barbour & Mead, 2012). There is a lack of understanding of fatigue from both patients and nursing staff, leading to patients not reporting fatigue. For instance in a study by Zedlitz et al., (2012) only 17% of the participants had been informed about the symptoms of fatigue and their impact which indicates that there is no sufficient education on the matter. While many studies have examined post-stroke fatigue, there is still a lack of understanding regarding its associated factors and what is its relationship with cognitive impairment. It is essential to investigate potential cognitive aspects of fatigue because this may contribute to the effective diagnosis and prevention of fatigue. Studies that have looked into the relationship between cognition and fatigue have produced contradictory results and the designs and measurements that they used compromise the integrity of the results. Therefore this project focused on post-stroke fatigue. Fatigue after stroke is further discussed later in the thesis in more details.

1.5 Fatigue

1.5.1 Definition of Fatigue

The term fatigue is used to describe feelings of exhaustion and a lack of energy that occur during physical and/or mental activities, disproportionate to the exertion caused, that does not ameliorate with average rest (Staub & Bogousslavsky, 2001; De Groot et al., 2003). Individuals suffering from fatigue are unable to sustain mental effort for long periods of time, take longer to regain energy and usually have difficulties with stress, concentration, social interactions and emotional instability (Johansson, Berglund, & Rönnbäck, 2009; Johansson, Starmark, Berglund, Rödholm, & Rönnbäck, 2010; Lindqvist & Malmgren, 1993; Rödholm, Starmark, Svensson, & Von Essen, 2001). It is among the commonest consequences of stroke and can have an impact on morbidity, duration of hospitalisation mood, rehabilitation, quality of life, driving and return to work (Barbour & Mead, 2012; Moran et al., 2013). The UK Stroke Forum, (2014) highlighted the impact of fatigue on all aspects of rehabilitation and life after stroke, and the importance of this research area. In addition, fatigue management and prevention are ranked among the top research priorities after stroke by both stroke survivors and professionals (Pollock, St George, Fenton, & Firkins, 2014) and a recent survey conducted in stroke wards across Scotland showed that fatigue management is top priority for stroke nurses (Rowat, Pollock, St George, Cowey, Booth & Lawrence, 2016).

1.5.2 Fatigue in the General Adult Population

Acknowledging the impact of fatigue on patients with clinical conditions, is challenging since fatigue may also occur

in the general population. There is a fine line between normal and abnormal fatigue (Cella, Lai, Chang, Peterman, & Slavin, 2002; Dagfinrud, Vollestad, Loge, Kvien, & Mengshoel, 2005). Fatigue in the general population tends to be temporary whereas disease specific fatigue tends to be persistent, more extreme and long-term (Dagfinrud et al., 2005). David et al., (1990) reported that 10.2% of men and 10.6% of women that attended general practices had high levels of fatigue. In a study conducted in Norway, it was reported that 50% (20% of men and 30% of women) of the general population complained about symptoms of tiredness and fatigue (Hjermstad, Fayers, Bjordal, & Kaasa, 1998). Glaus, (1998) reported that 55% of healthy individuals referred to physical symptoms of fatigue, 21% referred to affective symptoms of fatigue and 24% referred to cognitive symptoms of fatigue.

The predictors of fatigue in the general population have been examined. For instance, women tend to report fatigue more frequently than men (Lerdal, Wahl, Rustøen, Hanestad, & Moum, 2005; Loge, Ekeberg, & Kaasa, 1998; Pawlikowska et al., 1994; Schwarz, Krauss, & Hinz, 2003; Watt et al., 2000). Level of education has been inversely correlated with fatigue (Lerdal et al., 2005). Age and psychological distress have been positively correlated with fatigue (Lerdal et al., 2005; Schwarz et al., 2003; Pawlikowska et al., 1994). Individuals from the general population are more likely to experience fatigue if they have any physical or mental comorbidities (Pawlikowska et al., 1994; Lerdal et al., 2005; Watt et al., 2000).

1.5.3 Fatigue Prevalence in Conditions Other Than Stroke

Fatigue is a very common symptom in many medical and chronic conditions. Cancer patients frequently experience

cancer-related fatigue symptoms and it is estimated that around 50%-90% of cancer patients are fatigued (Campos, Hassan, Riechelmann, & Del Giglio, 2011; Wagner & Cella, 2004; Weis, 2011). For many cancer survivors, fatigue is a persistent problem even after the cessation of their chemotherapy or radiotherapy (Campos et al., 2011) and fatigue is ranked by patients as one of their the most distressing symptoms (Butt et al., 2008). Factors most commonly associated with cancer related fatigue are: cancer treatment and medication, immune activation, depression, stress, sleeping patterns, infections, hormonal changes (such as thyroid) and anemia (Campos et al., 2011; Cella et al., 2002; Weis, 2011).

HIV patients also experience high levels of fatigue with an estimated prevalence between 20%-60% (Adinolfi, 2001; Sullivan, Dworkin, & Adult and Adolescent Spectrum of HIV Disease Investigators, 2003) and it has been reported that it is multifaceted and complex, as it has been associated with anemia, thyroid dysfunction, infections, eating and sleeping habits, depression, anxiety and medication (Adinolfi, 2001). It has also been suggested that in order to treat HIV related fatigue, physicians need to examine underlying components of fatigue (Sullivan et al., 2003).

People with traumatic brain injury also have high levels of fatigue with estimated prevalence between 21% and 73% (Mollayeva et al., 2014). Several factors may contribute to the development of fatigue after traumatic brain injury such as substance abuse prior to the injury, insomnia, depression, anxiety, medical disability and marital status. No significant effect of sex, injury severity and education has been found on fatigue (Norrie et al., 2010). Fatigue in traumatic brain injury is complex and multifaceted (Mollayeva et al., 2014).

Fatigue is reported to be in the three most disabling symptoms for patients with multiple sclerosis (Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994; Freal, Kraft, & Coryell, 1984; Hadjimichael, Vollmer, & Oleen-Burkey, 2008; Krupp, Alvarez, LaRocca, & Scheinberg, 1988) with an estimated prevalence between 53% and 90% (Strober, 2015). As in other clinical conditions, various factors are associated with severity of fatigue, such as depression, anxiety and immunologic abnormalities, (Braley & Chervin, 2010).

Fatigue is also a common symptom in people with Parkinson's disease. It is estimated that around 40% experience fatigue. Fatigue in people with Parkinson's disease seems to be independent of depression, cognitive impairment and sleeping patters (De Groot et al., 2003). Fatigue in Parkinson's disease can be either acute or chronic and to have a significant impact on people's life (Karlsen, Larsen, Tandberg, & Jørgensen, 1999).

The question of whether there is any significant difference between post-stroke fatigue and fatigue in multiple sclerosis has been addressed by Lukoschek, Sterr, Claros-Salinas, Gütler, & Dettmers, (2015), who reported that fatigue in people with stroke is similar to fatigue in people with MS however fatigue in people with MS was more frequent. They also found that there was an association between fatigue and working capacity in people with multiple sclerosis but not in stroke, which is perhaps due to the fact that people with multiple sclerosis are usually younger and fatigue may therefore have a greater impact on work. Another observation that indicates a similar fatigue profile is that fatigue in most other chronic conditions can manifest in both physical and cognitive manner (De Groot et al., 2003; Johansson et al., 2009). Although the abovementioned conditions differ in

terms of their pathology, it seems that fatigue is experienced in similar ways across patients. As no robust studies have been conducted to date to examine fundamental differences between medical conditions with regards to fatigue, it is reasonable to assume that fatigue has a similar profile across medical conditions. Although, the aetiology of fatigue may differ, the experience of fatigue is debilitating regardless of the disease condition and can have a great impact on quality of life.

1.5.4 Prevalence of Fatigue after Stroke

Fatigue differs in quality and duration from typical symptoms of tiredness, by being more persistent and intense (Kirkevold, Christensen, Andersen, Johansen, & Harder, 2012). It is among the most common symptoms experienced by stroke survivors, and is reported to be overwhelming (Crosby, Munshi, Karat, Worthington, & Lincoln, 2012; Glader et al., 2002; Ingles et al., 1999). The estimated prevalence of post-stroke fatigue ranges from 30-70% (Schepers, Visser-Meily, Ketalaar & Lindeman, 2006; Naess, Nyland, Thomassen, Aarseth, & Myhr, 2005; Carlsson, Moller, & Blomstrand, 2004; De Groot et al., 2003; Glader et al., 2002; Ingles et al., 1999; Staub & Bogousslavsky, 2001; Winward, Sackley, Metha, & Rothwell, 2009). The variation of these percentages can be attributed to the time since stroke onset that the assessment takes place and the fact that fatigue is very abstract, subjective, multifaceted and complex which compromises its measurement, prediction and treatment (Aaronson et al., 1999).

Another issue that limits measuring the prevalence of fatigue after stroke is the lack of a standard definition. Falconer, Walsh, & Harbison (2010), showed that the

expression of fatigue by an individual depends on the terminology used and the sex of the individual. They showed that when individuals are asked if they are "fatigued" they are less likely to express symptoms of fatigue, than if they are simply asked if they are feeling "tired".

1.5.5 Causes of Fatigue after Stroke

As fatigue is multifaceted, there are various explanations with regards to its causal mechanisms. It was initially argued that fatigue is a response to dysfunctions in the central nervous system and other stroke associated pathophysiology (Kutlubaev & Mead, 2012; Staub & Bogousslavsky, 2001). Contemporary theories indicate that fatigue is a disease specific symptom, which can exist independently from its associated factors (Mead et al., 2011; van Eijsden, van de Port, Visser-Meily, & Kwakkel, 2012). With regards to physical activity and movement, a theoretical framework of unpleasant symptoms introduced by Lenz, Suppe, Gift, Pugh, & Milligan, (1995) suggests that the reduction of ambulatory activity may have an effect on fatigue. The hypothesis is that when the body is tired due to physical deterioration, fatigue signals the need for rest, which suggests that fatigue is an automatic response to decreased mobility.

Another explanation of fatigue is that it is due to an active inflammatory response. The immunology of stroke may be implicated in the development of fatigue. For instance, inflammation caused by cerebral ischemia may be mediated by cytokines (inflammatory molecules). Inflammation leads to secretion of various cytokines crucial to immune signalling, which adversely influence mood, libido, psychomotor functioning, sleep patterns, appetite and fatigue (Barritt & Smithard, 2011). Pro-inflammatory cytokines are thought to

induce post-stroke fatigue by affecting appetite, sleep, social withdrawal and causing pain and fever. Cognitive fatigue is thought to be the outcome of impairment in glutamate signalling, caused by the effects of pro-inflammatory cytokines, which is considered to be crucial for information gathering and processing (Ormstad & Eilertsen, 2015).

Another model of fatigue has been recently introduced and is concerned with motor cortex excitability. According to this model, voluntary effort can exacerbate fatigue (Kuppuswamy, Clark, Turner, Rothwell, & Ward, 2015). Voluntary effort is regulated by various biological systems, such as the perception of task related effort, motivational and limbic systems (such as depression), cognitive processing, sensory and motor components and other homeostatic mechanisms (such as sleep disturbances). Volitional movement depends on the perceived task related effort and the output of M1 (primary motor cortex). It has been shown that stroke survivors with high fatigue levels have low corticospinal excitability and that highly perceived task related effort is associated with more central activation failure (the ability of transcranial magnetic stimulation to recruit additional muscle force in the M1 than the existing output) (Kuppuswamy, Clark, Turner, et al., 2015). Motor cortex excitability can affect reaction and movement time therefore low motor cortex excitability in the lesioned hemisphere may be responsible for the development of fatigue after stroke (Kuppuswamy, Clark, Sandhu, Rothwell, & Ward, 2015). In essence, excitability of cortical motor pathways is compromised in patients with post-stroke fatigue and the latter may be attributed to motor speed. The theory by Kuppuswamy et al. (2015) is also based on the abovementioned theory regarding pro-inflammatory cytokines and the authors suggested that inflammatory processes may be a potential

cause of the longer term changes in the sensorimotor system which results in fatigue.

From a psychosocial point of view, according to a model of fatigue described by Ormstad & Eilertsen (2015) the main characteristics of fatigue after stroke are: feelings of unjustified tiredness and lack of energy, the need to take frequent breaks and naps and hypersensitivity to stress. It has also been suggested that post-stroke fatigue occurs in patients with cognitive difficulties due to the fact that brain plasticity is forming alternative pathways in an attempt to compensate for the cognitive loss after brain injury; this is called *coping theory* (Boksem, Meijman, & Lorist, 2006). Thus, for example, when people are incapable of concentrating easily, the individual has to recruit all of his/her cognitive control resulting in increased distractibility, cognitive overloading and excessive use of monitoring (Boksem et al., 2006). Hence, patients with cognitive impairment may experience fatigue due to their cognitive impairment rather than other emotional or physical factors.

1.5.6 Fatigue Onset

There is conflicting evidence regarding the time of onset of post-stroke fatigue. It is generally believed that it occurs in the acute phase (Choi-Kwon & Kim, 2011), with some studies reporting the development of fatigue within one week post-stroke (Choi-Kwon, Han, Kwon, & Kim, 2005 ; Christensen, Johnsen, Watt, Harder, Kirkevold & Andersen, 2008). However, another study suggested that post-stroke fatigue increased over time (Schepers, Visser-Meily, Ketelaar, & Lindeman, 2006), while van de Port, Kwakkel, Schepers, Heinemans, & Lindeman, (2007) argued that post-stroke

fatigue peaks 12 months post-stroke.

1.5.7 Factors Associated with Fatigue after Stroke

Post-stroke fatigue may be attributed to physical, psychosocial and cognitive factors as well as lesion location (Vuletić, Lezaić, & Morović, 2011; Choi-Kwon & Kim, 2011; Jaracz, Mielcarek, & Kozubski, 2007; Kutlubaev, Duncan, & Mead, 2012; Michael, Allen, & Macko, 2003). Factors that are associated with fatigue may be consequences or predictors as an association does not reflect causality. *Physical factors* are associated with the development of fatigue (Zedlitz, Visser-Meily, Schepers, Geurts, & Fasotti, 2011). Post-stroke fatigue has been associated with poor health and mobility problems (De Groot et al., 2003; van Eijsden et al., 2012) and sleep disturbances, such as insomnia, excessive sleepiness, interruptions while sleeping (Appelros, 2006; Halvor Naess, Lunde, Brogger, & Waje-Andreassen, 2012; Park et al., 2009; Schepers, Visser-Meily, Ketelaar, & Lindeman, 2006). Mobility and independence levels are associated with the presence of fatigue. According to Mead, Bernhardt, & Kwakkel, (2012) many observational studies indicate that stroke patients spend a significant amount of time in hospital wards after their stroke, with limited independence and mobility which in turn decrease fitness levels which may support the association between fatigue and mobility and independence.

A systematic review by Duncan, Kutlubaev, Dennis, Greig, & Mead, (2012) revealed that despite having reasons to believe that fitness can influence fatigue after stroke, evidence shows that such an association has not been confirmed. Furthermore, vitamin B12 deficiency has also been associated with fatigue after stroke. Stroke survivors have lower levels of B12 vitamin than healthy matched individuals (Pieters et al.,

2009). B12 vitamin deficiency has been implicated as a risk factor of stroke (Nygård et al., 1997), and enhancers of B12 vitamin have been used successfully in the treatment and prevention of stroke (Butler et al., 2006; Saposnik, 2011). Compiling the above evidence, a recent study (Huijts, Duits, Staals, & van Oostenbrugge, 2012) reported that there is a significant effect of B12 deficiency on stroke survivors' experience of fatigue and that the former is independently associated with the presence of fatigue in first-ever lacunar stroke patients.

Lesion location has also been associated with fatigue. It was shown that basal ganglia infarcts, as opposed to brainstem and cerebellar infarcts, were more common in patients with post-stroke fatigue, and that the presence of brain stem infarction was an independent predictor of the presence of post-stroke fatigue (Tang et al., 2010). It has also been documented that right hemisphere stroke results in a higher prevalence of fatigue than left hemisphere (Stein, Gordon, & Hibbard, 1996), and that right insular stroke results more often in fatigue than other types of stroke (Manes, Paradiso, & Robinson, 1999).

Psychosocial factors associated with fatigue include both psychological and environmental factors. Depression and anxiety have been consistently associated with fatigue, with high fatigue levels being associated with higher anxiety and depression scores (Annoni, Staub, Bogousslavsky & Brioschi, 2008; De Groot et al., 2003). Perception of loss of life control has also been found to be associated with fatigue through the mechanisms of locus of control, with patients who experience fatigue reporting more often that they believe that they have no power over their lives after their stroke (Gramigna et al., 2007). Furthermore, coping strategies have been associated

with post-stroke fatigue, with stroke patients with fatigue resorting to avoidance and negative coping strategies as well as reporting less orientation towards problem-solving more often than healthy individuals (Jaracz, Mielcarek, & Kozubski, 2007; Wu, Barugh, Macleod, & Mead, 2014; Zedlitz et al., 2011).

Self-efficacy has been associated with confidence in the ability to perform activities and therefore it is believed that efficacy is a contributing psychological factor in the presence of fatigue (Zedlitz et al., 2011; Michael et al., 2003). Finally, social support and general interaction with the immediate social network also seems to be important, with lower levels of social support resulting in higher fatigue severity (Lerdal et al., 2009; Schepers et al., 2006; Tang et al., 2010; Michael et al., 2003). However, Zedlitz et al., (2011) found that stroke survivors with fatigue reported higher levels of social support than healthy controls. It is not clear if perception of and/or need for social support is displayed in similar patterns in healthy and stroke affected individuals, therefore these results need further investigation.

Cognitive factors associated with fatigue have received less attention with regards to stroke compared to other neurological conditions. Fatigue has been associated with cognitive impairments, such as speed of information processing in multiple sclerosis (MS) (Andreasen, Spliid, Andersen, & Jakobsen, 2010) and traumatic brain injury (TBI) (Johansson, Berglund, & Rönnbäck, 2009), but the strength of the relationships is still unclear. The strength of the relationship between cognition and fatigue is also unclear in people with stroke. There are studies that have attempted to examine the relationship between fatigue and cognitive impairment after stroke and the majority of them did not find

any significant relationship between the two. However, most of these studies (for instance: Park et al., 2009; Schepers, Visser-Meily, Ketelaar, & Lindeman, 2006; van Eijsden et al., 2012) used the Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975) to assess cognition, which seems to not be sensitive enough to detect such a relationship (Blake, McKinney, Treece, Lee, & Lincoln, 2002; Nys et al., 2005). Other studies that used more extensive neuropsychological batteries (such as Hubacher et al., 2012; Radman et al., 2012) did report significant correlations, but there are studies that also used extensive neuropsychological batteries, that did not confirm an association (such as Winkens, Van Heugten, Fasotti, Wade, et al., 2009).

In a study that used data from 1080 British stroke patients, Mead et al., (2011) reported that all known factors that have been associated with fatigue, such as demographics and mood, only explained 30% of the variance in severity of fatigue, which suggests that there must potentially be other predictors, such as cognition. Based on the above, the current project examined the contribution of cognitive factors to the experience of fatigue.

1.5.8 Demographic Characteristics and Fatigue

Demographics also appear to be of importance in the development and presence of fatigue. It is suggested that fatigue affects women more than men (Barbour & Mead, 2012; Christensen et al., 2008; Glader, Stegmayr, & Asplund, 2002; Lerdal et al., 2011; Mead et al., 2011; Schepers et al., 2006). However, one study (Parks et al., 2012) found that younger age was a stronger predictor of fatigue than older age, and more specifically younger age was associated with the cognitive and psychosocial aspects of fatigue. Studies

have also shown an association between fatigue and level of education and employment (Naess & Nyland, 2013; Tang et al., 2010), living arrangements and marital status (Annoni et al., 2008). However the direction of causality in these relationships is not clear.

Falconer, Walsh, & Harbison (2010), showed that female stroke patients displayed greater variability in reported fatigue symptoms than male stroke patients. Men's scores in the Fatigue Severity Scale were strongly correlated with physical fatigue statements whereas women's responses included more diverse symptoms including cognitive, with most of the women being classified as more fatigued using simple fatigue scales.

Being single before stroke onset has also been associated with the presence of post-stroke fatigue (Choi-Kwon et al., 2005; Annoni, Staub, Bogousslavsky & Brioschi, 2008; Lerdal et al., 2011). There are however other studies do not support a relationship between fatigue and sex, age and marital status (Michael et al., 2003; Appelros, 2006; Choi-Kwon, Han, Kwon, & Kim, 2005; Carlsson, Moller, Blomstrand & Carlsson, 2003; Ingles, Eskes, & Phillips, 1999; Schepers et al., 2006). Such inconsistencies may be attributed to the different measures and the different types of participants included in the studies. Therefore the data on the association between post-stroke fatigue and socio-demographic factors are inconsistent.

1.5.9 Pre-stroke Fatigue and Previous Strokes

Pre-stroke fatigue has also been associated with the presence of post-stroke fatigue (Choi-Kwon et al., 2005; Annoni, Staub, Bogousslavsky & Brioschi, 2008; Lerdal et al., 2011). It is however possible that post-stroke fatigue differs

from pre-stroke fatigue in terms of severity (Annoni et al., 2008). Studies have also shown that fatigue is associated with previous strokes, with patients who have had more than one stroke being more likely to be fatigued (Glader et al., 2002; De Groot et al., 2003).

1.5.10 Association Between Fatigue and Depression after Stroke

Post-stroke fatigue has been found to be associated with post-stroke depression, which may in part be due to shared symptoms (Kutlubaev & Mead, 2013; Schepers et al., 2006; Tseng, Billinger, Gajewski, & Kluding, 2010). Some items in depression scales can lead to a misdiagnosis of fatigue as depression. For instance, items such as "I feel as if I am slowed down" can reflect either depression or fatigue, or both. Lack of motivation and energy occur in both. However, fatigue does not necessarily involve low self-esteem or guilt. Fatigue and depression also differ biologically. The hypothalamic-pituitary-adrenal axis, which is the complex of three endocrine glands, has a downwards regulation in fatigue, which means that it has decreased activity as opposed to depression, during which it is increased (hyperactivated) (Leone, 2010). There is also evidence that although pharmacological interventions can improve sleep difficulties caused by depression, fatigue remains unchanged (Brioschi et al., 2009).

Several studies have shown that there is a significant relationship between depression and fatigue after stroke (Hubacher et al., 2012; Lerdal et al., 2011; Radman et al., 2012), and the correlation coefficients in both the acute and the chronic phase of stroke range from r= .60 to .63. However, patients without depression also experience fatigue (van der Werf, van den Broek, Anten, & Bleijenberg, 2001). In

a recent study, 49% of patients with fatigue did not meet the criteria for depression (Parks et al., 2012). Studies have shown that less than half of fatigued patients experience depression (Carlsson, Moller, Blomstrand & Carlsson, 2003; Ingles et al., 1999) and that depression accounts for less than 30% of the variance in fatigue (Mead, Graham, Dorman, Bruins, Lewis, Dennis & Sandercock, 2011). In addition, studies have shown that while fluoxetine, duloxetine or citalopram can improve depression, fatigue remains unaffected (Choi-Kwon, Choi, Kwon, Kang, & Kim, 2007; Karaiskos, Tzavellas, Spengos, Vassilopoulou, & Paparrigopoulos, 2012). Therefore, although there is some evidence of a relationship between depression and fatigue, it appears that mood is not sufficient to explain the development and course of fatigue (Kutlubaev & Mead, 2013), and that fatigue should be treated as a separate symptom (Johansson & Rönnbäck, 2012).

It is likely that depression is associated with fatigue because they overlap in symptomatology. Most studies do not exclude depressed patients and evidence regarding post-stroke fatigue in the absence of post-stroke depression is sparse (Glader et al., 2002).

It is very challenging to measure fatigue in stroke settings and even more challenging is the choice of appropriate fatigue measures. Before proceeding to discuss the various fatigue scales that are being used in stroke research, there needs to be an understanding of which psychometric properties determine whether a scale is good or not and how to decide on which properties are relevant to each study.

1.6 Psychometric Properties of Measurements

Psychometrics is the branch of science that is concerned with instrument development and adaptation; psychometrics assess whether instruments are reliable and valid in measuring a specific construct in different populations. Good psychometric properties are essential in order to confirm that the scale/test used is actually measuring what it is supposed to be measuring and that it does this consistently (Ginty, 2013).

There are two fundamental sets of psychometric properties: reliability and validity. The former is concerned with the dependability of an instrument and the latter is concerned with whether the instrument measures what it claims to measure. Reliability is *making* an instrument accurate and validity is *choosing* an appropriate instrument. There are several types of *reliability* and several types of *validity*.

1.6.1 Reliability

The main types of reliability are: internal consistency, test-retest reliability, split-half reliability and inter-rater reliability*. Internal consistency* measures the homogeneity of the test, that is whether the items of the instrument measure the same. Internal consistency is measured by Cronbach's alpha (α) and can range between 0-1; there are recommendations that correlation coefficients should be considered weak if they range from .1 to .3, moderate if they range from .4 to .6 and strong if they range from .7 to .9; (Hatcher, 2003). The higher the α values the stronger is the relationship measured; however, values very close to 1 (perfect correlation) may indicate item redundancy as the items measure virtually the same construct. *Test-retest*

reliability is the correlation between two scores obtained by administering the test twice (also known as temporal stability). It is used to monitor critical differences in diseases or interventions. Test-retest reliability is also described in terms of its strength according to the ranges recommended for internal consistency above [.1-.3= weak; .4-.6 moderate; .7-.9= strong (Hatcher, 2003)]. *Split-half reliability* assesses the correlation between the two equal halves of an instrument in order to show whether the two parts of the test are consistent with each other. *Inter-rater reliability (kw)* is concerned with the consensus among raters when there are more than one examiners; strong inter-rater reliability (as categorised for internal consistency) indicates strong consensus (Lindley, 2008; Litwin, 1995).

Reliability may be influenced by various factors such as scoring, context, mood, and administration instructions therefore reliability values only indicate an estimation of how precise the measurement is. Reliability can be improved by the use of concise and clear items with homogenous terminology; in addition, larger samples can also improve reliability studies. When considering self-report scales in the context of fatigue after stroke, internal consistency and test-retest reliability are of particular importance; when considering cognitive tests, test-retest reliability and inter-rater reliability are of interest (Schutte & Malouff, 1995).

1.6.2 Validity

Validity is concerned with the extent to which an instrument assesses what it claims to measure. As with reliability, there are also various indices to establish validity; *Face validity* tests whether the items of the scale appear to be relevant to what the instrument measures based on the

meaning of the items. It is recommended that validity coefficients above .80 are considered high (Schumacker & Lomax, 2010; Thompson, 2013). *Predictive validity* is concerned with the degree to which performance on the instrument can predict future outcomes. Two measures to describe predictive validity are *sensitivity* and *specificity*. Both these indices are used to evaluate diagnostic tests; sensitivity is concerned with the ability of the test to correctly identify individuals *with* the condition measured while specificity refers to the ability of the test to correctly identify those *without* the condition (Lalkhen & McCluskey, 2008). Receiver Operating Characteristics (ROC) curves are calculated to identify the optimum cut-off scores of the instruments, which maximizes both sensitivity and sensitivity. These two values are inversely associated, that is when sensitivity increases, specificity decreases and vice versa (Parikh, Mathai, Parikh, Chandra Sekhar, & Thomas, 2008). Diagnostic measures should possess at least 90% sensitivity and 60% specificity (Lincoln, Nicholl, Flannaghan, Leonard, & Van der Gucht, 2003).

Construct validity is concerned with how well the instrument measures the construct that it addresses (i.e. a correlation between instrument's scores and scores of measures of other associated constructs). The higher the coefficient values (as specified above for internal consistency), the higher the validity. *Convergent validity* is a subtype of construct validity and is the degree to which scores on the instrument are associated with variables which are supposed to be correlated with. Coefficients above .60 indicate high convergent validity (Polit & Beck, 2008). *Discriminant validity* is another type of construct validity and is the opposite of convergent validity, which means that the instrument scores are not correlated with variables they are not supposed to.

Validity coefficients below .85 indicate discriminant validity between tests but higher values above .85 indicate construct overlap (Henseler, Ringle, & Sarstedt, 2015).

Concurrent validity refers to the agreement between different instruments measuring the same construct; that is the correlation between their scores. Coefficients above .60 indicate good concurrent validity (Stanton & Stevenage, 2000). *Content validity* (or else, logical validity) is concerned with the extent to which the instrument takes into consideration all potential aspects of a given construct. Coefficients above .90 indicate nearly excellent content validity (Polit & Beck, 2006). *Criterion related validity* is established when scores on an instrument correlate with scores on a relevant external criterion. Criterion validity encompasses concurrent (relationship between performance and an independent criterion of performance) and predictive validity (the extent to which the instrument predicts performance) (McBurney & White, 2010; Rubin & Babbie, 2010).

There are several factors that compromise validity such as ambiguity in statements, unclear directions/instructions, difficult sentence structure, inadequate time limits or test length, administration and scoring (Christensen, 2006). When considering tests to evaluate post-stroke cognition, concurrent and predictive validity should be examined.

1.6.3 Floor/Ceiling Effects

Floor/ceiling effects refer to the degree that scores on the instrument gather around either the top (ceiling) or the bottom (floor) of the scoring system; ideally, instruments should not suffer any clustering at either end, however in practice this is very common (Upton & Upton, 2007). Floor

and ceiling effects of an instrument should be considered in evaluative studies; ceiling effects may cause intervention effects to be underestimated because the measure establishes a low ceiling of what the highest response may be. For example, if a test is being used to detect improvement over time, if scores are near the ceiling, then small changes will not be detected and therefore indicate no improvement whereas there has been improvement (Mitchell & Jolley, 2013).

In terms of stroke research, studies report on various psychometric properties with great variations in the values depending on study designs and populations included. While overall good psychometric profiles indicate a highly reliable and sensitive tool, in practical terms, only some of the properties described above are assessed by other studies. In terms of this thesis, internal consistency, test-retest reliability, concurrent and predictive validity are of particular interest. Instruments used in the thesis were reviewed against these psychometric indices and were chosen for use according to their values.

1.7 Fatigue Scales

Fatigue scales can be either unidimensional (measuring a single attribute) or multidimensional (measuring multiple attributes) (Friedman et al., 2010). These range from scales of cognitive fatigue to scales of quality of life, and can be inconsistent across studies. With regards to the type of fatigue that is measured by a scale, it is important to note that there are fatigue scales that differentiate between cognitive and physical (motor) aspects of fatigue such as the Fatigue Scale for Motor and Cognitive Functions (Penner et al., 2009) and the Modified Fatigue Impact Scale (Paralyzed Veterans of America, 1998) while others simply measure overall fatigue

(focusing on physical aspects) such as the Fatigue Severity Scale (Krupp et al., 1989). It has also been reported that when participants are asked if they are "tired" they are more likely to express symptoms of fatigue rather than when they are asked if they are "fatigued" (Falconer et al., 2010) which indicates that subjective interpretation is also essential. In addition, when applied to individuals with stroke, face validity of the scales is compromised. For instance, items that evaluate whether the individual feels weak may be misleading, as in most cases stroke survivors have physical weakness (Mead et al., 2007). Furthermore the lack of a standard definition of fatigue, affects the choice of measures used in its assessment.

1.7.1 Fatigue Scales Used in Stroke Research

This section discusses the fatigue scales that have been most commonly used in stroke research, as identified in the literature review; these are summarised in table 1 below. The most commonly used unidimensional fatigue scale in stroke research is the Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989), while the most commonly used multidimensional scales are the Fatigue Assessment Instrument (FAI; Schwartz, Jandorf, & Krupp, 1993), and the Fatigue Impact Scale (FIS; Fisk et al., 1994). Quality of life scales that include fatigue subscales, such as the Short Form-36 (SF-36; Vitality Subscale; Ware & Sherbourne, 1992), and visual analogue scales are also very commonly used (Dittner, Wessely, & Brown, 2004). The choice of fatigue scales depends on their psychometric properties. Below is a review of the psychometric properties of the scales; internal consistency, test-retest reliability and concurrent validity are

of particular importance for fatigue scales to assess fatigue.

1.7.2 Unidimensional Fatigue Scales

The Fatigue Severity Scale (FSS) (Krupp et al., 1989) measures fatigue severity and was initially used for individuals with multiple sclerosis and systemic lupus erythematosus (Neuberger, 2003). The FSS is among the most commonly used instruments to measure fatigue in people with chronic illnesses (Lerdal & Kottorp, 2011) and more particularly multiple sclerosis and stroke (Neuberger, 2003; Lerdal et al., 2009). It is a subscale of the Fatigue Assessment Inventory and its administration time is 5 minutes or less (Krupp et al., 1989). Although unidimensional, it assesses the functional effect of fatigue and its manifestations in the following aspects: social, physical, emotional and mental (Friedman et al., 2010). In addition, the scale has shown ability to differentiate between symptoms of fatigue and symptoms of depression (discriminant validity; Bailes et al., 2006) and has been shown to have higher internal consistency among other fatigue measurements (Whitehead, 2009). The FSS was shown to have very high internal consistency (α ranges = .81-.88), with test-retest reliability r= .84 in patients with multiple sclerosis and lupus erythematosus (Krupp et al., 1989; Neuberger, 2003). In stroke, the internal consistency of the scale was found to be very good (α = .86-.96) (Lerdal & Kottorp, 2011; Valko et al., 2008; Schepers et al., 2006; Valko, Bassetti, Bloch, Held, & Baumann, 2008; van de Port et al., 2007). It has been reported that a 7 item version of the FSS has higher internal consistency as it was found in studies in stroke, HIV/AIDS, multiple sclerosis and chronic neck pain (Johansson, Kottorp, Lee, Gay, & Lerdal, 2014; Lerdal, Kottorp, et al., 2011; Lerdal & Kottorp, 2011; Takasaki &

Treleaven, 2013). The concurrent validity of the shortened version of the scale was shown to be average to good when compared to the vitality subscale of the Short Form 36 (r ranged from -.56 to -.72) (Lerdal & Kottorp, 2011). Sensitivity and specificity of the scale for fatigue diagnosis have not been examined and the scale does not provide a definition of fatigue. There is no clear cut-off score for diagnosis however Valko, Bassetti, Bloch, Held, & Baumann, (2008) recommended a cut-off score of ≥4 in people with various conditions including stroke to detect people with fatigue.

1.7.3 Multidimensional Fatigue Scales

The FAI (Schwartz et al., 1993) measures fatigue severity and its consequences, situation specificity and responsiveness to sleep. It was initially developed for individuals with Hepatitis C and Parkinson's disease. Dittner et al., (2004) have referred to test-retest reliability as moderate and reported that it lacks sensitivity to change over time without providing any values. Despite the lack of information regarding its psychometric properties in people with stroke, Dittner et al. (2004) estimated that the internal consistency of the scale is expected to be similar to the values reported for the FSS as the scales are quite similar (the severity subscale of FAI is almost identical to the FSS as it includes 8 of the 9 items plus 3 extra) and because they are strongly correlated (concurrent validity r= .98) across different disease groups including stroke.

The FIS (Fisk, Ritvo, et al., 1994) measures the objective and perceived impact of fatigue on physical, cognitive and psychological aspects, and was developed for individuals with chronic fatigue syndrome and hypertension (Dittner et al., 2004; Lerdal et al., 2009). According to

Learmonth et al., (2013) the FIS has had good concurrent validity in people with multiple sclerosis with correlations between the FIS and other scales, such as the FSS, ranging from r=0.63 to r=0.75, while other studies have reported slightly higher values (Armutlu et al., 2007; Krupp et al., 1989). However psychometric properties of the scale in stroke samples are not available.

The Short Form 36 (SF-36) (Ware & Sherbourne, 1992) is a general health and quality of life scale with a vitality subscale that measures energy levels and fatigue. It has been used with people with several chronic illnesses (Hemmett, Holmes, Barnes, & Russell, 2004; Mosconi, Cifani, Crispino, Fossati, & Apolone, 2000; Picavet & Hoeymans, 2004). However, in a stroke sample the internal consistency and construct validity were lower and the vitality subscale had the lowest internal consistency coefficients (α=.68), and when compared to other scales the construct validity coefficients only ranged from r= .23 to .40 (Hagen, Bugge, & Alexander, 2003). In addition, O'Mahony, Rodgers, Thomson, Dobson, & James, (1998) found modest floor effects for the vitality subscale. No values regarding concurrent validity have been reported for people with stroke. Nevertheless, the scale has been used in stroke studies before.

Visual analogue scales have also been used in stroke studies to assess fatigue (Michael et al., 2003; Underwood, Clark, Blanton, Aycock, & Wolf, 2006). Specific values vary but the concurrent validity as indicated by the correlation between visual analogue fatigue scales and the 7 item FSS has been reported between r= -.40 and -.61 in stroke (Lerdal & Kottorp, 2011) while another study reported a slightly higher concurrent validity with a correlation r= .70 between VAS and FSS in stroke (Valko et al., 2008). The Visual Analogue

Fatigue Scale has shown strong inter-rater reliability (ICC values ranged between 0.829 and 0.893) in stroke (B. Tseng, Gajewski, & Kluding, 2010). However these scales overlook the severity of the phenomenon (construct validity) and are alleged to not have discriminant validity as they do not distinguish between fatigue and sleepiness (Vaishnavi, Makley, & Rao, 2011).

None of these scales have been developed for stroke patients (Mead et al., 2007) which compromises their use on stroke populations (Ormstad & Eilertsen, 2015). In addition, as summarised in table 1, there is lack of information regarding psychometric some properties of the scales in stroke.

Table 1: Summary of the Psychometric Properties of Interest of Most Common Fatigue Scales Used in Stroke Research

Scale	Psychometric Properties in Stroke		
	Reliability		Concurrent Validity
	Internal Consistency	Test-retest	
Fatigue Severity Scale	α= .86-.96	-	r= .56-.72 (7-item version)
Fatigue Assessment Instrument	- (but should be similar to FSS)	-	.98
Fatigue Impact Scale	-	-	-
Short Form-36 (Vitality Subscale)	α=.68	-	-
Visual Analogue Scales	-	-	r=.40-.61

Note: FSS: Fatigue Severity Scale

Given the known psychometric properties, the FSS seems to be the most reliable tool for assessing fatigue severity after stroke.

1.8 Issues with the Assessment of Post-stroke Fatigue

Some fatigue scales measure severity of fatigue, others measure frequency of fatigue and others only certain aspects of fatigue (such as only physical or only cognitive) (Zedlitz, Eijk, Kessels, Geurts, & Fasotti, 2012). There is a direct brain damage to consider; for instance, in stroke survivors with hemiparetic stroke, the inability to activate normal motor patterns, results in excessive metabolic and cardiovascular effort to substitute the lack of energy (Michael, 2014). Likewise, in traumatic brain injury fatigue is considered to be a symptom of a combination of lack of sleep, brain changes and impaired excitability in the motor cortex (Bushnik, Englander, & Wright, 2008). Therefore, fatigue has been mostly treated in neurological conditions as a by-product of impaired physical functioning.

Another factor that compromises the accurate assessment of fatigue after stroke is the fact that the majority of the fatigue measures that are currently available cannot be completed by stroke patients with aphasia (McGeough et al., 2009; Tseng et al., 2010). There are some visual analogue scales that are developed for these individuals, but these only give an approximation of fatigue as there is no common agreed interpretation of each level among participants; they are also usually only included in studies with different designs as people with aphasia are usually excluded from most studies.

1.9 Cognitive Impairment

According to Neisser (1967), cognition is the collective set of all mental processes that regulate the reception of sensory

input and its interpretation, storage, retrieval, elaboration, and replication, even in the absence of stimulation. Cognition involves multiple interdependent and overlapping domains (Cumming, Marshall, et al., 2013). When these mental processes are disrupted they cause cognitive impairment. According to the Centers for Disease Control and Prevention, (2011) cognitive impairment is defined as trouble in using mental abilities to their maximum potential and is the discrepancy between the expected intellectual functioning and the current intellectual functioning.

1.9.1 Cognitive Impairment after Stroke

Since stroke affects several areas of the brain, stroke survivors are prone to cognitive impairment. Cognitive impairment is three times more common in people with stroke than in a healthy population and at least 25% of stroke patients will develop dementia (Desmond, Moroney, Sano, Stern, & Merino, 2002; Tatemichi et al., 1993). Some stroke survivors will recover, however many will be unable to carry out daily activities as a consequence of cognitive impairment (Danovska, Stamenov, Alexandrova, & Peychinska, 2012; Winkens, Van Heugten, Fasotti, Duits, & Wade, 2006). Usually cognitive impairment is apparent instantly after stroke onset but some stroke survivors may experience delayed cognitive impairment (Brainin et al., 2015). Cognitive impairment after stroke has been defined as the appearance of deficits within 3 months of the stroke incident, that are present for at least 6 months thereafter and that are unrelated to any other clinical or psychiatric comorbid condition (Vakhnina, Nikitina, Parfenov, & Yakhno, 2009). A recent survey conducted in stroke wards across Scotland showed that cognition is second in the top priorities for stroke nurses (Rowat, et al., 2016).

1.9.2 Significance of Cognitive Impairment after Stroke

In a study conducted by Mok et al., (2004) 82.1% of the participants believed that the cognitive impairment they experienced resulted directly from their stroke. The majority of stroke survivors rank memory, attention and mental speed difficulties among their most disabling symptoms in the chronic phase (Cumming et al., 2013; Johansson et al., 2012; Mansueti, de Frias, Bub, & Dixon, 2008; Röding, Glader, Malm, Eriksson, & Lindström, 2009; Tatemichi et al., 1994). In addition, stroke survivors with impairment of speed of information processing report in qualitative interviews that they had widespread difficulties in their everyday life (Winkens et al., 2006). Mood and cognitive capacity can affect functional outcome and consequently quality of life (Patel, Coshall, Rudd, & Wolfe, 2003; Pohjasvaara, Vataja, Leppävuori, Kaste, & Erkinjuntti, 2001). Therefore not including these types of assessments in stroke trials may compromise the understanding of associated factors (Lees, Fearon, Harrison, Broomfield, & Quinn, 2012).

1.9.3 Prevalence and Types of Cognitive Impairment after Stroke

Evidence from a literature review conducted by Danovska et al., (2012) suggests that around 70% of stroke survivors develop cognitive impairments in the acute phase, however many of these will resolve quickly due to reperfusion and brain plasticity. Cumming et al., (2013), suggested that in the acute phase of stroke, cognitive impairment is more likely to include impairment of executive function, while at one year post-stroke it is more likely to include impairment of attention and then at 5 years post-stroke, with speed of information

processing, verbal and visual memory, and executive function. Overall, impairments of attention, executive function and speed of information processing tend to persist and are unrelated to time post-stroke (Winkens et al., 2006; Cumming et al., 2013).

Brainin et al., (2015) reported that the prevalence of cognitive impairment was 7% for first-ever stroke survivors in population-based studies and 41% in hospital based studies on survivors with recurrent strokes and pre-stroke dementia; this perhaps indicates that pre-existing dementia and number of strokes are associated with the presence of cognitive impairment. Evidence shows 50-70% of stroke survivors suffer cognitive impairment (Hochstenbach, Mulder, van Limbeek, Donders, & Schoonderwaldt, 1998; Mok et al., 2004; Cumming et al., 2013; Danovska et al., 2012; Rasquin et al., 2002). A systematic review reported that between 20-37% of stroke patients with lacunar stroke develop cognitive impairment or dementia (Makin, Turpin, Dennis, & Wardlaw, 2013). However, it is difficult to determine the prevalence due to the differences in settings, populations and designs.

The frequency of impairment varies according to the cognitive domains affected. Between 21% and 38% suffer language impairments, such as aphasia (Bhogal, Teasell, & Speechley, 2003; Dickey et al., 2010; Kauhanen et al., 2000; Pedersen, Jørgensen, Nakayama, Raaschou, & Olsen, 1995; Pedersen, Vinter, & Olsen, 2004; Wityk & Llinas, 2007), 23% to 55% have memory impairment (Hochstenbach et al., 1998; Snaphaan & de Leeuw, 2007; Khedr et al., 2009; Kokmen, Whisnant, O'Fallon, Chu, & Beard, 1996), 28% to 57% have apraxia (Donkervoort, Dekker, van den Ende, Stehmann-Saris, & Deelman, 2000), 20% to 80% have visuospatial neglect (Kalra, Perez, Gupta, & Wittink, 1997; Ting et al.,

2011), 25% to 92% have attention impairment (Barker-Collo, Feigin, Lawes, Parag, & Senior, 2010; Hyndman, Pickering, & Ashburn, 2008; Leśniak, Bak, Czepiel, Seniów, & Członkowska, 2008; Nys, 2005; Stapleton, Ashburn, & Stack, 2001) and 50% to 70% experience impairment of speed of information processing and reaction time slowness (Hochstenbach et al., 1998; Winkens et al., 2006).

Cognitive impairment after stroke leads to cognitive complaints. These are the stroke survivors' perceived deterioration after their stroke. The prevalence of subjective cognitive complaints varies between 29% and 92% depending on when they are measured and which domains are assessed, with complaints about mental speed, memory and concentration being the most frequent (van Rijsbergen, Mark, de Kort, & Sitskoorn, 2014). There is evidence that subjective cognitive complaints may be attributed to other factors such as mood (depression and stress), negative affectivity sleeping patterns, openness and conscientiousness (Lamb, Anderson, Saling, & Dewey, 2013; Slavin et al., 2010; Stenfors, Marklund, Magnusson Hanson, Theorell, & Nilsson, 2013, 2014) much more than to objective cognitive performance (Maaijwee et al., 2014; Slavin et al., 2010). This may lead to misdiagnosis of cognitive impairment (Edmonds, Delano-Wood, Galasko, Salmon, & Bondi, 2014). Patients' perspectives do not correlate highly with objective tests of cognitive impairment. For example, memory related complaints have been shown to be associated with tests of every day related tasks, as opposed to more conventional memory tests, implicating the ecological validity of some of the tests (Lincoln & Tinson, 1989). Subjective cognitive complaints are not usually measured in stroke studies, but they also contribute to the decrease of quality of life after

stroke (van Rijsbergen et al., 2014).

1.9.4 Impairment of Attention and Speed of Information Processing after Stroke

Impairments of attention and speed of information processing are particularly common after stroke. The frequency of attention deficits has been estimated between 25%-92% in the acute stage (Barker-Collo, Feigin, Lawes, Parag, & Senior, 2010; Hyndman, Pickering, & Ashburn, 2008) and 54% of stroke survivors have had a prominent impairment of attention 1 year post-stroke (Leśniak et al., 2008). The frequency of impairment of speed of information processing has an estimated prevalence between 50% and 70% (Hochstenbach et al., 1998; Winkens et al., 2006). Evidence suggests that processing speed is the most common post-stroke cognitive deficit (Ballard et al., 2003; Barker-Collo, Feigin, Parag, Lawes, & Senior, 2010; Brand et al., 2014; Hochstenbach et al., 1998; Hurford, Charidimou, Fox, Cipolotti, & Werring, 2013; Rasquin, Lodder, & Verhey, 2005). Some stroke survivors self-rank speed of information processing as one of their disabling symptoms (Winkens et al., 2006) and also objectively manifest processing speed deficits (Barker-Collo et al., 2010; Hochstenbach et al., 1998; Hurford et al., 2013). Speed of information processing is also thought to be responsible for various other cognitive deficits after stroke such as memory and attention (Rosano et al., 2012; Rosano, Brach, Studenski, Longstreth, & Newman, 2007; Su, Wuang, Lin, & Su, 2015).

Evidence in other conditions, such as multiple sclerosis, hyperactivity disorder, schizophrenia and traumatic brain injury, suggests that speed of information processing is implicated in the regulation of several other cognitive domains

such as: intelligence (Bugg, Zook, DeLosh, Davalos, & Davis, 2006), verbal fluency, (Elgamal, Roy, & Sharratt, 2011) episodic memory (Lee et al., 2012), attention, working memory and executive function (McGrath et al., 2011; Rodríguez-Sánchez, Crespo-Facorro, González-Blanch, Perez-Iglesias, & Vázquez-Barquero, 2007; Willmott, Ponsford, Hocking, & Schönberger, 2009), verbal and visual spatial information (Diamond, Johnson, Kaufman, & Graves, 2008) and processing speed impairment may compromise performance in higher order cognitive tasks such as problem solving, planning, reasoning and mental flexibility (Kail & Salthouse, 1994).

1.9.5 Predictors of Cognitive Impairment after Stroke

Predictors of cognitive impairment following stroke are multiple. It is suggested that cognitive impairment is induced by blood flow reduction which causes brain dysfunction (Hillis et al., 2009). There is evidence that certain stroke characteristics, such as severity, lesion location and stroke type have an impact on the type of cognitive impairment. When the stroke lesion is localised, it may cause selective impairments (for instance neglect or aphasia) while silent infarcts, white matter lesions, global cerebral atrophy and medial-temporal lobe atrophy are more likely to affect several cognitive domains (Brainin et al., 2015; Cumming, Marshall, et al., 2013; Gottesman & Hillis, 2010). A right hemisphere lesion is more likely to cause impairment of both selective and divided attention than a left hemisphere lesion (Hyndman et al., 2008; McDowd, Filion, Pohl, Richards, & Stiers, 2003; Robertson, Ridgeway, Greenfield, & Parr, 1997).

Certain biomarkers are also associated with the presence post-stroke cognitive impairment; for instance, the B

secretase enzyme, receptor levels for advanced glycation, vitamin B12, folic acid levels and homocysteine as well as inflammatory markers such as the C-reactive protein, erythrocyte sedimentation rate and interleukin 6 have been associated with post-stroke cognitive impairment (Brainin et al., 2015). Furthermore, patient demographic characteristics, such as age, sex and education, are also associated with the severity of cognitive impairment after stroke, with women, older people and the less educated being more vulnerable (Leys, Hénon, Mackowiak-Cordoliani, & Pasquier, 2005; Tang et al., 2004; Brainin et al., 2015; Tatemichi et al., 1993). Vascular risk factors such as atrial fibrillation and diabetes are also associated with post-stroke dementia (Pendlebury & Rothwell, 2009) while a recurrent stroke onset is associated with the severity cognitive impairment (Sun, Tan, & Yu, 2014).

1.9.6 Assessment of Cognitive Abilities

There are several cognitive tests available. The tests used in existing studies vary and so do their purposes and psychometric properties. These are: *comprehensive neuropsychological batteries, brief screening tests*, *domain specific tests and subjective cognitive impairment tests*. The purpose of this section is to present the most commonly used cognitive tests in research relevant to fatigue after stroke and not to present a comprehensive list. There are some tests which are used commonly in stroke research, or are developed for stroke patients however they may not be used in research with regards to fatigue. These are briefly acknowledged and discussed in the context of their relevance to such research.

Table 2 summarises these tests. The tests presented were identified either from individual studies within the

context of fatigue and cognitive impairment after stroke and the cognitive domains most likely to be affected by fatigue. The choice of cognitive tests depends on their psychometric properties. Below is a review of the psychometric properties of the tests; test-retest reliability, inter-rater reliability, construct validity and predictive validity (for domain specific tests) are of particular interest for cognitive tests. However, some tests have some practical considerations when being used on people with stroke and these are described alongside each test that is being reviewed. Therefore the following section is an attempt to collect and present what is known for each test so that there is an idea of how appropriate they are for use in stroke.

1.9.7 Comprehensive Neuropsychological Batteries

There are several cognitive batteries which attempt to measure several cognitive domains. For instance, the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 2008), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998) and the Neuropsychological Assessment Batter (NAB; Stern & White, 2003) have been used before in stroke. However, they are too lengthy for research purposes and depending on the research question, may not be efficient in assessment of large numbers of people. Many of these are not appropriate for use in stroke settings routinely as they are long and tiring, although the sub-tests can be used separately for domain specific assessment (Lincoln et al., 2012). They also assess multiple cognitive domains and therefore are only appropriate when a comprehensive assessment across several cognitive domains is needed. They are not used in research in relation to fatigue after stroke and therefore these will not be reviewed here.

1.9.8 Brief Screening Cognitive Tests

Other brief screening tests are used in research and clinical practice for identifying those with cognitive impairment. The most commonly used is the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975). The MMSE is an assessment of cognitive state which assesses orientation, attention, memory, language, calculation and construction functions. Internal consistency in stroke was α= .60 (Toglia, Fitzgerald, O'Dell, Mastrogiovanni, & Lin, 2011), test-retest reliability in elderly individuals ranged between r= .55 and 0.59 (Tombaugh, 2005). The MMSE is highly correlated (r= .86) with the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) (concurrent validity) in a sample of older adults (Trzepacz et al., 2015). The sensitivity and the specificity for distinguishing between cognitively impaired and non-impaired patients in various medical conditions are reported to be 80% and 98% respectively. In stroke, the sensitivity ranges from 62% to 96% (Blake et al., 2002; Godefroy et al., 2011; Cumming, Churilov, Linden, & Bernhardt, 2013; Nys et al., 2005; Lees et al., 2014) and specificity ≥ 85% (Bour, Rasquin, Boreas, Limburg, & Verhey, 2010; Godefroy et al., 2011; Lees et al., 2014) in distinguishing between cognitively impaired and non-impaired patients. There is no optimal cut-off recommended for stroke (Blake et al., 2002) and no cut-off score has yielded sensitivity ≥ 80% and specificity ≥ than 60% in acute stroke (Nys et al., 2005). The higher specificity estimates indicate that the test is better at identifying those without cognitive impairment than identifying all those with cognitive impairment.

The test is used to predict cognitive performance. However, more recent studies on older individuals and on stroke populations have reported that the MMSE lacks

predictive value, it is not sensitive enough to detect cognitive impairment in acute stroke patients and that it suffers from ceiling effects (Bour, Rasquin, Boreas, Limburg, & Verhey, 2010; Nys et al., 2005; Spencer et al., 2013). The MMSE is a screening measure of global cognitive status which does not assess domain specific impairment and is not sensitive to stroke specific problems. Another limitation of the MMSE is that it does not assess executive functions, planning, visuo-spatial functions, and attention (Radman et al., 2012; Strauss, Sherman, & Spreen, 2006; Woodford & George, 2007). Despite evidence that suggests it is not suitable for stroke it is the most commonly used test to screen for cognitive impairment after stroke according to a review conducted by Lees, Fearon, Harrison, Broomfield, & Quinn, (2012).

The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) assesses several cognitive components such as visuo-spatial abilities, short-term memory and delayed recall, attention, working memory, language, time and place orientation and verbal fluency (Nasreddine et al., 2005). In stroke, internal consistency is reported to be α= .78 (Toglia et al., 2011). For predicting cognitive impairment after stroke, sensitivity of the test is reported to be between 77% and 94% compared to MMSE (Godefroy et al., 2011; Pendlebury, Mariz, Bull, Mehta, & Rothwell, 2012) but specificity is estimated to be lower ranging from 42% to 83% (Godefroy et al., 2011; Pendlebury et al., 2012) but still higher than MMSE (Burton & Tyson, 2015; Freitas, Simões, Alves, Duro, & Santana, 2012; Nasreddine et al., 2005).

The Oxford Cognitive Screen (OCS; Demeyere, Riddoch, Slavkova, Bickerton, & Humphreys, 2015) is developed specifically for stroke patients and it assesses attention, executive function, language, memory, number processing

and praxis. In stroke, internal consistency of the test was α= .72 and test-retest reliability ranges from r= .31 to .77 (Demeyere et al., 2015; A. P. Kong et al., 2016). In stroke, the sensitivity of the test ranges from 27.59% to 94.12% among the sub-tests and the specificity ranges from 70.10% to 98.31%; convergent validity ranges from r= .34 to .78 (Demeyere, Riddoch, Slavkova, Bickerton, & Humphreys, 2015) and concurrent validity with the MMSE and MoCA ranged from r= .47 to .71 and r= .19 to .69 respectively .

The Addenbrooke's Cognitive Examination III (Mathuranath, Nestor, Berrios, Rakowicz, & Hodges, 2000), the Cognistat (Kiernan, Mueller, Langston, & Van Dyke, 1987), the Screening Instrument for Neuropsychological Impairments in Stroke (SINS; Sødring, Laake, Sveen, Wyller, & Bautz-Holter, 1998) and the Clock Drawing Test (Shulman, 2000) are also used in clinical practice.

It is worth noting that while the above brief screening measures are useful for detecting cognitive impairment after stroke, they do not provide domain specific scores. Therefore they are not appropriate for studies which want to focus on particular cognitive domains separately. In addition, these tests do not assess speed of information processing which is very common after stroke and essential in relation to fatigue therefore using these alone would not be beneficial for researching the relationship between fatigue and impairment after stroke.

1.9.9 Domain Specific Tests of Attention and Speed of Information Processing

Since speed of information processing and attention are the most common symptoms objectively and subjectively observed after stroke, and since fatigue is more commonly described by stroke patients in terms of attention and speed of information processing, it is very likely that post-stroke fatigue is related to cognitive impairments of attention and speed of information processing. Attention and speed of information processing incorporate physical and mental abilities and changes in attention and speed of information processing may cause greater need to compensate for the impairment and therefore cause fatigue (Levine & Greenwald, 2009; Ponchel, Bombois, Bordet, & Hénon, 2015). Therefore, these cognitive domains will be the focus of the studies of the thesis.

Domain specific tests are available for all the cognitive impairments that occur in stroke. Based on the literature review of impairments and their effect on daily life, the most relevant impairments in terms of fatigue are attention and speed of information processing and so tests which assess impairment in those domains are reviewed below. The most common domain specific tests used to assess cognitive components usually affected by fatigue, are: the Symbol Digit Modalities, the Paced Auditory Serial Addition Test, the Stroop and the Trail Making Test.

The Symbol Digit Modalities Test (SDMT; Smith, 1991) assesses speed of information processing, concentration and sustained attention via tracking and visual scanning (Smith, 1991). The test assesses many overlapping cognitive components and results may indicate impairment in multiple domains (Strauss et al., 2006). Test-retest reliability of the

SDMT on healthy individuals ranges from r=0.76 to 0.80 (for the oral and the written form respectively) (López-Góngora, Querol, & Escartín, 2015; Strauss et al., 2006). One study evaluated test-retest reliability of oral form in people with stroke (Koh et al., 2011) and found test-retest reliability to be r= .89. Concurrent validity of the test is moderate as it is revealed through correlations with the Brief Repeatable Battery for the Assessment of Neuropsychological Status (BRBN; Rao, 1990) (r= .58 to .72) the Trail Making Test (TMT; Army Individual Test Battery, 1944) (r= .47 to .62) and the Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977) (r= .38 to .47) in people with multiple sclerosis (Berrigan et al., 2014; Sonder, Burggraaff, Knol, Polman, & Uitdehaag, 2014) and ranges from weak to high as revealed by correlations with the Test of Everyday Attention Attention (TEA; Robertson, Ward, Ridgeway, & Nimmo-Smith, 1996) (r= .11 to .72) in traumatic brain injury. It is has high sensitivity of 80% in detecting early cognitive impairment in people with multiple sclerosis (López-Góngora et al., 2015; Strauss et al., 2006).

The Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977) is a measure of sustained attention, working memory, mental flexibility and speed of information processing (Strauss et al., 2006). It is considered to have high internal consistency in healthy adults with values ranging from α=0.90 to 0.96 (Strauss et al., 2006). Test re-test reliability values from various conditions including traumatic brain injury, range from r= .93 to .97 (Tombaugh, 2006). Concurrent validity is estimated to be moderate according to correlation coefficients with the Trail Making Test (TMT; Army Individual Test Battery, 1944) in community-living adults (r= .55 to .57) (O'Donnell, Macgregor, Dabrowski, Oestreicher, &

Romero, 1994). Sensitivity and specificity for detecting cognitive impairment in people with multiple sclerosis was 74% and 65& respectively (Rosti, Hämäläinen, Koivisto, & Hokkanen, 2007). One of its disadvantages is that the difficulty of the task can cause frustration to the participants which in turn may affect their performance (Tombaugh, 2006). In addition, the test relies a lot on intelligence and mathematical abilities which may complicate its use (Sherman, Strauss, & Spellacy, 1997).

The Stroop (Golden & Freshwater, 2002) is a test of executive dysfunction, measuring selective attention, concentration, working memory and the effect of interference (Golden & Freshwater, 2002). Test retest reliability ranges from .83 to .91 in healthy individuals (Spreen & Strauss, 1998; Strauss et al., 2006). The test is recommended for use in stroke (NINDS Common Data Elements, 2014) as an assessment of interference and attention. Concurrent validity is average as revealed by correlations with the Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977) (r= .31) and the Trail Making Test (TMT; Army Individual Test Battery, 1944) (r= .55) in healthy adults (May & Hasher, 1998a). In people with post-concussion syndrome, sensitivity to detect interference effects was 22%-25% and specificity 93%-96% (Cicerone & Azulay, 2002; Macleod & Prior, 1996). The test requires intact visual capacity and cannot be used with colour-blind individuals (Strauss et al., 2006).

The Trail Making Test (TMT; Army Individual Test Battery, 1944) is a test of mental flexibility, visual search, speed of information processing and executive functions (Army Individual Test Battery, 1944). It is quick and easy to administer and has good test-retest reliability r= .86 to .94 in people with major depressive disorder (S. Wagner, Helmreich,

Dahmen, Lieb, & Tadic, 2011). It is reported to have high predictive validity for brain damage in people with stroke (Reitan, 1958). In stroke, the test was shown to be more sensitive to executive impairment than the Digit Span Test subtest of the Wechsler Memory Scale (WMS; Wechsler, 1945) (no values described) and the correlations coefficients with stroke severity (measured by the National Institute of Health Stroke Scale; NIHSS) ranged from .26 to .45 (criterion validity) (Tamez et al., 2011). Concurrent validity is estimated to be moderate according to correlation coefficients with the PASAT (r= .55 to .57) (O'Donnell et al., 1994) and the Symbol Digit Modalities Test (SDMT; Smith, 1991) (r= .47 to .62). However, patients with severe head injuries only make a few errors implying poor sensitivity to the presence of cognitive impairment (Iverson, Lange, Green, & Franzen, 2002; Ruffolo, Guilmette, & Willis, 2000).

It is worth noting that, there are other domain specific cognitive tests of attention which are used in stroke research, such as the Test of Everyday Attention (TEA; Robertson, Ward, Ridgeway, & Nimmo-Smith, 1996). The TEA assesses selective sustained and divided attention as well as switching ability. The test simulates everyday tasks (ecological validity) which makes it appropriate for assessment in rehabilitation settings (Chan, Lai, & Robertson, 2006). However, the test is very tiring and long, which makes it impractical for use in research with regards to fatigue (see Chen, Koh, Hsieh, & Hsueh, 2013 for its use in stroke). The Five Digit Test (Sedó, 2004) can also be used as an alternative to the Stroop to measure selective attention, has not been used in research with relation to fatigue. In addition, the Dot Cancellation from the Stroke Drivers Screening Assessment (DC, SDSA; Nouri & Lincoln, 1994) is a measure of attention and executive abilities

(Radford & Lincoln, 2004) and is used in order to assess driving capacity after stroke. The Speed of Information Processing from the Adult Memory Information Processing Battery (AMIPB, Coughlan & Hollows, 1985) is a measure of speed of information processing is recommended for use in stroke populations over other tests because the test accounts for motor capacity which is often affected by stroke survivors (Skilbec, 1992). However, these tests have not been used in research relative to fatigue after stroke.

1.9.10 Subjective Cognitive Impairment Tests

Finally, perceived/subjective cognitive impairment scales are also used in research to measure perceived cognitive impairment manifested in everyday life. Depending on their objective, some studies use self-rated questionnaires, or questionnaires that are completed by the patients' carer or clinician. These questionnaires are easy to use and aim to measure the outcome of the perception of cognitive impairment in the patients' and/or carers' quality of life. There is great heterogeneity in terms of the scales used to measure subjective cognitive complaints and most of these tests lack information with regards to their psychometric properties (van Rijsbergen et al., 2014). Likewise, with regards to fatigue, many scales address cognitive components of fatigue as subjective cognitive complaints (for instance asking participants if they are more forgetful after their stroke; if the participant answers positively that may simply mean they are more forgetful but do not feel more fatigued). Therefore, when the objective is to measure cognitive impairment as a result of stroke, it may be more appropriate to use domain specific objective cognitive tests.

Table 2: Summary of the Psychometric Properties of Cognitive Tests Used in Research Relevant to Fatigue after Stroke

Test	Psychometric Properties in Stroke				
	Reliability		Validity		
	Inter-rater Reliability	Test-retest Reliability	Construct Validity	Predictive Validity to Detect Cognitive Impairment	
				Sensitivity	Specificity
Symbol Digits Modalities Test	-	oral version: r= .89	-	-	-
Paced Auditory Serial Addition Test	-	-	-	-	-
Stroop	-	-	-	-	-
Trail Making Test	-	-	-	Poor Sensitivity; No Values	-

There seems to be lack of information regarding psychometric properties in stroke populations of most cognitive tests. However, psychometric properties of cognitive tests should remain stable across medical conditions so evidence from other medical conditions may be indicative for stroke. The test which has been mostly examined in fatigue after stroke is the general screening test the MMSE and that is possibly due to the fact that this test is most commonly used in practice as well as it is brief and easy to administer in ward

settings and has been around for the longest. The key message of this section is that there is considerable heterogeneity regarding cognitive tests used across studies and some prevalent tools seem to not be suitable for stroke populations or to assess cognitive domains in relation to fatigue.

The following section summarises the relationship between cognition and depression after stroke as depression may be a confounding variable in measuring cognition after stroke.

1.10 Relationship Between Depression and Cognitive Impairment After Stroke

Depression has been reported to have be associated with cognitive impairment in the general geriatric population (Ruchinskas & Curyto, 2003) and to speed up the cognitive deterioration (Modrego & Ferrández, 2004). Kalaria & Ballard, (2001) and Talelli et al., (2004) found a significant association between depression and cognition at one year post stroke and those with depression are more likely to develop dementia. It is also reported that 54.2% of stroke survivors with depression developed dementia 15 months after their stroke while only 7.1% of stroke survivors without depression did (Teasell & Hussein, 2014). In addition, cognitive abilities improve when depression is treated. For example, Kimura, Robinson, & Kosier, (2000) found that stroke patients who were given pharmacological treatment for their depression, had greater cognitive recovery once their depression remitted as opposed to those in the placebo treatment. Cognitive impairment due to depression may be sometimes manifested as so-called pseudodementia (subjective cognitive impairment) which is defined as poor cognitive performance

which does not reflect real dementia (Birkett, 2012). It is challenging to distinguish between pseudodementia and dementia however the former usually develops immediately after a stroke as opposed to having a gradual onset (which is the case with dementia) (Birkett, 2012). It has been suggested that some subjective cognitive complaints are due to depression (Garcia-Ptacek et al., 2014). Perhaps this is another reason for not using subjective cognitive tests in studies that examine the relationship between fatigue and cognition as they may reflect depression rather than cognitive impairment.

1.11 Cognitive Fatigue

In a qualitative study, participants differentiated between cognitive, physical and generic fatigue by categorizing their symptoms as "tiredness in the muscles", "a general feeling of tiredness" or "mental tiredness" (Barbour & Mead, 2012). Chaudhuri & Behan (2004) compiled a general framework of fatigue, distinguishing between peripheral and central (cognitive/mental) fatigue. The former refers to muscle weakness and fatigability due to neuromuscular dysfunction and is the same construct as physical fatigue (Barbour & Mead, 2012). Central fatigue is characterized by constant exhaustion and an overall failure to monitor and maintain executive performance under sustained cognitive effort and is equivalent to cognitive fatigue (Holtzer, Shuman, Mahoney, Lipton, & Verghese, 2011). Patients suffering from cognitive fatigue commonly display deterioration in cognitive domains, such as memory, attention, and information processing (Chaudhuri & Behan, 2004).

1.11.1 Cognitive Fatigue after Stroke

Only a few studies have examined the relationship between fatigue and cognitive abilities post-stroke. Most of these studies did not detect any significant relationships and those who did, indicated a relationship between fatigue attention and speed of information processing (Radman et al., 2012; Hubacher et al., 2012). Radman et al., (2012) found that cognition was associated with fatigue in stroke patients with high levels of depression, whereas in the absence of depression it was not. This suggests a relationship between depression and cognition, a hypothesis that has been previously confirmed in studies showing associations between depression and memory, attention, problem solving, language and speed of information processing (Kauhanen et al., 1999; Terroni et al., 2012), suggesting a pattern that involves cognition, mood and fatigue in a model of fatigue development after stroke.

1.11.2 Cognitive Fatigue in Other Conditions

The relation between cognitive impairment and fatigue has also been examined in different medical conditions. For instance, studies in cancer patients undergoing chemotherapy, showed that there is an association between fatigue and subjective cognitive complaints but not between fatigue and objective cognitive impairment (Castellon et al., 2004; Tchen et al., 2003; Vardy, 2008). Furthermore, a study in HIV/AIDS patients showed that subjective cognitive complaints were associated with fatigue but not with objective verbal learning and motor function (Millikin, Rourke, Halman, & Power, 2002).

In other neurological disorders, the evidence is similar. For example, in multiple sclerosis, fatigue was associated with cognitive complaints but not with objective memory and

attention performance (Jougleux-Vie et al., 2014; Kinsinger, Lattie, & Mohr, 2010; Middleton, Denney, Lynch, & Parmenter, 2006). In traumatic brain injury, Johansson, Berglund, & Rönnbäck, (2009) reported that subjective mental fatigue was associated with objective cognitive performance (speed of information processing); however cognitive fatigue was assessed as cognitive complaints and therefore this relationship may only mean that the perceived cognitive impairment of the participants corresponded accurately to their objective cognitive performance. All evidence suggests that there may be a relationship between perceived/subjective cognitive impairment and fatigue but not with actual cognitive impairment.

1.12 Methods of Measuring the Relationship between Fatigue and Cognitive Impairment

One of the most commonly used terms to refer to the link between variables is the term *"association"*. This term is used to reflect that two or more variables are somehow connected to each other; an association does not necessarily indicate causality which is usually described with the term *"effect".* In statistical context, an association is usually measure by correlational analyses.

Correlation analysis is the technique used to measure the closeness and the linearity of the relationship between continuous variables. These variables are connected in such a way that any changes in variable X would cause changes in variable Y and vice versa (Sharma, 2005). In reality, most variables are expected to be correlated to a certain extent, however this relationship is significant when it is unlikely to be due to chance. The strength of the relationship is also of interest. The correlation coefficient r values range from 0-1

with higher values indicating stronger relationship (Gravetter & Wallnau, 2008). The values can be either positive (when values on variable X increase, so do values in variable Y and vice versa) or negative (when values on variable X increase variables on Y decrease and vice versa).

Correlations are most commonly measured by either the *Pearson's r* or the *Spearman's* r_s ; the former is used for normally distributed data to examine the degree of linear relationship between variables and the latter is used for skewed data to examine the direction of a relationship (Gravetter & Wallnau, 2008; Weinberg & Abramowitz, 2002). Categorical data associations may be determined by calculating either a *point-Biserial* correlation (when one of the variables is categorical) or a *phi-coefficient* (when both variables are categorical). They both provide information about the strength of the relationship. However, correlations measure linear associations but not agreement. It is possible that variables can correlate yet disagree and that correlations can be misleading in examining agreement (Bunce et al., 2009). The agreement between categorical variables is measured by *Cohen's Kappa* statistic κ; the Kappa can assess both the bias and the precision between the agreement (W. Tang, Hu, Zhang, Wu, & He, 2015). A *chi-square* (based on frequencies-when both variables are categorical) will show an association but does not indicate relationship strength (Gravetter & Wallnau, 2008; Morgan, Leech, Gloeckner, & Barrett, 2011).

The predictive value of each variable to the other is assessed by conducting a *regression analysis*. A regression analysis assumes that one of the variables is dependent on the other(s) (Archdeacon, 1994) and allows for prediction of which values of X correspond to which values of X (Gravetter

& Wallnau, 2008). In order to conduct regression, there need to be significant associations but may also be conducted in order to reduce number of analyses due to small sample sizes. There are two types of regression: *linear regression* for continuous variables and *logistic regression* for categorical variables (Hellevik, 2009). In the case of more than one independent variable, a *multiple regression* is conducted. Multiple regression aims to predict the values of a variable (dependent variable) based on the values of other (independent) variables. There are two types of multiple regression: *enter* and *stepwise*. The enter *method* uses a hierarchical model which includes all variables in the equation and determines the regression coefficients for the each of the variables at the stage that they are added to the equation(Albright, Winston, & Zappe, 2009). Stepwise multiple regression only enters the good predictor variables into the equation in order to narrow down the model; this is done either by using the whole model and extracting the variable with the smallest sum of squares at each step (*backward elimination*) or by adding the variable with the highest correlation coefficient with the independent variable at each stage (*forward selection*) (Rawilings, Pantula, & Dickey, 1998). Finally, a *path analysis* which is another type of multiple regression, may be employed to examine a hypothesized causality among the variables in a simultaneous analysis (instead of separately which is the case with multiple regression), but it cannot indicate the direction of such relationship (Olobatuyi, 2006).

While correlation designs are good for examining the relationship between variables, the findings may be misinterpreted. One challenge to interpreting a correlation is that a linear significant relationship may reflect that these two

variables are both independently associated with a third variable (Bewick, Cheek, & Ball, 2003). Regression analysis will be able to determine whether this has occurred. Correlations are unable to indicate causation and therefore a strong significant correlation only indicates that the variables are somehow related but they are not necessarily causative (Bewick et al., 2003). In addition, correlations assume a linear relationship between variables. However, curved relationships are also possible and correlation analyses do not detect them. The advantage of correlational analysis is that it allows for prediction which in clinical settings when designing interventions is of high significance.

An alternative approach in assessing cognitive fatigue would be to compare stroke patients with and without fatigue on cognitive tests. This would require analysis using a t-test or a Mann Whitney U test. *Tests of mean differences* are able to generate information based on whether the mean of group 1 is higher or lower than the mean of group 2 and whether this difference is significant. The assumptions of t-tests require that both groups have similar sample sizes and standard deviations for the comparison to be accurate (data can be either interval, ordinal, nominal or ratio type but usually a combination is required; Vaughan, 2001). Such a requirement indicates the challenge of comparison in experimental designs where it is not possible to obtain equal numbers in groups. This thesis is heavily focused on correlational analyses for many reasons; to begin with, the literature review showed that the majority of studies examined the topic in question with correlations. The measures used for both fatigue and cognition are continuous. In addition, it wasn't known whether it would be feasible to recruit approximately similar samples of people with stroke with and without fatigue.

1.13 Conclusion

This chapter summarised that both fatigue and cognitive impairment are very common and debilitating after stroke. There may be an underlying relationship between fatigue and cognitive impairment after stroke because many stroke survivors refer to cognitive aspects of fatigue. Therefore a systematic review was conducted next to summarise the previous research on the relation between fatigue and cognition after stroke.

1.14 Aims of the Thesis

Identifying the factors that are associated with post-stroke fatigue can lead to the development of treatments. The main aim of this project was to examine the relationship between cognitive impairment and fatigue after stroke. The aims were to: 1) systematically review current evidence on the relationship between cognitive impairment and fatigue after stroke; 2) examine the relationship between fatigue and cognitive impairment in the acute phase in first ever stroke survivors without depression; 3) examine the relationship between fatigue and cognitive impairment in the acute phase in first ever stroke survivors with depression; 4) examine the unidimensionality and the reliability of the FSS and 5) examine the relationship between fatigue and cognitive impairment in chronic stroke survivors measuring cognitive aspects of fatigue.

Chapter 2: Systematic Review

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2.1 Abstract

Background:

Many stroke survivors experience fatigue, which is associated with a variety of factors including cognitive impairment. A few studies have examined the relationship between fatigue and cognition and have obtained conflicting results.

Objective:

The aim of the study was to review the literature on the relationship between fatigue and cognition post-stroke.

Methods:

The following databases were searched: EMBASE (1980-February, 2014), PsycInfo (1806-February, 2014), CINAHL (1937-February, 2014), MEDLINE (1946-February, 2014), Ethos (1600-February, 2014) and DART (1999-February, 2014). Reference lists of relevant papers were screened and the citation indices of the included papers were searched using Web of Science. Studies were considered if they were on adult stroke patients and assessed the following: fatigue with quantitative measurements ($\geq$3 response categories), cognition using objective measurements and the relationship between fatigue and cognition.

Results:

Overall, 413 papers were identified, of which 11 were included. Four studies found significant correlations between fatigue and: memory, attention, speed of information processing and reading speed (r= .36 to .46). Seven studies found no significant relationship with global cognitive impairment. Most studies had limitations; quality scores ranged from 7 to 9 on the Critical Appraisal Skills Programme Checklists and from 1 to 6 on the Newcastle Ottawa Scale.

Conclusions:

There was insufficient evidence to support or refute a relationship between fatigue and cognition post-stroke. More robust studies are needed.

2.2 Introduction

Fatigue is frequently reported after stroke (Barbour & Mead, 2012). It is conceptualised as disproportionate mental or physical exhaustion and lack of energy triggered by simple activities that do not ameliorate with ordinary rest (De Groot et al., 2003; Staub & Bogousslavsky, 2001). However, there is no universally agreed-upon definition, despite the consensus that fatigue is clinically significant, which makes it difficult to diagnose and impedes its assessment (De Groot et al., 2003). The reason for such lack of definition stems from the fact that fatigue is complex.

While the exact aetiology of fatigue is unclear, it is argued that post-stroke fatigue is multifaceted and studies have revealed associations between fatigue and several factors, including biological (neuroanatomical abnormalities and neurotransmitter dysregulations, lesion location,

corticomotor components and impaired movement speed) (Kuppuswamy, Clark, Turner, Rothwell, & Ward, 2015; Kuppuswamy, Clark, Sandhu, Rothwell, & Ward, 2015; Kutlubaev et al., 2012), psychological (Jaracz et al., 2007a; Schepers et al., 2006), social support (Michael et al., 2003) and physical (Duncan, Kutlubaev, Dennis, Greig & Mead, 2012; Ingles, Eskes, & Phillips, 1999).

Due to the lack of a standard definition, different terminology is used which complicates its understanding. The lack of definition has been extensively discussed in previous papers (Aaronson et al., 1999; Barbour & Mead, 2012; De Groot et al., 2003; Falconer et al., 2010; Staub & Bogousslavsky, 2001). For the purpose of this review, fatigue was defined as a subjective feeling of physical or mental exhaustion and weariness (Mead et al., 2007; van de Port et al., 2007).

Studies show that the prevalence of fatigue after stroke ranges from 28% to 77% (Christensen, Johnsen, Watt, Harder, Kirkevold & Andersen, 2008; Zedlitz, Visser-Meily, Schepers, Geurts, & Fasotti, 2011; Feigin et al., 2012; Michael, 2014). Variations in prevalence may be attributed to methodological differences in studies and the fact that fatigue is multifactorial and complex (Aaronson et al., 1999). In addition, fatigue prevalence depends on the definition of fatigue, participant characteristics and the measures used (Annoni, Staub, Bogousslavsky, & Brioschi, 2008; Christensen et al., 2008; Choi-Kwon & Kim, 2011). Fatigue may persist for up to 12 months post-stroke (van der Werf et al., 2001) but some individuals may experience it for even longer (Ingles et al., 1999; Michael et al., 2003).

Many stroke patients experience mental or physical fatigue, which differs in quality and duration from the typical

symptoms of tiredness in that it rarely ameliorates with ordinary rest (Kirkevold et al., 2012). Post-stroke fatigue may interfere with rehabilitation (Glader, Stegmayr, & Asplund, 2002), return to work and daily activities and compromise independence (Andersen, Christensen, Kirkevold, & Johnsen, 2012). Post-stroke fatigue is also a significant predictor of long-term mortality (Glader, Stegmayr, & Asplund, 2002; Naess & Nyland, 2013). Therefore post-stroke fatigue is of clinical significance.

Despite the multifaceted nature of fatigue, only a few studies have examined the association between fatigue and cognition (Raji, Al Snih, Ostir, Markides, & Ottenbacher, 2010; Samper-Ternent, Al Snih, Raji, Markides, & Ottenbacher, 2008). Evidence shows that 50-70% of stroke survivors perform poorly in neuropsychological tests (Hochstenbach et al., 1998; Rasquin et al., 2002). Cognitive impairment is observed in many stroke survivors and includes impairment of memory (Novitzke, 2008), attention (Barker-Collo et al., 2010), concentration (Rasquin et al., 2002) mental speed (Winkens et al., 2006), cognitive control (Li et al., 2013), language (Pedersen et al., 2004), visual perception (Jutai et al., 2003), and executive functioning (Poulin, Korner-Bitensky, Dawson, & Bherer, 2012).

Neuropsychologists have suggested a distinction between physical and mental fatigue, with the former being concerned with physical manifestations of fatigue (such as the need to take a break between activities) and the latter with mental slowness (such as difficulty with concentration) (Chaudhuri & Behan, 2004). Mental fatigue is commonly reported and can hinder full recovery (Johansson et al., 2012). However, the relationship between post-stroke fatigue and cognitive impairment has rarely been examined. Some studies

that address this question have not found any significant relationship between the two (Schepers et al., 2006; van Eijsden et al., 2012), whereas others have found that attention and speed of information processing were associated with fatigue after stroke (Appelros, 2006; Hubacher et al., 2012; Winkens, Van Heugten, Fasotti, & Wade, 2009).

Systematic reviews are currently the most efficient method of reviewing the existing literature and justifying further research (Moher, Liberati, Tetzlaff, & Altman, 2009). There is a systematic review (Ponchel et al., 2015) that investigated factors associated with fatigue, including cognition, however there was no previous review examining the relationship between cognition and fatigue after stroke.

2.3 Objective

The aim was to review the correlation between the severity of fatigue, as assessed on questionnaire measures, and cognitive abilities after stroke in adults.

2.4 Methods

The review followed the guidelines provided by the Centre for Reviews and Dissemination (CRD; Centre for Review and Dissemination, 2009). The PRISMA Statement for systematic reviews (Moher et al., 2009) was consulted for presenting the data and the process of conducting the review; a study flow diagram is provided based on the PRISMA requirements.

2.4.1 Type of Participants

Studies were included if: (1) their sample included stroke patients, or at least 75% of participants were stroke patients. If stroke patients were less than 75%, studies were

included if they reported or provided separate data for the stroke patients. Stroke was defined as a clinical syndrome of presumed vascular origin, typified by rapidly developed clinical signs of focal or global disturbance of cerebral functions, lasting more than 24 hours with no apparent cause other than vascular origin, as provided by the World Health Organisation (Aho et al., 1980). Subarachnoid haemorrhage (SAH) was not included because it requires different management from stroke (i.e., surgical operation) (Bederson et al., 2009; Sacco et al., 2013) and if a study included both stroke and SAH patients, it was included only if 75% of them were stroke patients or if separate data were available; (2) the sample included adults aged 18 years or over, or in the case that children were included only if separate results were available for those aged 18 years and over.

2.4.2 Type of Studies

Studies were included if they: (3) used the term "fatigue". Studies that assessed concepts related to fatigue, such as exhaustion, lack of energy, vitality or tiredness, were included if they reported these to be aspects of fatigue. Frailty was not considered as fatigue in this review because the term is highly associated with old age and natural ageing processes rather than as an explicit disease symptom. Despite the fact that fatigue might be a symptom of frailty, these two are distinctive (Avlund, 2013); (4) included an assessment of fatigue that provided a quantitative score of at least three response categories. The reason, is that a yes/no or agree/disagree format would only give information regarding the presence of fatigue and not allow correlations with severity of fatigue to be examined. If the study evaluated tiredness for example, but assessed it with any assessment other than a

fatigue scale, it was not included. These fatigue assessments included questionnaires, rating scales, visual analogue and ranking scales. Furthermore, the SF-36 (Ware & Sherbourne, 1992) vitality subscale was considered as it is described as a measure of energy/fatigue. Studies which involved interviews on fatigue or ratings of fatigue as present or absent were not included; (5) reported on any aspect of cognition. This included any reference to memory, attention, spatial abilities, visual neglect, speed of information processing, mental flexibility, executive function, mental slowness, orientation, concentration, cognitive control, decision making, problem solving, ataxia, apraxia, mental speed, reasoning and learning. Studies of language impairment were not included. People with language problems have difficulty completing cognitive assessments and are usually excluded from such studies (El Hachioui et al., 2013). Therefore, it was decided to not include papers that reported only patients with language impairment; (6) assessed cognition using an objective standardised quantitative measure. Studies using self-report assessments of cognition were not included as these have been shown to be more closely correlated with mood and confidence than cognitive function (Payne & Schnapp, 2014); (7) examined the relation between fatigue, as defined and specified in (3) and (4) above, and cognition, as defined and specified in (5) and (6) above. There were no restrictions regarding publication time or language. Translations were obtained for studies in languages other than English.

2.4.3 Exclusion Criteria

Systematic, narrative and literature reviews were not included.

2.4.4 Data Extraction

Searching syntax was developed based on key words that were identified as essential throughout literature. The author and the supervisors contributed to the syntax formation and the authors (CL) conducted the searching. For each of the studies meeting the above criteria, the author (CL) conducted the data extraction and the quality assessment, while the supervisor (NL) checked the details. The extraction was concerned with: (1) participants characteristics (age, sex, type of stroke and time since stroke onset); (2) fatigue assessment methods; (3) cognitive assessment methods; (4) study design (settings and procedure); and (5) results (any association reported between fatigue and cognitive impairment).

2.4.5 Quality Assessment

Quality assessment was conducted with the Critical Appraisal Skills Programme Checklists (CASP, 2014) and with the Newcastle-Ottawa Scale (NOS; Wells et al., 2009). Both scales were used in order to assess the quality of the papers from different perspectives as these two tools concentrate on different aspects. The designs considered were case-control studies and cohort studies. In case-control studies, case subjects needed to have the outcome (fatigue) and be compared to controls, which are subjects without the outcome but from the same population (i.e. stroke patients without fatigue)(CASP, 2013; Song & Chung, 2010). In cohort studies, an exposed population may be followed to assess the course and incidence of the case and gather data regarding multiple outcomes of the exposure (CASP, 2013; Song & Chung, 2010). So a group of stroke patients would be followed to

ascertain who develops fatigue over time. For the purpose of this review, case-control studies were only appropriate if they compared stroke patients with and without fatigue on measures of cognitive impairment, or compared those with and without cognitive impairment on measures of fatigue. Comparison between stroke patients and healthy controls were not relevant to the study question, and when the relation between fatigue and cognitive impairment was examined in these studies was evaluated as single-group cohort.

Quality assessment was conducted with the Critical Appraisal Skills Programme Checklists (CASP) quality assessment tool for cohort studies (CASP, 2014). CASP consists of 12 items that examine the context of the study results in relation to their validity, content and scientific contribution. The CASP was chosen because it has open-ended questions and allows for a more subjective interpretation of findings than other tools such as the Newcastle-Ottawa Scale (NOS; Wells et al., 2009)which have standard set responses that may not be applicable to all studies. Each question was answered "yes", "no" or "can't tell". In order to provide a quality index, a score of 1 was given for every "yes" answer and 0 for every "no" or "can't tell" answer. For the items that are open-ended (7 and 12) no points were given, but notes were taken to help with the overall quality assessment of the study, whereas item 8 (also an open-ended item) was given a point if the results were precise. The results of the CASP scoring were categorised as following: 0-3= poor quality; 4-8=average quality; 9-12=high quality.

The Newcastle-Ottawa Scale (NOS; Wells et al., 2009) for cohort studies was also used to compare the quality indices between the scales. The NOS scale assesses three major areas: selection, comparability and exposure (case-control

studies) or outcome (cohort studies) with 8 items; each item has some alternative responses and a star is given for each statement that reflects high quality (with the exception of the "compatibility" item which can be awarded up to 2 stars); therefore the NOS scores range from 0-9 (Stang, 2010). The results of the NOS scoring were categorised as following: 0-3 stars= poor quality; 4-6 stars= average quality; 7-9 stars=high quality. The NOS was chosen because it has more precise items than the CASP (CASP, 2014) and together the tools offered a more comprehensive evaluation of the papers.

2.4.6 Data Synthesis and Correlation Classification

The correlation coefficients between fatigue and cognition were summarised. Correlations were considered statistically significant at the 5% level of significance. The classification of the strength of correlation varied. It is generally suggested that correlation values (r) from .1 to .3 are considered weak, from .4 to .6 moderate, .7 to .9 strong and 1 is a perfect correlation (Hatcher, 2003).

2.4.7 Search Methods for Identification of Studies

An electronic search for published studies was conducted in the following databases: EMBASE (1980-February, 2014), PsycInfo (1806- February, 2014), CINAHL (1937- February, 2014), MEDLINE (1946- February, 2014). The Ethos (UK dissertations; 1600- February, 2014) and the DART (European Theses Portal; 1999- February, 2014) databases were also searched for unpublished academic work in theses and dissertations.

The first four databases were searched with a separate strategy adjusted to the operating system of each database (see appendices for strategies). The dissertation databases

were searched using keywords and their associated terms or synonyms; the same keywords were used to form the other searches (see appendices, page 297 for key words). Finally, the reference lists of relevant systematic and narrative reviews and of the studies included, were further scanned for potential studies. The citation indexes of included studies were searched on Web of Science.

2.4.8 Study Selection

Potentially relevant papers were identified from their titles and abstracts based on the inclusion criteria. The full text versions of those that met the criteria were obtained. If it was not clear from the abstract the full text was obtained, and if in doubt the authors were contacted for clarifications. Papers that met the criteria were reviewed and duplicates were removed using the Mendeley referencing system. The third author (NL) confirmed their eligibility and a decision was made as to which studies to include.

2.5 Results

The initial electronic search conducted in February 2014 identified 387 papers. In total, 11 studies fulfilled the inclusion criteria. Diagram 1 outlines the study selection process and tables 3, 4, 5, 6, 7 and 8 summarise the included studies. After duplicates were removed (n=69), 318 papers were assessed against the criteria. At this stage, 310 were excluded for not including stroke patients (n=191), not including the term fatigue (n=25), not assessing fatigue (n=57), not considering any cognitive domain (n=13), not assessing cognition (n=4), not assessing the relationship between fatigue and cognition (n=19). One additional paper was excluded because its full text version was not accessible. The

reference lists of the included papers were scanned for potentially relevant papers missed in the initial searching phase; one paper (Naess, Nyland, Thomassen, Aarseth, & Myhr, 2005) was identified from the reference lists of five of the included papers (Hubacher et al., 2012; Johansson & Rönnbäck, 2012; Naess & Nyland, 2013; Park et al., 2009; Radman et al., 2012) and was included. One paper (Johansson & Rönnbäck, 2012) was identified by chance on the web and another paper (Kutlubaev et al., 2013) was identified in the reference list of a narrative review; they were both included.

Conducting a search on Web of Science of the citation indexes of these 11 papers identified a further 149 papers which were also assessed against the inclusion criteria. There were no duplicates among these 149 papers, however there were some duplicates of papers already identified in the initial search (n=57), which were removed. Of the remaining 92 papers, none met the criteria and were excluded for either not having stroke patients (n=12), not using the term fatigue (n=16), not assessing fatigue (n=25), not including any cognitive domain (n=26), not assessing cognition (n=0) or not assessing the relationship between fatigue and cognition (n=13). Data and details regarding the excluded papers are available from the authors upon request.

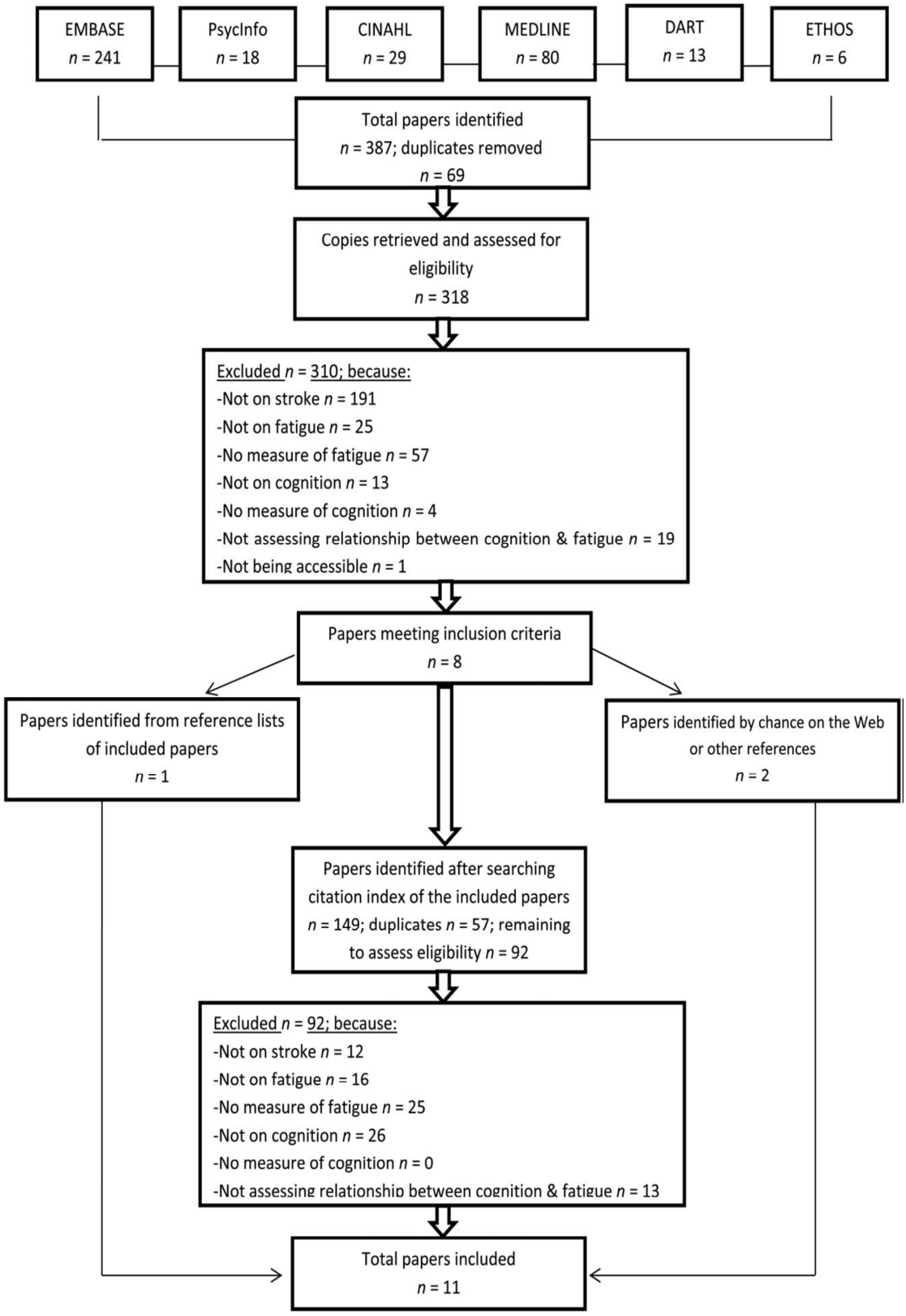


Diagram 1: Study Flow

2.5.1 Demographic Characteristics

The demographic characteristics of the participants are summarised in table 3. Overall, the studies provided data on 1597 participants post-stroke 982 men (62%) and 615 women (38%). Generally, the studies had a small sample and only two (Tang et al., 2010; van Eijsden et al., 2012) had more than 200 participants.

Sample sizes ranged from 24 to 458. The mean age in studies ranged from 47.2 (SD= 8.3) to 66.2 (SD=11.7) years (median values ranged from 47.8 to 70.5). The time since stroke onset at recruitment ranged from 7 days to 18 years with one study (Hubacher et al., 2012) not reporting this information.

One study (Tang et al., 2010) reported a median of 5 years (range 0-25) and another (Johansson & Rönnbäck, 2012) a mean of 14.8 years (SD=2.8) years spent in education, and information from four other studies (Naess & Nyland, 2013; Naess et al., 2005; Hubacher et al., 2012; Winkens, Van Heugten, Fasotti, & Wade, 2009) indicated that 237 participants had attended higher, 27 secondary and 15 primary education. Five studies did not provide relevant information on education. The proportion of married participants was reported in five studies and ranged from 27 to 83%. Six studies did not report marital status (Hubacher et al., 2012; Johansson & Rönnbäck, 2012; Naess et al., 2005; Radman et al., 2012; Winkens, Van Heugten, Fasotti, & Wade, 2009).

Table 3: Participants' Demographic Characteristics

Study	N	Age	Gender	Marital Status	Education	Country
Hubacher et al. (2012)	31	59.9±10.30	81%±19%	NS	Secondary: 5±16 College: 20±65 University: 2±7	Switzerland & Germany
Johansson & Rönnbäck (2012)	24	54.2±7.0	45.8%±54.1%	NS	Years spent in education: 14.8±2.8	Sweden
Kutlubaev et al. (2013)	107	70.5[a]	62%±38%	NS	NS	UK
Naess & Nyland (2013)	190	47.2±8.3	57%± 43%	Married: 27%	Higher education: 86%	Norway
Naess, Nyland, Thomassen, Aarseth & Myhr (2005)	192	47.8[a]	57.3%±46.3	NS	Higher education: 29.7%	Norway
Park et al. (2009)	40	59.9±11.8	65%±35%	With partner: 82.5%	NS	Korea
Radman et al. (2012)	109	51.1±13.8	66%±34%	NS	NS	Switzerland
Schepers, Visser-Meily, Ketelaar, & Lindeman (2006)	167	56.4±11.4	59%±41%	With partner: 73.7%	NS	Netherlands
Tang et al. (2010)	458	66.2±11.7	61.6%±38.4%	Married: 74.6%	Years spent in education: 5[a]	Hong Kong
van Eijsden, van de Port, Visser-Meily & Kwakkel (2012)	242	57.1±10.3	64.9%±35.1%	With partner: 82.8%	NS	Netherlands
Winkens, Van Heugten, Fasotti & Wade (2009)	37	54.8±12.1	70.27%±29.72%	NS	Primary: 40.5% Secondary: 29.8% Higher: 29.8%	Netherlands

Note: N= Number of Participants; Males±females; Mean±SD; NS: Not Specified.

2.5.2 Medical Characteristics

The medical characteristics of the participants are summarised in table 4. Of the total 809 (51%) participants had ischemic stroke, 197 (12%) haemorrhagic stroke and 591 (37%) were unspecified; 206 (13%) participants had a recurrent stroke whereas the rest had a first stroke. Of the total 331 (21%) participants suffered a right hemisphere stroke, 270 (17%) a left hemisphere stroke and 35 (2.1%) were non-lateralised bilateral 4 (0.3%), subcortical 20 (1.3%), brainstem 3 (0.2%), cerebellum 3 (0.2%), or other 5 (0.3%). Four studies (Kutlubaev et al., 2013; Naess et al., 2005;

Naess & Nyland, 2013; Tang et al., 2010) did not provide information on lateralisation and one study (Winkens, Van Heugten, Fasotti, Wade, et al., 2009) reported missing data for 5 participants; in total, information regarding lateralisation was missing for 952 participants (59%). Two participants had suffered a sub-arachnoid haemorrhage (SAH) (0.1%).

Five hundred and thirty eight (36%) of the participants had a major comorbidity, as reported by five studies (Johansson & Rönnbäck, 2012; Naess et al., 2005; Naess & Nyland, 2013; Park et al., 2009; Schepers et al., 2006). Four studies mentioned hypertension, hypertonia, diabetes mellitus and cardiovascular diseases, migraine and depression, whereas one did not specify these. Seven studies did not report comorbidities.

Table 4: Participants' Medical Characteristics

Study	Stroke Type	Previous Stroke	Comorbidities	Time Since Stroke Onset	Source
Hubacher et al. (2012)	90%±10%	First: 23±74 Second: 4±13 Third: 2±7	NS	NS	8 Rehabilitation Centres
Johansson & Rönnbäck (2012)	SAH:2; Left: 3; Right: 6; Brainstem: 3; Cerebellum: 3	16.6%	Hypertonia (% NS)	6.1±7.1 years	Hospital & Community
Kutlubaev et al. (2013)	30%±8.4%	42%	NS	1 month	Hospital
Naess & Nyland (2013)	Ischaemic	No	Myocardial Infarct: 47%; Diabetes: 65%	18 years	Community Database
Naess et al. (2005)	Cerebral Infarction	Yes, 9.4%	Depression: 38.6%; Migraine: 17.9%; Myocardial Infarction: 10.0% ; Angina Pectoris: 5.8%; Diabetes Mellitus:11.1%; Hypertension: 35.8%	6 years	Hospital Registry
Park et al. (2009)	62.5%±37.5%	No	Hypertension: 72.5%;Diabetes mellitus: 32.5%;Cardiac disease: 17.5%	37.2±27.4	Rehabilitation Centre
Radman et al. (2012)	NS	No	No	7 days	Acute Stroke Unit
Schepers et al. (2006)	68.9%±31.1%	No	55.1% (NS what comorbidities)	1 year post-stroke	4 Rehabilitation Centres
Tang et al. (2010)	NS	Recurrent: 21.4%	No	3 months	Acute Stroke Unit
van Eijsden et al. (2012)	80.9%±19.1	Recurrent: 9.5%	NS	97.0±46.9	Rehabilitation Centre
Winkens et al. (2009)	83.78%±16.21%	Previous: 32.4%	No	234±160	5 Rehabilitation Centres

Note: Ischemic±Haemorrhagic; Mean±SD; NS: Not Specified.

2.5.3 Settings, Design and Quality Assessment

Settings and design of the studies are summarised in tables 4 and 6. Three of the studies (Winkens et al., 2009; Naess et al., 2005; Johansson & Rönnbäck, 2012) included controls in their designs but for the purpose of this review, only the case subjects were relevant. Time since stroke onset at baseline assessment ranged from 7 days to 18 years. Five studies had a follow-up in their design and six did not (Park et al., 2009; Johansson & Rönnbäck, 2012; Naess & Nyland, 2013; Naess et al., 2005; Kutlubaev et al., 2013; Tang et al., 2010). Time of follow-up ranged from 2 weeks to 1 year post-stroke. Seven studies were single-centre and four studies were multi-centre. Two studies were conducted in Asia (Park et al., 2009; Tang et al., 2010) and the rest were conducted in Western Europe.

As summarised in table 5, 3 studies were considered to be of high quality and 8 studies were considered to be of average quality according to the CASP list while 8 were considered to be of poor quality and 3 of average quality according to the NOS scale.

Table 5: Quality Indices According to CASP and NOS

Study	CASP Quality Index	NOS Quality Index
Winkens et al., (2009)	Validity 5 (max. 8)	Selection ** (max. 4)
	Results 1 (max. 2)	Comparability 0 (max. 2)
	Applicability 1 (max. 2)	Outcome 0 (max. 3)
	Total:7 (max. 12) **AVERAGE**	Total: 2 (max. 9) **POOR**
Naess et al., (2005)	Validity 5 (max. 8)	Selection ** (max. 4)
	Results 1 (max. 2)	Comparability 0 (max. 2)
	Applicability 2 (max. 2)	Outcome 0 (NO FOLLOW-UP) (max. 3)
	Total:8 (max. 12) **AVERAGE**	Total: 2 (max. 9) **POOR**
Johansson & Rönnbäck, (2012)	Validity 5 (max. 8)	Selection ** (max. 4)
	Results 2 (max. 2)	Comparability 0 (max. 2)
	Applicability 2 (max. 2)	Outcome 0 (NO FOLLOW-UP) (max. 3)
	Total:9 (max. 12) **HIGH**	Total: 2 (max. 9) **POOR**
Tang et al., (2010)	Validity 5 (max. 8)	Selection ** (max. 4)
	Results 1 (max. 2)	Comparability * (max. 2)
	Applicability 2 (max. 2)	Outcome 0 (NO FOLLOW-UP) (max. 3)
	Total:8 (max. 12) **AVERAGE**	Total: 3 (max. 9) **POOR**
Schepers et al., (2006)	Validity 6 (max. 8)	Selection ** (max. 4)
	Results 1 (max. 2)	Comparability 0 (max. 2)
	Applicability 1 (max. 2)	Outcome ** (max. 3)
	Total:8 (max. 12) **AVERAGE**	Total: 6 (max. 9) **AVERAGE**
Radman et al., (2012)	Validity 7 (max. 8)	Selection ** (max. 4)
	Results 1 (max. 2)	Comparability * (max. 2)
	Applicability 1	Outcome ** (max. 3)
	Total:9 (max. 12) **HIGH**	Total: 5 (max. 9) **AVERAGE**
Park et al., (2009)	Validity 4 (max. 8)	Selection ** (max. 4)
	Results 1 (max. 2)	Comparability * (max. 2)
	Applicability 2 (max. 2)	Outcome 0 (NO FOLLOW-UP) (max. 3)
	Total:7 (max. 12) **AVERAGE**	Total:3 (max. 9) **POOR**
Kutlubaev et al., (2013)	Validity 5 (max. 8)	Selection ** (max. 4)
	Results 1 (max. 2)	Comparability 0 (max. 2)
	Applicability 2 (max. 2)	Outcome 0 (NO FOLLOW-UP) (max. 3)
	Total:8 (max. 12) **AVERAGE**	Total:2 (max. 9) **POOR**
Hubacher et al., (2012)	Validity 4 (max. 8)	Selection ** (max. 4)
	Results 2 (max. 2)	Comparability * (max. 2)
	Applicability 2 (max. 2)	Outcome 0 (max. 3)
	Total:8 (max. 12) **AVERAGE**	Total:3 (max. 9) **POOR**
van Eijsden et al., (2012)	Validity 6 (max. 8)	Selection ** (max. 4)
	Results 0 (max. 2)	Comparability * (max. 2)
	Applicability 0 (max. 2)	Outcome ** (max. 3)
	Total:9 (max. 12) **HIGH**	Total:5 (max. 9) **AVERAGE**
Naess & Nyland, (2013)	Validity 5 (max. 8)	Selection * (max. 4)
	Results 1 (max. 2)	Comparability 0 (max. 2)
	Applicability 2 (max. 2)	Outcome 0 (NO FOLLOW-UP) (max. 3)
	Total:8 (max. 12) **AVERAGE**	Total:1 (max. 9) **POOR**

The majority of the studies were of either poor or average quality according to both CASP and NOS tools.

2.5.4 Fatigue

Details regarding fatigue scales and scores are summarised in table 6. Eight studies used one assessment of fatigue and three used more than one instrument (Hubacher et al., 2012; Tang et al., 2010; Winkens, Van Heugten, Fasotti, & Wade, 2009). Eight studies used the Fatigue Severity Scale (fatigue severity; FSS) (Krupp et al., 1989); the remaining studies each used a different scale.

In the eight studies using the FSS, the mean fatigue score ranged from 3.1 (SD=1.4) to 4.1 (SD=1.7). Three studies (Hubacher et al., 2012; Johansson & Rönnbäck, 2012; Winkens, Van Heugten, Fasotti, & Wade, 2009) measured cognitive fatigue whereas eight only reported overall fatigue. Four of the seven longitudinal studies reported that fatigue remained stable over time whereas three studies (Schepers et al., 2006; Winkens, Van Heugten, Fasotti, & Wade, 2009; Hubacher et al., 2012) reported that fatigue increased over time. According to cut-off scores, 900 (57%) participants were not fatigued and 697 (44%) participants were fatigued.

Table 6: Baseline Fatigue and Follow-Up Fatigue and Cognitive Impairment Values

Study	Fatigue Score	Follow-Up
Hubacher et al. (2012)	FSS: 3.00±0.32; FSMC-S: 42.29±3.06; FSMC-C:19.63±1.61; FSMC-M: 22.67±1.74; MFIS: 26.79±3.86	4 weeks: FSS: 3.73±0.39; FSMC-S:52.92±4.18; FSMC-C:24.92±2.12; FSMC-M:28.00±2.21; MFIS:32.21±4.27
Johansson & Rönnbäck (2012)	MFS: 18.4±4.9	No
Kutlubaev et al. (2013)	FAS_1: 23ª	No
Naess & Nyland (2013)	FSS:4.0±1.6	No
Naess et al. (2005)	FSS:4.14±1.65	No
Park et al. (2009)	FSS: 3.6±1.5	No
Radman et al. (2012)	FAI: 3.2±1.8	1 year FAI: 3.3±1.7 Cognitive impairment: 34.3%
Schepers et al.(2006)	FSS:4.1±1.3	6 Months FSS: 4.5±1.2; 1 Year: FSS: 4.7±1.3; MMSE: 11.4% Impaired
Tang et al. (2010)	FSS: 3.1±1.4; SF-36: 64.6±21.3	No
van Eijsden et al. (2012)	FSS: 4.1±1.7	24 weeks: FSS: 4.1±1.7
Winkens et al. (2009)	FSS: 3.5±1.5 MSQ: 34.5±20.5	2 weeks: MSQ: 44.3±18.6

Note: FAS1: Fatigue Assessment Scale; FAS2: verbal fluency task; FAI: Fatigue Assessment Instrument; FSS: Fatigue Severity Scale; MFS: Mental Fatigue Scale; SAMFS: Self-Assessment for Mental Fatigue Scale; SF-36: Short Form (36) Health Survey; MFIS: Modified Fatigue Impact Scale; FSMC: Fatigue Scale for Motor and Cognitive Function (C: Cognitive Subscale; M: Motor Subscale; S: Sum score); MSQ: Mental Slowness Questionnaire; MMSE: Mini Mental State Examination; Mean±SD.

2.5.5 Cognitive Impairment

Cognitive tests and their scores are summarised in table 7. Seven studies used the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) (Naess & Nyland, 2013; Park et al., 2009; Tang et al., 2010; van Eijsden et al., 2012). Three studies used the Trail Making Test-Parts A and B (mental flexibility, visual search, speed of information processing and executive functions) (TMT; Army Individual Test Battery, 1944) (Johansson & Rönnbäck, 2012; Schepers et al., 2006; Winkens, Van Heugten, Fasotti, Wade, et al.,

2009) to assess executive function. The mean score on the MMSE across three studies (Naess & Nyland, 2013; Park et al., 2009; van Eijsden et al., 2012) ranged from 28.0 (SD=1.7) to 28.2 (SD=2.1). Three studies (Kutlubaev et al., 2013; Schepers et al., 2006; Tang et al., 2010) reported that median on the MMSE ranged from 27 to 28. One study (Naess et al., 2005) reported that the majority of their participants scored ≥28 on the MSSE. The mean scores in the studies that used Trail Making Test ranged from 40.4 to 62.8 for Task A and from 83.7 to 153.9 for Task B with median of 123 for task B.

Table7: Cognitive Assessments and Their Scores

Study	Tests & Ability	Score
Hubacher et al. (2012)	Verbal & visual short & long term memory, speed of information processing, working memory and executive functions	SRT-LTS: -0.41±1.52; SRT-CLTR: -0.36±1.27; SRTDR: -1.10±1.80; 10/36 spatial recall test: 0.24±1.15; 10/36; DR: 0.16±1.30; SDMT: -1.14±1.46; WLG: -1.39±0.87; PASAT: -1.11±1.33
Johansson & Rönnbäck (2012)	attention, verbal fluency, motor speed, divided attention, visual scanning, reading speed, mouse clicks, speed of information processing, working memory	TMT: A 40.4±15.0; B 83.7±28.4; C 98.3±45.2; D 167.0±58.4; D 1.5±1.4; DSC 62.61±0.6; DS Total 14.3±4.0 [Forward 8.3±2.0; Backward 6.0±2.2]; FAS_2 38.0±15.1; Reading Speed 2.8±0.68; Mouse Clicks 39.4±8.3; Mouse Clicks & Counting Digits 36.4±8.8; Computer Errors 4.1±2.9
Kutlubaev et al. (2013)	orientation, attention, memory, calculation, language, construction functions	MMSE: 27[¤]
Naess & Nyland (2013)	orientation, attention, memory, calculation, language, construction functions	MMSE: 28.2±2.1
Naess et al. (2005)	orientation, attention, memory, calculation, language, construction functions	MMSE: 73% (140 participants) = 28; 19% (37 participants)= 25-27; 8% (15 individuals)= <25
Park et al. (2009)	orientation, attention, memory, calculation, language, construction functions	MMSE: 28.15±2.95
Radman et al. (2012)	Stroop, phasic alert, divided attention, D2, letter fluency, non-verbal directed fluency, digit span, Corsi blocks; Rey auditory verbal memory ;sustained attention, long term memory; executive functions	30.3% showed abnormal performance
Schepers et al.(2006)	orientation, attention, memory, calculation, language, construction functions, motor speed, complex visual scanning	MMSE: 28.0 [¤]; TMT-B: Time:123.0[¤]; Correct Connections 24.0[¤]
Tang et al. (2010)	orientation, attention, memory, calculation, language, construction functions	MMSE: 27[¤]
van Eijsden et al. (2012)	orientation, attention, memory, calculation, language, construction functions	MMSE: 28.0±1.7
Winkens et al. (2009)	memory, attention, reaction time, speed of information processing	TMTA 62.8±38.1; TMTB 153.9±112.8; Stroop 1 66.2±25.5; Stroop 2; 89.4±42.8; Stroop 3 156.3±74.0; SRTT 0.51±0.58; AVLT 40.1±11.6; SDMT Written 28.4±10.4; SDMT Verbal; 35.9±11.6 ;PASAT 35.3±9.6

Note: MMSE: Mini Mental State Examination; BRBN: Brief Repeatable Battery of Neuropsychological Tests; ; TMT-A: Trail Making Test-part A; TMT-B: Trail Making Test-part B; TMT-C: trail making tests plus months; TMT-D: trail making tests plus months and days of the week; SRT-LTS : Selective Reminding Test – Long-Term Storage; SRT-CLTR : Selective

Reminding Test – Consistent Long-Term Retrieval; SRT-DR : Selective Reminding Test – Delayed Recall; 10/36-DR: Spatial Recall Test – Delayed Recall; SDMT: Symbol Digits Modalities Test; PASAT: Paced Auditory Serial Addition Test; Digit Span: Digit Span; DSC: Digit Symbol Coding; WLG: Word List Generation; AVLT: Auditory Verbal learning Test; SRTT: Simple Reaction Time Task; Mean±SD; Median$^{\overline{\Gamma}}$; Mean□.

2.5.6 Correlations Between Fatigue and Cognition After Stroke

Table 8 summarises the correlations between measures of fatigue and measures of cognitive function. Seven studies (Kutlubaev et al., 2013; Naess et al., 2005; Naess & Nyland, 2013; Park et al., 2009; Schepers et al., 2006; Winkens, Van Heugten, Fasotti, & Wade, 2009; van Eijsden et al., 2012) found no significant correlation ($p>.05$) between cognitive variables and fatigue whereas four found significant correlations ($p<.05$) (Hubacher et al., 2012; Johansson & Rönnbäck, 2012; Radman et al., 2012; Tang et al., 2010). The correlation between cognition and fatigue after stroke ranged from r= .36 to .54. Significant correlations were found with Symbol Digit in two studies (Hubacher et al., 2012; Johansson & Rönnbäck, 2012) (.44, .52, .59) and with speed of information processing in two studies (Hubacher et al., 2012; Johansson & Rönnbäck, 2012) (r= .50-.46). Significant correlations were also found with Selective Reminding Test (SRT; Buschke & Fuld, 1974) (verbal memory) and Word List Generation (WLG; Rao, Leo, Bernardin, & Unverzagt, 1991) (semantic verbal fluency). The Modified Fatigue Impact Scale (MFIS; Fisk et al., 1994) cognitive sub-scale revealed four significant correlations with the cognitive tests, whereas the motor sub-scale was only correlated with mental speed. The cognitive sub-scale of the Fatigue Scale for Motor and Cognitive Function (FSMC; Penner et al., 2009) revealed four significant correlations with the cognitive tests, whereas the

motor sub-scale revealed three.

Of the 77 correlation coefficients calculated, 21 were significant and 56 were not. Overall, the above coefficients suggest that there is an association between concentration, sustained attention, speed of information processing, memory retrieval and verbal fluency and fatigue after stroke, but not with global cognitive impairment.

Table 8: Correlations between Fatigue and Cognitive Measurements

Study	Correlations							
Hubacher et al. (2012)	r	FSS	MFIS	MFIS-C	MFIS-M	FSMC-S	FSMC-C	FSMC-M
	SRT-LTS	-0.18	-0.36*	-0.38*	-0.29	-0.35	-0.39*	-0.36
	SRT-CLTR	-0.16	-0.39*	-0.38*	-0.34	-0.31	-0.36*	-0.22
	SRTDR	-0.28	-0.30	-0.33	-0.22	-0.27	-0.34	-0.17
	10/36 spatial recall	-0.08	-0.14	-0.05	-0.22	-0.34	-0.26	-0.39*
	10/36 DR	-0.18	-0.14	-0.08	-0.22	-0.32	-0.26	-0.34
	SDMT	-0.23	-0.44*	-0.45*	-0.39*	-0.52*	-0.54*	-0.43*
	WLG	-0.14	-0.41*	-0.41*	-0.31	-0.20	-0.33	-0.05
	PASAT	-0.21	-0.17	-0.25	-0.08	-0.50*	-0.44*	-0.44*
Johansson & Rönnbäck (2012)	DSC: R= -0.59* Number of Errors in Computer Test: r= 0.46*							
Kutlubaev et al. (2013)	0.62[β]							
Naess & Nyland (2013)	-0.08[r]							
Naess et al. (2005)	>0.05, non-significant							
Park et al. (2009)	-0.10[β]							
Radman et al. (2012)	Significant relationships between sustained & divided attention, long-term memory, executive functions and fatigue (Values NS)*							
Schepers et al.(2006)	-MMSE: .03[r] -TMT-B: Time: 0.03; Correct Connections: -0.03[r]							
Tang et al. (2010)	SF-36: 0.145[r]*							
van Eijsden et al. (2012)	0.104[rj][96]							
Winkens et al. (2009)	MSQ: TMTA 0.05; TMTB 0.09; Stroop 1 -0.13; Stroop 2 0.01; Stroop 3 -0.21; SRTT -0.04; AVLT -0.02; SDMT Written 0.16; SDMT Verbal 0.09; PASAT -0.28							

Note: FAS1: Fatigue Assessment Scale; FAS2: verbal fluency task; FAI: Fatigue Assessment Instrument; FSS: Fatigue Severity Scale; MFS: Mental Fatigue Scale; SAMFS: Self-Assessment for Mental Fatigue Scale; SF-36: Short Form (36) Health Survey; MFIS: Modified Fatigue Impact Scale; FSMC: Fatigue Scale for Motor and Cognitive Function (C: Cognitive Subscale; M: Motor Subscale; S: Sum score); MMSE: Mini Mental State

Examination; BRBN: Brief Repeatable Battery of Neuropsychological Tests; ; TMT-A: Trail Making Test-part A; TMT-B: Trail Making Test-part B; TMT-C: trail making tests plus months; TMT-D: trail making tests plus months and days of the week; SRT-LTS : Selective Reminding Test – Long-Term Storage; SRT-CLTR : Selective Reminding Test – Consistent Long-Term Retrieval; SRT-DR : Selective Reminding Test – Delayed Recall; 10/36-DR: Spatial Recall Test – Delayed Recall; SDMT: Symbol Digits Modalities Test; PASAT: Paced Auditory Serial Addition Test; Digit Span: Digit Span; DSC: Digit Symbol Coding; WLG: Word List Generation; AVLT: Auditory Verbal learning Test; SRTT: Simple Reaction Time Task; MSQ: Mental Slowness Questionnaire; ∫: p value <0.2; Significant correlation*; r: Pearson's Correlation; ρ: Spearman's Correlation ; $^{\infty}$: Regression Value; NS: Not Specified;

-All p values are set to 0.05 unless otherwise specified

2.6 Discussion

The majority of the correlations between cognition and fatigue after stroke were not significant (p>.05). Only four of the 11 studies revealed significant correlations between fatigue and divided attention, sustained attention, speed of information processing, long-term memory and concentration. The studies revealed either non-significant or weak to moderate correlations. Non-significant or weak significant correlations between cognition and fatigue could potentially be attributed to participants in the sample having low levels of fatigue or minimal cognitive impairment. With regard to fatigue, the majority of the studies used the FSS to measure fatigue. The mean fatigue score across the studies was 4 on the FSS, indicating that fatigue was low in their samples. Half of the studies reported a mean fatigue scores just slightly above the cut-off indicating low levels of fatigue.

The majority of the studies used the MMSE (Folstein et al., 1975) and reported low levels of cognitive impairment for

the majority of the participants. The MMSE, as discussed in more depth in chapter 1, is not sensitive to stroke specific cognitive impairment (Blake et al., 2002; Cumming, Marshall, et al., 2013; Nys et al., 2005). Therefore the majority of the studies used a test of cognition which will not detect the cognitive impairments likely to be associated with fatigue. The results are similar to those of another systematic review (Ponchel et al., 2015) which examined the effect of cognitive disorders on post-stroke fatigue. According to this review, the majority of the identified studies used the MMSE and did not reveal significant relationships with a fatigue scale. The authors highlighted the importance of using domain specific cognitive tests which are more sensitive to stroke related cognitive impairment.

The majority of the significant correlation coefficients came from the same study (Hubacher et al., 2012) which used the FSMC and the MFIS that assess cognitive manifestations of fatigue. Therefore these scales are more likely to correlate significantly with cognitive impairment due to symptom overlap. For instance, the MFIS includes items such as: "I have been forgetful" (targeting memory), "I had trouble concentrating" (which targets attention), and "My thinking has been slowed down" (speed of information processing) and the FSMC items such as: "My powers of concentration decrease considerably when I'm under stress" (attention) and "During episodes of exhaustion, I am noticeably more forgetful" (memory). When the scores are separated for cognitive and motor sub-scales within the scales, many of them are attributed to the cognitive components of fatigue being correlated with cognitive impairment. More general fatigue scales such as the FSS, did not reveal such relationships. This could be due either to the cognitive measures used (mostly

the MMSE in these studies) or to the fact that the FSS does not measure cognitive components of fatigue. Fatigue scales that consider cognitive symptoms may reflect subjective cognitive complaints rather than fatigue. The results seem to be in accordance with studies in other medical conditions. For instance, studies in cancer patients undergoing chemotherapy (Castellon et al., 2004; Tchen et al., 2003; Vardy, 2008), HIV/AIDS patients (Millikin et al., 2002), multiple sclerosis patients (Jougleux-Vie et al., 2014; Kinsinger et al., 2010; Middleton et al., 2006) and patients with traumatic brain injury, (Johansson, Berglund, & Rönnbäck, 2009) have reported that subjective mental fatigue was associated with subjective cognitive performance but not with objective cognitive performance. The majority of the significant correlations in this review, were from a study that assessed mental fatigue as a cognitive complaint (Hubacher et al., 2012). All these indicate that there may be a significant relationship between subjective cognitive impairment and fatigue, but not with cognitive ability. Therefore, it is essential to assess general fatigue as well as perceived cognitive fatigue and to compare their relationship with cognitive impairment.

Most studies used more than one measures of fatigue or cognition and produced inconsistent results. For example, Winkens et al., (2009) used both Trail Making Test A and B (TMT; Army Individual Test Battery, 1944) and B and the Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977) to measure speed of information processing, and both PASAT and the Symbol Digit Modalities Test (SDMT; Smith, 1991) to measure working memory, speed of information processing and sustained attention. None of the above tests was significantly correlated with the Mental Slowness Questionnaire (MSQ; Winkens et al., 2009), as a measure of

fatigue.

The inconsistency of the measures makes the interpretation of results difficult. Hubacher et al., (2012) used three scales of fatigue and correlated each of them with all eight subtests of the Brief Repeatable Battery of Neuropsychological Tests (BRB-N; Rao, 1990) battery. Sustained attention was measured by SDMT and PASAT. The latter was significantly correlated with the FSMC, however when sustained attention was measured with SDMT, it was not significantly associated with any of the fatigue scales. The authors acknowledged that the PASAT is also a measure of working memory and SDMT a measure of mental speed. It is therefore unclear which components were, or were not associated in each correlation. It is difficult to conclude whether cognitive domains were significantly associated with fatigue, or whether the lack of significant relationship was due to the measures used. There is a need for more studies with more appropriate measures for fatigue and cognition.

It appears that fatigue scales that measure general fatigue symptoms rather than cognitive subcomponents, would be more appropriate in measuring fatigue to assess evidence of an association with cognitive impairment. The majority of the studies, did not include cognitive tests because their objective was not to measure and associate cognitive impairment with fatigue. They mostly used global cognitive status assessments such as the MMSE as screening measures for participant inclusion/exclusion to the study. Therefore it would appear that tests that are designed to address specific cognitive impairments would be more appropriate. A combination of a general fatigue scale with a domain-specific cognitive measure is more likely to assess accurately the relationship between fatigue and cognitive impairment after

stroke.

Most of the studies were of poor or average quality according to the CASP and NOS guidelines.Although different, these two tools may be complementary in the way that they assess quality from different viewpoints. Aside from both covering similar aspects of study design, the CASP is also concerned with the applicability of the findings and the significance of the topic that is being addressed. However, the CASP list is very objective and open to interpretation; the CASP list is also long and has poorly defined items. For instance item 3, asks to rate whether the exposure was accurately measured to minimise bias. This is a very broad item and as the probes suggest, type of measurements, psychometric properties and design need to be taken into consideration. It is however possible that a study used the right type of tools (objective/subjective/carer version) but they do not have good psychometric properties. Likewise, it is possible to use a highly reliable scale which is not valid for the purpose of the review and therefore the interpretation by each reviewer may vary.

Despite being endorsed by the Cochrane Collaboration (Zeng et al., 2015), it is also acknowledged that the NOS does not assess quality of the reporting and if researchers want to assess these aspects as well, may use a different tool (Margulis et al., 2014). The NOS has some further disadvantages. Another limitation that the NOS holds is that it also, does not address issues with standardisation and/or psychometric properties and appropriateness of the measures used as was the case with the CASP. Therefore even a combination of both scales was not very accurate indicators of the quality of the studies. In addition, NOS has been reported to not have very high reliability among reviewers (Hartling et

al., 2013) which highlights the significance of subjectivity. There is no consensus about which tool is best and there is great homogeneity in what is considered in each one. Therefore interpretation of quality indices by such tools can only be indicative and should be interpreted with caution (Katrak, Bialocerkowski, Massy-Westropp, Kumar, & Grimmer, 2004). The items of the scales do not fully address the qualities of interest for this systematic review which shows that although there are scales available to assess quality they are not always helpful and therefore the studies included in the systematic review were also assessed in terms of their contents.

It is possible that no significant associations were found because there is no significant relationship between cognition and fatigue post-stroke. However, there are other possible explanations for why the studies did not reveal significant associations between fatigue and cognitive impairment after stroke. For instance, some of the participants had major comorbidities (such as diabetes mellitus, cardiac disease and hypertension), which could significantly affect the experience of fatigue.

Another consideration is that some studies assessed fatigue within a month of the acute phase (Radman et al., 2012; Schepers et al., 2006), whereas others assessed it within the chronic phase (Johansson & Rönnbäck, 2012; Naess et al., 2005; Naess & Nyland, 2013; Winkens, Van Heugten, Fasotti, Wade, et al., 2009). However, there is conflicting evidence with regards to time of fatigue onset. Some studies reported fatigue being related to the acute phase (Choi-Kwon et al., 2005; Christensen et al., 2008), while other studies have argued that fatigue is a long-term issue. For instance, Schepers et al., (2006) reported that fatigue tends to increase

over time, while van de Port, Kwakkel, Schepers, Heinemans, & Lindeman, (2007) found that fatigue peaks at approximately 12 months post-stroke. The results of the systematic review did not reveal any specific pattern. Fatigue was similar across studies and scores did not differ significantly according to time of assessment. The three highest scores according to FSS were spread out across the acute, middle and chronic phase of stroke. Lower scores were also found in the acute, middle and chronic phase. When comparing data between baseline and follow-up assessments within the same longitudinal studies (Hubacher et al., 2012; Radman et al., 2012; Schepers et al., 2006; van Eijsden et al., 2012; Winkens, Van Heugten, Fasotti, Wade, et al., 2009), a pattern emerges suggesting that fatigue tends to increase to some extent over time. Cognitive impairment tends to decrease over time (Danovska et al., 2012) and so any relationship between the two would be expected to be negative. Given that the time of onset and peak of fatigue is controversial, the fact that the above studies considered different time frames does not allow conclusive interpretations.

The papers had some more limitations. Most of them did not make it clear which type of correlation they used and therefore it is not possible to assess whether the statistical analyses followed were appropriate (parametric vs non-parametric). In addition, the majority of the studies had very small samples. One study did not provide correlation coefficient values (Radman et al., 2012) and another (van Eijsden et al., 2012) was considered of moderate quality because there was not sufficient information nor justification as to why they excluded individuals with limited mobility and the significance level was .2 which is higher than the conventionally used level of .05. Some studies did not report

some information. After establishing contact with authors of the two papers (Radman et al., 2012; van Eijsden et al., 2012), they could not provide the correlation coefficients.

This systematic review had limitations. It did not include studies that analysed their data with logistic regression. The inclusion criterion for the fatigue scales was that the scale had at least three response categories, which means that studies that used no/yes for the presence of fatigue were excluded. This means that the review may have missed studies with information on the presence of fatigue rather than severity and its association to cognitive impairment. However, only one study with such analysis was detected (Appelros, 2006) and the relationship between fatigue (yes/no) and cognition (MMSE) was not significant which is consistent with the results of the majority of the studies included. Another potential limitation is that more gerontological, medical and social sciences orientated databases such as AgeLine and Science Direct, would have identified more papers; However, it is likely that the databases searched identified the majority of studies on the topic because they provided results drawn from medical, psychological and nursing journals. Another imitation is that due to the nature of their search engines, some dissertation databases could not be searched in a systematic way identical to the one used in this review. The searching strategy included two thesis databases; but these would not include all dissertations (one is only for the UK and the other only for Europe) and therefore it is possible that other suitable studies were not included.

Furthermore, despite the exclusion of papers on people with SAH, one paper (Park et al., 2009) was included because it indicated there were only a few participants with the condition. The authors were contacted regarding the

percentage of the participants with SAH, but there was no response. The paper was included on the basis that sub-arachnoid haemorrhage is far less common than other stroke types and on the assumption that the proportion of people with SAH would be low. Two studies (Naess et al., 2005; Naess & Nyland, 2013) mentioned an age range between 15 and 49 years. After contacting the authors, only one participant was 17 years old at the baseline and 30 at the follow-up, and therefore these papers were included. Despite no language restriction, the use of English terms in the search strategies limited the results to papers that had an abstract and key words in English. Therefore, some papers in other languages may have been missed.

2.7 Conclusion

The findings of this review demonstrated that there was no evidence of a significant association between fatigue and global cognitive status after stroke. However, there was some evidence to suggest that attention, memory and speed of information processing may be significantly associated with fatigue. Future studies should incorporate the use of both domain-specific and global cognitive tests, and investigate the association with general fatigue and cognitive fatigue scales. Furthermore, future studies could also include both subjective ratings of cognition and objective cognitive tests and examine their relationship to both general and cognitive fatigue scales. In summary, more studies are needed with measures that are sensitive to cognitive impairment after stroke and with fatigue scales that do not address cognitive components of fatigue. This will enable a more accurate investigation of the relationship between fatigue and cognitive impairment after stroke.

Chapter 3: Investigation of the Relationship Between Fatigue and Cognition After Stroke In the Absence of Depression: A Longitudinal Cohort Study (Study 1)

3.1 Abstract

Background: Fatigue is very common after stroke. Previous research has suggested cognitive impairment may be related to fatigue. **Objective:** To examine the relationship between cognitive impairment and fatigue in first time stroke survivors without depression. **Design:** Longitudinal cohort study. **Settings:** Stroke wards in Nottingham University Hospitals, University Hospitals of Leicester, Salford Royal and University College London Hospitals. **Participants:** Stroke patients with no history of dementia, no previous stroke and without depression (≥7 on the Brief Assessment Schedule for Depression Cards), in the acute/sub-acute phase of stroke (recruited as a part of the Nottingham Fatigue After Stroke Study) were invited to join the study. **Measurements:** Participants were assessed on: Fatigue Severity Scale (fatigue), Dot Cancellation (sustained attention), Victoria Stroop Colour Test (selective attention) and Information Processing Test from the Adult Memory Information Processing Battery. **Results:** A total of 268 participants were assessed 4-6 weeks after stroke. The results indicated clinically significant fatigue levels in 42% of the participants and low frequency of impairment in attention and speed of information processing (range 5-9%). There was a small increase in fatigue at 6 month follow-up assessment. No significant associations were revealed between either baseline or follow-up fatigue and any of the cognitive tests. **Limitations:** Most participants had a lacunar stroke which resulted in low levels

of cognitive impairment; no follow-up data was collected regarding cognition. **Conclusion:** There was no evidence of an association between fatigue and impairments of attention and speed of information processing.

3.2 Introduction

The systematic review conducted prior to this study (Lagogianni, Thomas, & Lincoln, 2016), indicated that there is insufficient evidence regarding the relationship between fatigue and cognition after stroke. Differences in design, sample characteristics, methods and the definition of fatigue made it difficult to conclude whether fatigue is associated with cognitive impairment. Furthermore, the majority of studies examining this relationship included patients with comorbid depression which may conceal the relationship between fatigue and other factors. In addition, the review suggested that the cognitive domains most likely to be affected by fatigue were attention and speed of information processing. This indicated that cognitive impairment should be measured with domain specific standardized tests and not with screening measures designed to detect dementia such as the Mini Mental State Examination (Folstein et al., 1975). Domain specific cognitive tests are more likely to detect mild cognitive impairment related to fatigue. General fatigue scales are more likely to assess an overall experience of fatigue instead of focusing only on cognitive aspects of fatigue which may represent subjective cognitive complaints and not just fatigue (Lagogianni et al., 2016).

3.3 Objectives

The aims of this study were to examine: 1) the relationship between sustained attention, selective attention,

speed of information processing and fatigue in the acute phase of stroke in the absence of depression and 2) the relationship between sustained attention, selective attention, speed of information processing in the acute stroke phase and fatigue 6 months after stroke.

3.4 Ethical Approval and Funding

The Cognition and Fatigue After Stroke Study (Cog-FAST; funded by the Vice Chancellor's Scholarship for Research Excellence-European Union; Scholarship Reference Number: RFDX42DB2) is a subcomponent of a larger study conducted by the University of Nottingham, Nottingham Fatigue After Stroke Study (Not-FAST; funded by the Stroke Association; ref: TSA 2012/04) which was granted approval by the NRES Committee East Midlands-Northampton in June 2013 (REC Reference Number: 13/EM/0187; Protocol Number: 13037; IRAS Project ID: 124341), the Nottingham Clinical Research Centre (Research & Innovation, Reference: 13SR003; CSP:124341), the University Hospitals of Leicester (UHL CSP: 124341), Salford Royal (R&D reference: 2013/101st) and the University College London Hospitals (NRES Reference: 13/EM/0187) (see appendices).

3.5 Method

3.5.1 Design

A within subjects design was used with fatigue as the dependent variable (1 level; general fatigue) and measures of speed of information processing, selective attention and sustained attention as predictor variables. The cohort study was longitudinal and used quantitative methods (questionnaires); correlations were conducted to determine

the relationship between the dependent and the independent variables.

3.5.2 Settings and Recruitment

The study was multicentre and included four NHS Trust sites in England in order to recruit sufficient number of people for the Nottingham Fatigue after Stroke study (NotFAST; from which this study was derived). The NHS trusts included were: Nottingham University Hospitals NHS Trust; University Hospitals of Leicester NHS Trust; Salford Royal Hospitals NHS Trust; National Hospital for Neurology and Neurosurgery (University College London Hospital) NHS Trust. Potential participants were identified within 4 weeks of their admission to a hospital following a first stroke, by clinical staff and the Stroke Research Network nurses.

3.5.3 Participants and Procedure

Participants were included if they: were over 18 years old; had a stroke according to clinical staff on the hospital wards; had no history of previous stroke documented in their medical notes and gave consent. Exclusion criteria were that participants: did not speak the English language; had documented dementia in their medical history prior to their stroke, had aphasia or had depression as determined by screening measures described below. Participants were approached and given an information sheet and were introduced to the study and given information regarding the study process. Potential participants were given 24 hours to think about whether they wanted to join the study or not, and to discuss their concerns or questions with the ward staff or their family. They were then approached again and those who agreed to take part in the study were given a consent form to

sign. Medical or research staff completed a demographic sheet by either extracting details from the patients' medical notes or by asking them directly for descriptive reasons. Participants were informed that they would be contacted by a research assistant, a psychologist or a postgraduate student within 6 weeks of their stroke onset date. Two researchers, including the author, conducted the assessments in Nottingham (LH & CL) and Leicester (EB & CL) and one researcher conducted the assessments in Salford (HM) and one in London (EC). The author (CL) was also responsible for data input to databases, site coordination (Leicester and supported Nottingham), data storage, and data quality checks. The researchers arranged an appointment for a baseline assessment either at their residence or in the hospital. Those still in hospital were examined within ward settings.

For the baseline assessments, a researcher met with the participants and explained again the aim and the process of the study and asked them if they still agreed to participate. It was made clear that their data will be anonymised and treated with confidentiality. All participants were identified by their initials and a unique study code. They were informed that they could withdraw at any time without it affecting their medical care. Participants were assessed individually and in privacy. The duration of the study was 2 years (6 months per participant). At the end of the baseline assessment, participants were thanked for their contribution to the study and their willingness to participate. They were told that if they were interested in the findings of the study they could contact the research team for a summary. They were reminded that the study had a second stage and were asked to confirm that they would remain in the study and be contacted to complete stage 2, 6 months later.

3.5.4 Measurements

Baseline assessment included the following questionnaires and cognitive tests, in order to select participants, and was identical to NotFAST:

3.5.4.1 Sheffield Screening Test for Acquired Language Disorders (SSTALD; Syder, Body, Parker, & Boddy, 1993)

The SSTALD was designed as a screening instrument to detect language difficulties. It assesses both receptive and expressive language skills but not writing and reading (Lincoln, Kneebone, Macniven, & Morris, 2012). Inter-rater reliability has been reported to be good but specific values were not reported (Syder et al., 1993). It has been compared with the Frenchay Aphasia Screening Test (FAST; Enderby, Wood, & Wade, 1987) in conditions such as brain injury and stroke and while SSTALD's predictive value was similar to FAST's in detecting language difficulties it does not require further equipment and is not affected by visual neglect (Al-Khawaja, Wade, & Collin, 1996). The SSTALD yielded 100% specificity, 89% sensitivity and 90% accuracy in detecting aphasia after stroke (Al-Khawaja et al., 1996). Blake, McKinney, Treece, Lee, & Lincoln, (2002) validated the SSTALD in stroke patients to confirm sensitivity according to cut off scores, and recommended it for identifying language deficits post-stroke on the basis that it was sensitive and specific to detect those with language problems.

Receptive skills are assessed by asking the individual to provide verbal and non-verbal responses to items of increasing complexity. The patient was asked to point at several items in the room (single or combined), produce execute combined actions, understand the meaning of words

and a short narrative paragraph. Expressive skills were assessed by asking participants to produce synonyms of words, identify well-known places, describe a complex task (making a cup of tea), define words and justify certain actions. The SSTALD was scored by giving 1 point to each correct answer. The overall maximum score is 20 (maximum receptive skills score=9; maximum expressive skills score=11). Cut-off scores vary according to age (≤59 years old= 17; 60-69 years old=16; ≥70=15). Lower scores indicate higher impairment (Syder et al., 1993). Individuals with language disorders were expected to not be able to understand the context of the tests or follow instructions for the completion of the cognitive tests. Those who scored below cut-offs at the SSTALD according to the age groups provided above, were thanked for their time and they were told that at that moment they were not suitable for the study.

The remaining participants were given the following questionnaires to provide a description of the sample for this study and these measures were part of the main NotFAST study:

3.5.4.2 Brief Assessment Schedule for Depression Cards (BASDEC; (Adshead, Cody, & Pitt, 1992)

The BASDEC is a measure to detect depression in older individuals and is suitable for hospital ward settings because it is brief (Adshead et al., 1992). Adshead et al., (1992) reported that the psychometric properties of BASDEC are good with high sensitivity (71%) and specificity (88%) [positive predictive value: 74%; negative predictive value: 86%] compared to the Geriatric Depression Scale (GDS; Yesavage et al., 1982). In acute stroke, the BASDEC yielded an internal

consistency of α= .77 with test-retest reliability r= .66 (Healey, Kneebone, Carroll, & Anderson, 2008). Concurrent validity in relation to the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1997) ranged from r= .40 to .57 and criterion validity in relation to the SCID when considering major depression diagnosis was reported to be good. Sensitivity to screen for depression was 100% and specificity 95% in older stroke patients (Healey et al., 2008).

The current study used a questionnaire format of the BASDEC so that it was possible to post it to the participants for the follow-up assessment. The questionnaire comprises 19 items which require participants to respond according to their current emotional state. The scale has a "true/false" format and each "True" response scored 1 point-except items 4 and 8 ("I've given up hope"; "I've seriously considered suicide") which scored 2 points- and "False" responses scored 0. The questionnaire version does not have "I don't know" responses which is the case with the cards. The maximum score was 21 (higher scores indicate higher depression levels) and cut off score for indicating depression was $\geq$7. Administration time is estimated at approximately 4 minutes which makes it suitable for use in hospital ward settings (Adshead et al., 1992).

The BASDEC was chosen for its clarity, brevity and effectiveness in screening for depression in acute stroke patients. Participants completed BASDEC and the SSTALD in order to determine whether they met the study criteria. Those who scored high on the BASDEC ($\geq$7) were excluded and were briefly informed about where to seek extra help if needed. The principal investigator of the study was notified. The remaining participants were given the following questionnaires.

The NotFAST study examined various predictors of fatigue and used the following 4 questionnaires to measure independence of daily activities, functional mobility, and anxiety. These variables were not included in any inferential analysis for the current thesis but were merely incorporated in order to describe the sample and assist in future reviews and meta-analyses.

3.5.4.3 Rivermead Mobility Index (RMI; Collen, Wade, Robb, & Bradshaw, 1991)

The RMI is a measure of functional mobility initially developed for patients with stroke and brain injury. It comprises 14 self-reported items and one direct observation item (item 5: Observe standing for 10 seconds without any aid or support). Item 5 was not used in the current study since it would not be possible to complete in the postal follow up. The items are scored in a yes/no format with yes answers gaining 1 point and no answers gaining 0 points. The maximum score was 14 in the present study and minimum was 0. Higher scores indicate better mobility. The administration time is estimated to be 3-5 minutes (Collen et al., 1991).

The psychometric properties of the scale have been classified as very good with overall test-retest reliability r= .96 in people with chronic stroke (Chen et al., 2007; Green, Forster, & Young, 2001) and very high inter-rater reliability (r= .92) in people with acute stroke (Hsueh, Wang, Sheu, & Hsieh, 2003). In a study of first-stroke patients (Antonucci, Aprile, & Paolucci, 2002), a Rasch analysis confirmed the hierarchy of items and that item difficulty was stable over time which was also supported by Hsieh, Hsueh, & Mao, (2000). The scale was included to assess patients' mobility (Collen et al., 1991). It was chosen over others due to being self-report.

3.5.4.4 Nottingham Extended Activities of Daily Living Scale (NEADL; Nouri & Lincoln, 1987)

The NEADL is a measure of independence in instrumental activities of daily living of stroke patients. It consists of 22 items which assess independence across four domains: mobility (items 1-6), kitchen (items 7-11), domestic (items 12-16) and leisure (items 17-22). The scale is scored on 4 response categories which are coded as: "not at all" (0 points); "with help" (1 point); "on your own with difficulty" (2 points); "on your own" (3 points). It was designed to be dichotomous and to distinguish dependent from independent patients so the four possible answers provided are combined in a 0-1 format (das Nair, Moreton, & Lincoln, 2011). Therefore 0 point is given for "not at all" and "with help" responses whereas 1 point is given for each "on my own with difficulty" and "on my own". The maximum possible score is 22 with higher scores indicating greater independence.

Test-retest reliability was reported to be r= .60 (Green, Forster, & Young, 2001), and inter-rater reliability ranged from r= .82 to .99 (Schlote, Krüger, Topp, & Wallesch, 2004). The scale has high correlation with the Frenchay Activities Index (Schuling, De Haan, Limburg, & Groenier, 1993) (ρ=.80) (concurrent validity) (van de Weg, Kuik, & Lankhorst, 1999). It was included to measure patients' level of independence in instrumental activities of daily living before and after stroke and was chosen because it has good responsiveness (Wu et al., 2011) and low likelihood of floor and ceiling effects (Sarker, Rudd, Douiri, & Wolfe, 2012).

3.5.4.5 Barthel Index (BI; Wade & Collin, 1988)

The BI is a 10 item scale used to assess independence in

personal self-care activities of daily living (Duncan et al., 1997). The items assess independence in mobility (transfer, walking) and self-care (bathing, feeding, grooming, toilet use and continence) (Sulter, Steen, & De Keyser, 1999). There are several variations of the BI; in the current study, the version by Wade & Collin, (1988) was used. This version differs in terms of administration and interpretation. For instance, according to the guidelines recommended by Wade & Collin, (1988) the score should be based on what the individual *does* and not what s/he *can do*. It is also recommended that aids are allowed and do not affect scoring of independence; however, if people require supervision or verbal encouragement they are not considered to be independent (also cited in Fricke & Unsworth, 2010). This version uses a score which ranges from 0 to 20 with higher scores indicating higher independence (Wade & Collin, 1988).

The BI is among the most frequently used measures of disability in stroke (Cioncoloni et al., 2012; Hsueh, Lee, & Hsieh, 2001; Quinn, Langhorne, & Stott, 2011) and studies in acute stroke have shown very good psychometric properties. The internal consistency of the scale ranges from α= .68 to .94 when used on stroke samples (Duffy, Gajree, Langhorne, Stott, & Quinn, 2013; Hsueh, Lee, & Hsieh, 2001; Hsueh, Lin, Jeng, & Hsieh, 2002), good inter-rater reliability (kw= .93) (Duffy et al., 2013) and was strongly correlated with other measures of activities such as the Modified Rankin Scale (Wolfe, Taub, Woodrow, & Burney, 1991) (concurrent validity) (r= -.88) and the motor component of the Functional Independence Measure (FIM; Keith, Granger, Hamilton, & Sherwin, 1987) (r= .94) (Kwon, Hartzema, Duncan, & Min-Lai, 2004). It was chosen to facilitate comparison with previous research as it is the most commonly used measure of

activities of daily living and is recommended for stroke patients (Harrison, McArthur, & Quinn, 2013; Quinn et al., 2011).

*3.5.4.6 Beck Anxiety Invent*ory *(BAI; Beck & Steer, 1990)*

The BAI is a self-report inventory developed to measure the severity of clinical anxiety in adults and adolescents. It comprises 21 items which are rated on a 4-point Likert scale (0=not at all - 3=severely gaining equivalent points: "not at all" answer gains 0 points, "mildly" answers gain 1 point, "moderately" answers gain 2 points and "severely" answers gain 3 points) (Beck & Steer, 1990). The items were selected in order to eliminate symptom overlap with depression (Beck & Steer, 1990). BAI is split to two factors which evaluate cognitive and physiological symptoms of anxiety.

Internal consistency alphas range from .90-.94 and test-retest reliability from .62-.93 when used on psychiatric patients (Julian, 2011). The concurrent validity of the BAI is also reported to be r= .51 and r= .81 when compared to the Hamilton Anxiety Rating Scale (Hamilton, 1960) and the Symptom Checklist-90 (Derogatis, Lipman, & Covi, 1973) respectively (Beck & Steer, 1990). There is no optimal cut-off score for the BAI however Leyfer, Ruberg, & Woodruff-Borden, (2006) suggested that when using ≥20 as a cut-off score, sensitivity was 67% and specificity 93%. in relation to anxiety diagnosis using the Anxiety Disorders Interview Schedule (ADIS-IV) (Brown, DiNardo, & Barlow, 1994). Lincoln et al., (2012) suggested that the BAI is one of the few appropriate screening measures of anxiety for stroke patients and was therefore chosen for the current study.

In the current study, the BAI was used to assess symptoms of anxiety. Participants were asked to respond

according to how they had felt the past week. Items were summed and total scores range from 0-63 (0-7=minimal; 8-15=mild; 16-25=moderate; 26-63=severe) (Beck & Steer, 1990).

The main dependent variable was fatigue assessed on the Fatigue Severity Scale:

3.5.4.7 Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, (1989)

The scale comprises 9 items measuring fatigue severity and its impact on daily activities. Each item is responded to a 7-point Likert scale (1=strongly disagree - 7=strongly agree) (Lerdal & Kottorp, 2011). All responses are summed and divided by number of items (9). The score comes from calculating a mean score which is then divided by number of items. The maximum overall score is 7 with higher scores indicating higher levels of fatigue (Neuberger, 2003). Generally, there is no clearly defined cut-off score for the FSS, however, Valko, Bassetti, Bloch, Held, & Baumann, (2008) in line with previous research in multiple sclerosis (Armutlu et al., 2007; Kaynak et al., 2006), recommended the use of a cut-off score of ≥4 which detected fatigue in 49% of stroke patients. Therefore, a cut-off score of 4 was used in this study (≥4= fatigued; ≤3=not fatigued). The FSS has very good psychometric properties and has been extensively used in stroke research (Choi-Kwon et al., 2005; Ingles et al., 1999; Kathleen Michael & Macko, 2007; Valko et al., 2008). More information regarding the background and psychometric properties of the FSS can be found in chapter 1 in the *Unidimensional Fatigue Scales* section.

Participants were then presented with the cognitive tests as measures of the independent variables. The tests included in the current study were chosen on the basis that they were measures of speed of information processing and attention, which are found to be related to fatigue in previous research. The cognitive assessment included the following tests:

3.5.4.8 Dot Cancellation from the Stroke Drivers Screening Assessment (DC, SDSA; Nouri & Lincoln, 1994)

Dot cancellation of the Stroke Drivers Screening Assessment (SDSA; Nouri & Lincoln, 1994) is based on the Buordon-Wiersma test (Grewel, 1953) that requires participants to cross out groups of four dots. It consists of an A4 master sheet with groups of dots arranged in 25 rows with 25 dot groups in each row. Some groups comprise three dots, some four and some five. Participants are asked to work down the page and cross out all groups with four dots. The task is timed and the time limit is 15 minutes. Participants are given a chance to practice in the first row and feedback is given to them. Beyond this point no further assistance is provided. The tests gives three final scores: time taken to complete the task (range 0-900 seconds-if not completed then the 15 minutes limit is recorded); the number of groups of 4 dots missed (range 0-208) and the number of omissions, that is groups of 3 and/or 5 dots wrongly identified (range 0-412) (Nouri & Lincoln, 1994).

The test assesses sustained attention and concentration and does not require memory capacity (Nouri & Lincoln, 1994; Radford, Lincoln, & Murray-Leslie, 2004). Visual inattention and sustained attention are measured by the number of items missed and by the number of incorrect detections. Lincoln &

Fanthome, (1994) reported good test-retest reliability for the dot cancellation task (time taken r= .63; errors r= .75; false positives r= .38). The Dot Cancellation is associated with the Stroop (Golden & Freshwater, 2002) and the Trail Making Test (TMT; Army Individual Test Battery, 1944) scores (r= .37 and .36 respectively) (Radford & Lincoln, 2004) (concurrent validity) which suggests that they measure executive abilities and attention. There are no sensitivity and specificity values for the subtest alone and has only been evaluated as part of the whole driving screening test for stroke survivors (Nouri & Lincoln, 1994). The test is long and is expected to induce fatigue. In addition, the test form was divided into two sections: A and B consisting 12 rows each (the first row is for practice purposes and was not considered). The score of errors in each section was recorded. Sections A and B were compared using t-tests to examine whether there is a significant difference in the scores. The cut-off scores used to classify the participants as cognitively impaired/non-impaired were based on 2 standard deviations above the cut-off scores for healthy participants provided in the manual.

*3.5.4.9 Information Processing From the Adult Memory Information Processing Batte*ry *(AMIPB, Coughlan & Hollows, 1985)*

The AMIPB is a set of tests that measure several cognitive functions such as: memory, learning and information processing. It consists of 6 verbal and non-verbal subtests (immediate and delayed story recall, word-list learning, design learning, copying a figure and information processing which has two subtasks: information processing and motor speed cancellation). The information processing subtests (Form 1) were used to assess speed of information processing.

The information processing is one of the subtests (task A); it comprises 105 rows of 5 random numbers between 10 and 99 in a set of 21 blocks spread over an A4 sheet. The participant is asked to cross out the 2nd highest number in each row which consists of 5 digits each time. They are given 4 minutes to cross as many as possible. The total score is the total number of correct answers (Coughlan & Hollows, 1985). The motor speed cancellation task consists of 18 sets of 10 digits number elevens (11). Participants are given 20 seconds to cross out as many as possible. The motor speed test is used to calculate an adjusted score between speed taken to cross out the elevens and the number of items attempted in task A. This allows an estimate whether poor performance on task A is due to cognitive or motor slowness. The adjusted score outcome come from the following equation: Task A Adjusted Score = (12 * Task A total *Task A speed)/ (12 * Task a speed –Task A total) [number 12 is: 4 (minutes for task A) x 60 (seconds in each minute)= 240; 240/20 (seconds for task B)= 12]. The higher the score, the better the performance is.

Test-retest reliability of the information processing tasks have been reported to be r= .89 (Weldon, 1998). The intra-rater reliability in a sample with individuals with multiple sclerosis was r= .97 (Vlaar & Wade, 2003). There are no studies that have assessed the validity of the test but Vlaar & Wade (2003) indicated validity based on correlations r= .82 with the Short Orientation Memory Concentration Test (SOMC; Wade & Vergis, 1999) which measures working memory and attention (in a sample of people with multiple sclerosis). Speed of information processing is the only subtest of the battery that is not affected by demographics and (Lezak, 2004). These two tests were chosen because they measure speed of information processing and provide an adjusted score

to correct for motor impairment. Cut-off scores vary according to age groups and each participant included in the study was assessed individually according to the cut-off score for his/her age group provided in the manual. The test is often preferred for use in stroke populations as other tests require intact motor capacity which is often affected by stroke survivors (Skilbec, 1992).

3.5.4.10 Victoria Stroop Test (VST; Regard, 1981)

The VST is a test of executive dysfunction measuring selective attention, concentration and interference susceptibility (Gwizdka, 2010). It has been used to measure mental fatigue and cognitive control, as well as maintaining a goal and working memory (Rauch & Schmitt, 2008). Several versions of the Stroop are available (Golden, Victoria, Trenerry and D-KEFS). The Victoria version was used. The test involves names of colours printed in coloured ink. Trial I *(Dots)* requires the individual to name the colour of the dots; Trial II *(Words)* requires the individual to name the colours the words are printed in; Trial III *(Colour Words)* again requires participants to name the colour the words are printed in but this time the words also state a colour name. The words are printed in a different colour than the one indicated by the actual word. There are 24 items in each trial. Participants were initially given a separate practice row in order to check whether participant clearly understood the task. Only trials II and III were used in the current study.

The test is timed but there is no time limit although it is expected to take longer to complete trial I than trial II. The interference score is derived from time trail II subtracted from time trail I (Stroop time= stroop time II-stroop time I), (Stuss, Floden, Alexander, Levine, & Katz, 2001). Errors made

and time taken to complete the subtests were recorded. Low interference scores indicate a lower interference effect (Adleman et al., 2002). Cut-off scores were based on 2 standard deviations above the cut-off scores according to age group, cited in Strauss et al., (2006). For more details regarding concurrent and predictive (sensitivity and specificity) validity of the Stroop, please refer to Chapter 1, in the *Domain Specific Tests of Attention and Speed of Information Processing* section.

The Stroop is recommended for use in stroke research and practice by the Neurological Disorders and Stroke department of the National Institute of Health (NIH) (NINDS Common Data Elements, 2014) as a measure of cognitive flexibility and processing speed and attention (May & Hasher, 1998). The Victoria version was chosen because it is short which makes it appropriate for use with stroke patients. It was included in the study to measure attention and concentration.

The following assessments were also administered as part of the Not-FAST study: the Sleep Hygiene Index (Mastin, Bryson, & Corwyn, 2006) to assess sleeping patterns, the Impact of Events Scale (Weiss & Marmar, 1997) to measure the subjective significance of a traumatic event and the 6-Meter Timed Walk Test to measure walking speed. Pre-stroke versions of the Rivermead Mobility Index, the Nottingham Extended Activities of Daily Living Scale and the Fatigue Severity Scale with items in past tense were also administered in order to estimate the participants' pre-morbid functional mobility, independence and level of fatigue prior to their stroke respectively. Data obtained by these tests was not used in Cog-FAST.

The follow-up occurred 6 months after participants' stroke date. A mortality check was conducted by the researchers prior to the follow-up using participants' NHS number and calling their GP. If they were alive, the questionnaires relating to post-stroke functioning used at baseline were posted to the participants' address with a prepaid envelope. Participants were asked to complete the questionnaires themselves according to their current condition and send them back in a pre-paid envelope. Follow-up assessments included the following:

3.5.5 Follow-Up Assessments (6 months after stroke):

- Brief Assessment Schedule for Depression Cards
- Beck Anxiety Inventory
- Fatigue Severity Scale
- Barthel Index
- Rivermead Mobility Index (post-stroke)
- Nottingham Extended Activities of Daily Living Scale (post-stroke)

Participants who did not return follow-up questionnaires within the time limit were given a courtesy call to remind them or to check if they have received them in the first place. The researchers also offered the participants a home visit to help them fill the questionnaires if they needed to. No further action was taken after contact was made and it was confirmed that participants had received the questionnaires.

Cognitive tests were not conducted at follow-up because the funding did not cover for further home visits therefore the follow-up assessments were designed to be posted to the participants. Therefore it was not feasible to conduct cognitive tests at follow-up. The assessment data was kept separately

from participants' consent forms in a safe locked filing cabinet at each recruiting centre. They were all stored at the University of Nottingham.

3.5.6 Sample Size Estimation

According to Med Calc software, in order to achieve 80% power at a 0.05 level of significance, 13 participants are required per correlation (DeLisa, Gans, & Walsh, 2005; Howell, 2009). The study involved 10 independent variables, and therefore 130 participants were needed. Allowing 10% drop-out (which is based on previous studies conducted by the research team), a minimum of 165 participants were required. The effect size that we were interested in detecting was r= 0.7 in order to detect meaningful effect and not small (potentially attributable to chance) effects. SPSS version 22 for Windows was used to analyse data.

3.5.7 Statistical Methods

SPSS version 22 for Windows was used to analyse data. Data was treated and analysed by the author independently from NotFAST. Missing values were excluded pairwise to keep most data (Allison, 2001). The percentages of frequency for each variable (including demographic and medical characteristics) were calculated. Skewness and kurtosis were examined to determine the type of statistical analysis to be used. Pearson's correlations were conducted to determine the relationships between the normally distributed variables and Spearman's correlations were used for skewed variables. A paired t-test and a Wilcoxon's z test were computed for mean comparisons between groups for normally distributed and skewed data respectively. If the case of statistically significant

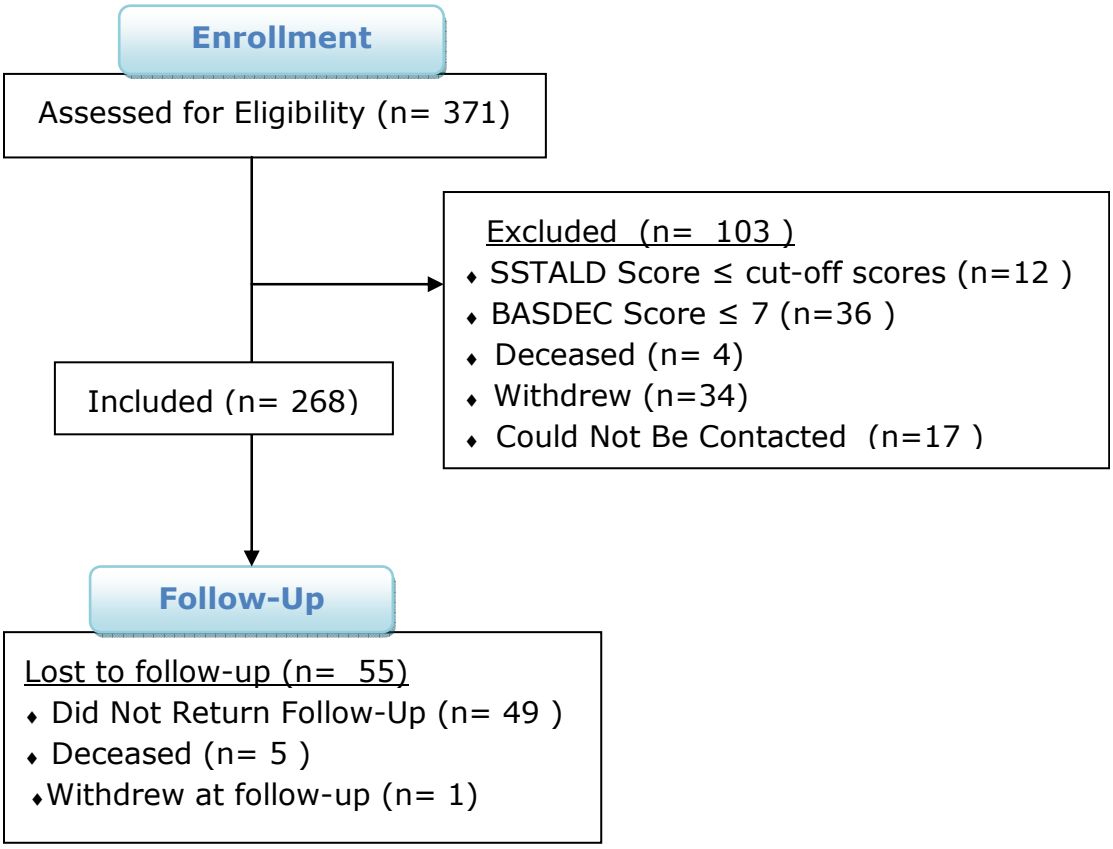
correlations, regression analysis would have been conducted for these variables.

3.6 Results

3.6.1 Recruitment

The Consort (2010) diagram 2 presents the study flow. Three hundred and seventy one stroke participants were invited to take part in the NotFAST study and were assessed for eligibility for the study criteria. Of these, one hundred and three were excluded for various reasons (see diagram 2). Two hundred and sixty-eight participants were recruited. Of the 268, 213 (79%) completed the follow-up assessments.

Diagram 2: Consort Study Flow Diagram



3.6.2 Demographic Characteristics

Tables 9, 10 and 11 show the location of recruitment and assessment, demographic characteristics and education and occupational characteristics of participants. There were 268 participants with an age range 24-94 years (mean: 67.84; SD: 13.56). Mean time since stroke onset was 23.61 days (SD: 13.15, range: 1-61).

Table 9. Location of Recruitment and Assessment

Location		Number	Percentage
Recruitment Site	Nottingham	96	36%
	Leicester	56	21%
	Salford	41	15%
	London	75	28%
Baseline Assessment	Home	164	61%
	Hospital Ward	79	30%
	Clinic/Other	25	9%

Most participants were recruited from Nottingham and were assessed at home.

Table 10. Demographic Characteristics at Baseline

Variable		Number	Percentage
Sex	Men	168	63%
	Women	100	37%
Ethnicity	White British	240	90%
	Mixed (Egyptian/English)	1	0.5%
	Asian	9	3%
	Black/African	13	5%
	Other	4	1%
	Missing	1	0.5%
Marital Status	Single/Widowed/Divorced	101	37%
	With Partner/Spouse	167	63%
Living Arrangements	Alone	85	32%
	With Other	183	68%

There was a relatively high proportion of men. The majority were white British, had a partner and were living with that person.

Table 11. Education and Occupational Characteristics at Baseline

Variable		Number	Percentage
Education	No Qualifications	59	22%
	GCSE Level	78	29%
	A Level	39	14%
	Vocational/Apprenticeship	30	11%
	Professional Qualifications	14	5%
	Higher Degree	34	13%
	Missing	14	6%
Employment Status	Retired	166	62%
	Working	90	33%
	Unemployed	11	4%
	Missing	1	1%
Current or Last Occupation	Managers	40	15%
	Professionals	62	23%
	Technicians & Associate Professionals	19	7%
	Clerical Support Workers	23	9%
	Service & Sales Workers	40	15%
	Skilled Agricultural, Forestry and Fishery Workers	2	1%
	Craft & Related Trades Workers	22	8%
	Plant & Machine Operators and Assemblers	19	7%
	Elementary Occupations	22	8%
	Armed Forces Occupations	4	2%
	Housewives/Never Worked	9	3%
	Missing	6	2%

Over half the participants were retired from work.

The medical characteristics are summarised in table 12.

Table 12. Medical Characteristics at Baseline

Variable		n	Percentage
Hemisphere Affected	Right	141	52%
	Left	113	42%
	Both	10	4%
	Missing	4	2%
Stroke Type	Ischaemic	243	90%
	Haemorrhagic	24	9%
	Missing	1	1%
Stroke Subtype	Total Anterior Circulation	14	5%
	Partial Anterior Circulation	67	25%
	Lacunar	87	32%
	Posterior Circulation	47	18%
	Missing	53	20%
Comorbidities	Cancer	14	5%
	Heart Disease	25	9%
	Respiratory	33	12%
	Diabetes	41	15%
	Transient Ischaemic Attack	25	9%
	Atrial Fibrillation	53	20%
	Heart Failure	6	2%
	Peripheral Vascular Disease	6	2%
	Anaemia	10	4%
	Insomnia	15	6%

The majority of participants had suffered unilateral ischaemic stroke and either partial anterior circulation or lacunar strokes.

The distribution of baseline assessment scores are summarised in tables 13 and 14; it was examined in order to determine whether data were normally distributed in order to determine the most appropriate method of statistical analysis.

Table 13. Distribution of Scores on Baseline Questionnaires

Measure	n	Percentiles				Mean	S.D.	Skewness	Kurtosis
		25th (low)	50th (Median)	75th (upper)	IQR				
Sheffield Screening Test for Acquired Language Disorders*	268	18.00	19.00	20.00	2	18.95	1.06	-0.98	0.69
Brief Assessment Schedule for Depression Cards*	268	1.00	2.00	4.00	3	2.36	1.81	0.39	-0.83
Rivermead Mobility Index	268	8.00	13.00	13.00	5	10.40	4.17	-1.09	-0.17
Nottingham Extended Activities of Daily Living*	268	8.00	17.00	21.00	13	14.55	7.04	-0.65	-1.11
Fatigue Severity Scale*	268	2.00	3.11	5.11	3.1	3.52	1.84	0.26	-1.15
Barthel Index	267	16.00	20.00	20.00	4	17.24	4.29	-1.68	1.94
Beck Anxiety Inventory	264	2.00	6.00	10.00	8	7.20	6.89	1.41	2.02

*Data Normally Distributed

**Note: Some of the participants refused to complete some of the test

Table 14. Distribution of Scores for Baseline Cognitive Assessments

Cognitive Assessments	n	Percentiles				Mean	S.D.	Skewness	Kurtosis
		25th (low)	50th (Median)	75th (upper)	IQR				
DC Time*	244	384.00	485.00	628.25	244	511.50	183.12	0.32	-0.20
DC Total Errors	244	7.00	15.00	31.75	25	30.64	39.22	1.89	2.58
DC False Positives	244	0.00	0.00	0.00	0	0.65	3.70	10.35	117.03
DC Section A Errors	244	3.00	6.00	14.00	11	11.59	14.15	2.16	4.78
DC Section B Errors	244	3.00	8.00	18.00	15	19.12	27.81	2.02	2.98
DC Difference Score	244	-1.00	1.00	5.75	7	7.54	20.33	2.75	7.84
AMIPB Items Attempted*	253	34.00	45.00	54.00	20	44.47	15.19	0.12	0.09
AMIPB Errors	253	1.00	2.00	3.00	2	3.34	7.84	6.21	42.62
AMIPB motor speed*	253	30.00	39.00	45.00	15	38.04	11.44	-0.04	-0.22
AMIPB % of Error	253	1.65	3.45	7.52	5.87	8.27	16.55	4.15	18.19
AMIPB Adjusted Score*	253	37.48	50.18	61.48	24.00	49.95	18.04	0.22	0.11
SVT A Time	252	20.06	25.00	34.75	15	30.67	26.27	7.88	82.85
SVT A Errors	252	0.00	0.00	0.00	0	0.35	1.22	6.07	50.22
SVT B Time	252	32.6	42.86	60.00	27	53.13	40.93	4.63	31.34
SVT B Errors	252	0.00	1.00	3.00	3	2.07	3.11	3.18	14.58
SVT Interference	252	8.77	17.00	27.00	18	22.46	26.94	3.01	21.76

*Data Normally Distributed

**Note: Some of the participants refused to complete some of the test

Skewness and kurtosis were examined and it was observed that participants' scores on most tests were skewed (>1; Bulmer, 1979; Miles & Shevlin, 2001). Therefore non-parametric statistics were used for these tests.

Table 15 summarises the percentage of impairment on each variable according to the cut-off scores of each measure.

Table 15: Frequency of Impairment in Each Domain at Baseline

Domain	**Measure**	**Number Above Cut-Off Scores (Percentage)**
Fatigue	Fatigue Severity Scale	113 (42%)
Anxiety	Beck Anxiety Inventory	minimal: 161 (60%); mild: 72 (27%); moderate: 24 (9%); severe :7 (2%); not completed test: 5 (2%)
Speed of Information Processing	Adult Memory Information Processing Battery (Adjusted Score)	24 (9%)
Sustained Attention & Concentration	Dot Cancellation (Time)	23 (9%)
Selective Attention & Concentration	Stroop Victoria Test (Interference)	14 (5%)

The proportion of participants with impairment of attention and concentration was low. Less than half of the participants were identified as fatigued and the majority had minimal anxiety.

3.6.3 Inferential Statistics

Table 16 summarises the correlations coefficients that were conducted to determine the relationship between fatigue as assessed on the FSS and the three cognitive tests.

Table 16: Correlations Between Post-Stroke Fatigue (FSS) and the Cognitive Tests

Correlation with Fatigue Severity Scale	**n**	**Correlation Coefficient**	**P Value**
Dot Cancellation Time Taken	244	-0.05[r]	0.39
Dot Cancellation Total Errors	244	-0.02[rs]	0.66
Dot Cancellation AB Difference Score	244	-0.02[rs]	0.69
Adult Memory Information Processing Battery-Adjusted Score	253	0.05[r]	0.38
Stroop Victoria Test Interference	252	-0.00[rs]	0.95

*r_s= Spearman; r=Pearson

There were no significant correlations ($p>0.05$) between the level of fatigue and cognitive abilities with very small correlation size. As no significant relationships were found, regression analysis was not conducted.

The dot cancellation test was divided into two sections in order to examine whether participants made more errors in the second section of the test.

Table 17 summarises the z values of the Wilcoxon's test which was performed to examine the difference between the means of the two sections (A and B):

Table 17: Difference Between the Mean Scores of Section A and Section B of the Dot Cancellation

	n	Mean	S.D.	Min.	Max.	Z	P value
Dot Cancellation Section A	244	11.59	14.15	0	81	-4.89	≤.001
Dot Cancellation Section B	244	19.12	27.81	0	122		

The results revealed that participants made significantly more errors in the second half of the test [Wilcoxon Z (244) = -4.89, p = ≤.001].

3.6.4 Follow-Up Assessments

Tables 18 and 19 summarise the demographic, education and occupational characteristics of the participants who did not complete follow-up assessments alongside those who did return the follow-up assessments. Two hundred and sixty-three follow-booklets were posted (5 participants were deceased and were not sent questionnaires). Fifty-five participants did not complete follow-up assessments (49 did not return the assessments; 5 were deceased; 1 withdrew

follow-up participation). A total of 213 follow-up assessments were returned (79.47% response rate; see Consort diagram above) and participants' mean age at follow-up was 68.87 (SD: 12.39, range: 27-93). Mean time since stroke onset that the follow-up assessments were completed was 197 days (SD: 31.64, Range: 92-430); twenty seven (13%) of the participants, who returned the follow-up, had had a recurrent stroke.

Table 18: Demographic Characteristics of Participants who did and Did Not Complete Follow-up Assessments

Variable		Did Not Return Follow-Up (55)		Did Return Follow-Up (213)	
		Number	Percentage	Number	Percentage
Sex	Men	35	64%	133	62%
	Women	20	36%	80	38%
Ethnicity	White British	46	84%	194	91%
	Mixed (Egyptian/English)	1	2%	0	0%
	Asian	3	5%	6	3%
	Black/African	3	5%	10	4%
	Other	2	4%	2	1%
	Missing	0	0%	1	1%
Marital Status	Single/Widowed/Divorced	23	42%	78	37%
	With Partner/Spouse	32	58%	135	63%
Living Arrangements	Alone	21	38%	64	30%
	With Other	34	62%	149	70%

The majority of the participants in both groups were white British males and with partner.

Table 19: Education and Occupational Characteristics of Participants who Did and Did Not Complete Follow-up Assessments

Variable		Did Not Return Follow-Up (55)		Did Return Follow-Up (213)	
		Number	Percentage	Number	Percentage
Education	No Qualifications	15	27%	44	21%
	GCSE Level	13	23%	65	31%
	A Level	9	16%	30	14%
	Vocational/Apprenticeship	1	2%	29	14%
	Professional Qualifications	2	4%	12	5%
	Higher Degree	14	26%	20	9%
	Missing	1	2%	13	6%
Employment Status	Retired	29	53%	137	64%
	Working	22	40%	68	32%
	Unemployed	4	7%	7	3%
	Missing	0	0%	1	1%
Current or Last Occupation	Managers	7	13%	33	15%
	Professionals	12	22%	50	24%
	Technicians & Associate Professionals	4	7%	15	7%
	Clerical Support Workers	3	5%	20	9%
	Service & Sales Workers	9	16%	31	15%
	Skilled Agricultural, Forestry and Fishery Workers	1	2%	1	1%
	Craft & Related Trades Workers	3	5%	19	9%
	Plant & Machine Operators and Assemblers	5	9%	14	6%
	Elementary Occupations	5	9%	17	8%
	Armed Forces Occupations	2	4%	2	1%
	Housewives/Never Worked	1	2%	8	4%
	Missing	3	6%	3	1%

The majority of the participants in both groups had no qualifications and were retired.

Table 20 summarises the medical characteristics of the 55 participants who did not complete follow-up assessments

alongside those 213 who did return the follow-up assessments:

Table 20. Medical Characteristics of the Participants Who Did and Did Not Complete Follow-Up Assessments

Variable		Did Not Return Follow-Up (55)		Did Return Follow-Up (213)	
		Number	Percentage	Number	Percentage
Hemisphere Affected	Right	28	51%	113	53%
	Left	25	45%	88	41%
	Both	0	0%	10	5%
	Missing	2	4%	2	1%
Stroke Type	Ischaemic	52	95%	191	89%
	Haemorrhagic	3	5%	21	10%
	Missing	0	0%	1	1%
Stroke Subtype	Total Anterior Circulation	3	6%	11	5%
	Partial Anterior Circulation	15	27%	52	24%
	Lacunar	20	36%	67	32%
	Posterior Circulation	8	15%	39	18%
	Missing	9	16%	44	21%
Comorbidities	Cancer	3	6%	11	5%
	Heart Disease	4	7%	21	10%
	Respiratory	8	15%	25	12%
	Diabetes	9	16%	32	15%
	Transient Ischaemic Attack	5	9%	20	9%
	Atrial Fibrillation	15	27%	38	18%
	Heart Failure	2	4%	4	2%
	Peripheral Vascular Disease	1	2%	5	2%
	Anaemia	1	2%	9	4%
	Insomnia	6	11%	9	4%

The majority of the participants had right, ischaemic lacunar strokes.

Table 21 summarises the frequency of scores above the cut-off points in each component at baseline for those participants who did not complete follow-up assessments:

Table 21: Frequency of Impairment in Each Variable at Baseline of Participants without Follow-Up Data

Domain	**Measure**	**Number Above Cut-Off Scores (percentage)**
Fatigue	Fatigue Severity Scale	28 (51%)
Anxiety	Beck Anxiety Inventory	minimal: 34 (62%); mild: 13 (24%); moderate: 5 (9%); severe: 3 (5%)
Speed of Information Processing	Adult Memory Information Processing Battery (Adjusted Score)	5 (10%)
Sustained Attention & Concentration	Dot Cancellation (Time)	6 (11%)
Selective Attention & Concentration	Stroop Victoria Test (Interference)	3 (6%)

Table 22 summarises the frequencies of impairment in each variable at follow-up.

Table 22: Frequency of Impairment in Each Domain at Follow-Up

Domain	Measure	Number Above Cut-Off Scores (percentage)
Fatigue	Fatigue Severity Scale	108 (51%)
Anxiety	Beck Anxiety Inventory	minimal: 132 (62%); mild: 44 (21%); moderate: 17 (8%); severe :9 (4%); not completed test: 11(5%)
Depression	Brief Assessment Schedule for Depression Cards	23 (11 %)

Almost half of the participants who returned follow-up assessments were identified as fatigued. Few participants had moderate or severe anxiety and few had depression.

Table 23 summarises descriptive statistics of the follow-up assessments:

Tabe 23: Descriptive Statistics for Follow-Up Assessments

Variable	n	Percentiles				Mean	SD	Skewness	Kurtosis
		25th (low)	50th (Median)	75th (upper)	IQR				
Fatigue (Fatigue Severity Scale)*	213	2.39	4.00	5.17	3	3.81	1.73	-0.03	-1.01
Depression (Brief Assessment Schedule for Depression Cards)	208	0.00	1.00	4.00	4	2.54	3.28	1.82	3.20
Anxiety (Beck Anxiety Inventory)	204	1.00	4.00	10.00	9	6.95	8.07	1.93	4.22
Independence in Personal Self-Care Activities (Barthel Index)	211	18.00	20.00	20.00	2	17.97	3.50	-2.37	5.88
Independence in Instrumental Activities of Daily Living (Nottingham Extended Activities of Daily Living)	213	16.00	20.00	22.00	6	17.80	5.27	-1.44	1.20
Functional Mobility (Rivermead Mobility Index)	213	10.00	13.00	14.00	4	11.62	3.29	-1.55	1.73

*Data Normally Distributed

Skewness and kurtosis were examined and it was observed that participants' scores on most dimensions were significantly skewed (>1; Bulmer, 1979; Miles & Shevlin, 2001). Therefore non-parametric statistics were used for these tests.

Table 24 shows the results of the paired t-test that was conducted for the variables with normal distribution in order to compare the baseline and follow-up assessments for participants who completed the follow-up assessments.

Table 24: Comparison of Baseline and Follow-up Assessments (Normally Distributed Data)

Measure	Assessment	Number	Mean	S.D.	95% Confidence Interval		t-Value	p-Value
					Lower	Upper		
Fatigue Severity Scale	Baseline	213	3.43	1.79	-0.62	-0.12	-2.96	.03
	Follow-Up	213	3.81	1.73				

The tests showed statistically significant differences between baseline and follow-up fatigue scores. More specifically, there was an increase of fatigue (Fatigue Severity Scale) [t (213) = -2.96; p<.05].

Table 25 shows the results of the Wilcoxon z-test which was conducted for variables with skewed distributions, or those with normal distribution at baseline and skewed distribution at follow-up.

Table 25: Comparison of Baseline and Follow-up Assessments (Skewed Data)

Measure	Assessment	Number	Mean	S.D.	Min.	Max.	Z-Value	p-Value
Beck Anxiety Inventory	Baseline	209	7.06	6.72	0	34	-0.85	.03
	Follow-Up	204	6.95	8.07	0	40		
Rivermead Mobility	Baseline	213	10.52	4.09	0	14	-4.40	≤.001
	Follow-Up	213	11.62	3.29	0	14		
Barthel Index	Baseline	212	17.42	17.42	1	20	-2.33	.02
	Follow-Up	211	17.97	17.97	2	20		
Brief Assessment for Depression Cards	Baseline	213	2.28	1.82	0	6	-0.45	0.64
	Follow-Up	208	2.54	3.28	0	16		
Nottingham Extended Activities of Daily Living	Baseline	213	14.62	6.90	0	22	-7.27	≤.001
	Follow-Up	213	17.80	5.27	1	22		

The tests showed statistically significant differences between baseline and follow-up assessments in all the variables measured except for depression (Brief Assessment Schedule for Depression Cards) which indicated some increase in depression but not statistically significant. More specifically there was a statistically significant increase in functional mobility (Rivermead Mobility) [Wilcoxon Z (213)= -4.40, p=0.001], in independence in personal self-care activities of daily living (Barthel Index) [Wilcoxon Z (211)= -

2.33, p=0.020] and in independence in instrumental activities of daily living (Nottingham Extended Activities of Daily Living) [Wilcoxon Z (213)= -7.27, p≤.001] over time whereas there was a decrease in anxiety (Beck Anxiety Inventory) [Wilcoxon Z (204)= -0.85, p=0.039].

Table 26 summarises the correlation coefficients that were revealed after performing Pearson's or Spearman's correlations (depending in the distribution of the variables):

Table 26: Correlation Values Between Fatigue at Follow-Up and Cognitive Assessments at Baseline

Correlation with Fatigue Severity Scale	**Number**	**Correlation Coefficient**	**P Value**
Dot Cancellation Time Taken	197	0.06^{r}	0.36
Dot Cancellation Total Errors	197	0.11^{rs}	0.11
Dot Cancellation AB Difference	197	0.12^{rs}	0.08
Adult Memory Information Processing Battery-Adjusted Score	202	-0.9^{r}	0.17
Stroop Victoria Test Interference	199	-0.01^{rs}	0.80

*r_s= Spearman; r=Pearson

Fatigue at follow-up was not significantly associated (p>0.05) with cognitive scores at baseline.

As no significant relationships were found, regression analysis was not conducted.

3.7 Discussion

The results of the study revealed low frequency of impairment in attention and concentration and medium fatigue frequency and no significant relationship between fatigue and cognitive impairment. In particular, of the 10 correlations calculated (5 between baseline fatigue and cognitive tests and 5 between follow-up fatigue and baseline cognitive tests) none was significant with very small correlation size. Fatigue as measured by the Fatigue Severity Scale and cognitive components such as sustained attention, selective attention, concentration and speed of information processing were not significantly associated in the sample examined. There was a significant increase of fatigue over time.

The finding that there were no significant associations between fatigue and cognition may be attributed to several factors. To begin with, the sample had very low frequency of impairment in attention and speed of information processing as indicated by the tests used. This may be because of the relatively high proportion of people with lacunar strokes (small infarcts) which tend to cause less damage because they affect small areas of brain tissue (Wardlaw, 2005). There is not sufficient evidence from other studies to compare though as most do not specify stroke subtype. And it is difficult to tell whether studies that report higher attention and speed of information processing impairment included less people with lacunar strokes. The low levels of cognitive impairment were probably affected by the recruitment process. Research nurses who assisted with identifying potential participants recruited from the acute stroke wards and not from the rehabilitation wards where it is more likely to find stroke survivors with more severe strokes.

Those who are more severely affected by their stroke and are in the acute wards are usually not in a stable enough condition to give consent or carry out cognitive assessments. If more people had been identified on rehabilitation wards then the proportion with impairments of attention and speed of information processing may have been higher. In addition, some studies have reported a relationship between depression and cognitive impairment (Ruchinskas & Curyto, 2003; Kalaria & Ballard, 2001; Talelli et al., 2004). Given the fact that people with high depression scores were excluded from the current study, this may be another explanation for the low cognitive impairment scores.

Another factor that may account for low frequency of impairment is the time of assessment; participants were recruited while still in hospital but most of them were assessed when discharged and at home. The mean time after stroke at that the assessment took place was 23.61 days with a range of 1-61 meaning that some participants were assessed up to two months post stroke. Some mild cognitive problems that appear after stroke spontaneously recover soon after the onset (Danovska et al., 2012) and perhaps some of these participants had recovered from their cognitive difficulties by the time of the assessment. Cumming et al., (2013) suggested in their systematic review that attention and speed of information processing are more likely to be evident in the chronic phase after stroke (1 and 5 years post-stroke respectively) as opposed to the acute phase which is more often associated with executive dysfunction. In the current study, participants were assessed in the acute phase of stroke and perhaps their speed of information processing impairment was too mild to be detected. Speed of information processing is a complex and multifaceted

cognitive component that incorporates overlapping executive components, such as attention and memory (Demaree, Frazier, & Johnson, 2008). Speed of information processing can either impact on other components (for instance cause impaired working memory) or may be a by-product of impaired executive functions as several studies only measure processing speed indirectly from other measures (Gerritsen, Berg, Deelman, Visser-Keizer, & de Jong, 2010). However speed of information processing may be a distinct component which is also associated with posterior regions (Malia, Raymond, Bewick, & Bennett, 1998) and white matter in the parietal and temporal cortices (Turken et al., 2008). Therefore, it is possible that some of the participants had only mild cognitive decline which was not detected by the tests at the time of the assessment. It is very likely that the findings of the study are only applicable to stroke survivors with low cognitive impairment and with medium levels of fatigue and that more impaired individuals would have generated different outcomes.

With regards to psychometric properties of the cognitive tests, despite the fact that there is not much information about the dot cancellation and the speed of information processing tests, these were chosen based on the fact that they are practical and correlate with several other tests of attention and speed of information processing. Choosing other tests which have revealed higher psychometric properties would have resulted in replicating previous studies and would likely not add any new information with regards to different tests. In addition, these two tests minimise the effect of memory and isolate attention and speed of information processing which has not been done in previous studies. Therefore, generalizability of findings

should be done with caution.

At this point, it is worth noting that one of the main limitations of this study was the fact that there were no follow-up assessments on the cognitive tests; this may have shed some light into whether participants developed cognitive impairment later in the course of their stroke recovery or not. The lack of follow up cognitive assessments does not allow monitoring the progression of cognitive impairment and whether there would be any increase or decrease over time and subsequently produce different observations with regards to its relationship with fatigue.

For instance, Johansson & Rönnbäck (2012), who reported a significant correlation between cognitive components of fatigue and speed of information processing, conducted the assessments on participants in the chronic phase of stroke and not in the acute phase. According to the systematic review conducted prior to this study as part of this thesis (see chapter 2) (Lagogianni et al., 2016) the only other studies that reported a significant correlation between fatigue and cognitive impairment were conducted by Hubacher et al. (2012) who did not specify time since stroke onset at the assessment (simply indicated "sub-acute") and by Tang et al. (2010) who conducted assessments in the acute phase but used the SF-36 (Ware & Sherbourne, 1992) and the MMSE (Folstein et al., 1975) and not a domain specific cognitive test so their results are not comparable with the current study. Perhaps the relationship in question is more apparent in the chronic phase of stroke.

Finally, another point worth noting is that cognition is a complex skill and subcomponents are processed throughout the brain. More than one cognitive domain may be associated with the development and presence of fatigue as opposed to

distinct ones (Kutlubaev & Mead, 2012) and therefore using more generic cognitive tests is more likely to detect cognitive impairment that may be relevant to fatigue. Therefore, although global cognitive status measurements such as the MMSE (Folstein et al., 1975) may not be ideal for identifying generalised cognitive impairment in stroke populations; more sensitive tests that assess general cognitive impairment, such as the MoCA and the OCS may be able to detect a relationship with fatigue; alternatively, studies could include a diverse range of tests to examine multiple overlapping cognitive domains such as the TMT, the PASAT and the SDMT.

With regards to the cognitive tests used in the current study, an analysis was conducted to examine whether participants tended to make more errors towards the second part of the dot cancellation test. There was a hypothesis that because the dot cancellation test is long and monotonous, it may cause participants to make more errors towards the end of the test due to temporal fatigue based on lack of interest and tediousness and provide a summary score which better reflects attention and concentration impairment. The results confirmed that the length of the test does have an impact on the participants' performance and that performance tends to worsen towards the second part of the dot cancellation. However, when the discrepancy score (difference between section A and B) was put into a correlational analysis with regards to fatigue, it was not significantly associated with fatigue; this indicates that the loss of concentration was not correlated with the frequency of their fatigue. Therefore, a reasonable interpretation of this information may be that, even the low percentage of impairment in attention and concentration on the dot cancellation, may not be

representative of the actual impairment percentages that were displayed by the sample.

The Fatigue Severity Scale, has been criticized as an inappropriate tool to assess fatigue due to its uni-dimensionality and the fact that it does not consider all possible aspects of fatigue (Dittner et al., 2004). In addition, the scale does not provide a definition of fatigue to the participant, which means that the scores obtained may refer to different characteristics of fatigue and assess aspects that differ from one individual to the other. It is however debatable whether that is a major obstacle in the measurement of fatigue, since fatigue is a very personal and subjective experience and it is expected that it will differ for each one (Aaronson et al., 1999). In people with stroke, a Rasch analysis (Lerdal & Kottorp, 2011) showed that the Fatigue Severity Scale has only one underlying component confirming unidimensionality however the high correlations among the items may indicate item redundancy.

In a systematic review Lagogianni et al., (2016) reported that the studies that did find a significant relationship between fatigue and cognition, were using domain specific cognitive tests, but not the Fatigue Severity Scale. This lack of significant associations between fatigue and the cognitive tests used, may also be attributed to the fatigue scale used. Therefore, the uni-dimensionality of the Fatigue Severity Scale, may not be appropriate for assessing cognitive components of fatigue. For instance, Hubacher et al. (2012), used three fatigue scales, the Fatigue Scale for Motor and Cognitive Functions (Penner et al., 2009), the Modified Fatigue Impact Scale (MFIS, Paralyzed Veterans of America, 1998) and the FSS. The Fatigue Severity Scale does not consider cognitive aspects of fatigue whereas the former

two scales do. The authors reported significant correlations between mental speed and memory and the cognitive and total scores of both the FSMC and the MFIS but none was significantly correlated with the total score of the FSS. It is therefore possible that, either only the cognitive components of fatigue are associated with cognitive impairment or that the FSMC and the MFIS reflect cognitive complaints rather than fatigue.

An informal observation made during assessment with the Fatigue Severity Scale is that the phrasing of the items may be slightly limiting: while many participants were expressing verbally that they were feeling very fatigued after their stroke, when it came to completing the Fatigue Severity Scale they had low scores. An example is item 2 "exercise brings on my fatigue". This may be a problematic item because many participants feel fatigued regardless of their exercise. In this case, they would have to opt for a low response category which would affect the overall scale score and generate lower fatigue frequency that are representative of fatigue in reality. However, this observation has not been reported in any studies and the Fatigue Severity Scale is considered to have low floor effects across other conditions such multiple sclerosis, obesity, Parkinson's disease and lupus erythematosus (Amtmann et al., 2012; Hagell et al., 2006; Impellizzeri, Agosti, De Col, & Sartorio, 2013; Mattsson, Möller, Lundberg, Gard, & Boström, 2008). A Rasch analysis in stroke (Lerdal & Kottorp, 2011) showed that items 1 and 2 (as used above as an example) generated unacceptable high mean square values and the authors recommended their removal.

Despite the limitations, the study also had strengths. To begin with, the recruitment process excluded stroke

survivors with depression; depression, cognition and fatigue are associated and the presence of depression may mask the relationship between fatigue and cognition. This has not been taken into consideration by other studies and evidence of such relationship in the absence of depression is sparse. The sample recruited for the study was large and larger than samples in other similar studies.

Another advantage is the fact that the cognitive measures used were domain specific neuropsychological tests and not general cognitive status screening tests. In addition, one distinct characteristic of the tests used is the fact that they do not rely on memory components as much as other attention or speed of information processing tests.

In addition, the sample did not have recurrent or multiple strokes so that there was less heterogeneity due to multiple events. This, focused more on the direct consequences of stroke related fatigue and cognitive impairment based on the stroke incident per Se. Combining the above, the findings of the study are informative of the fact that, speed of information processing and attention were not associated with fatigue in the absence of depression.

It is very likely that high fatigue and severe cognitive impairment deter participation in research. Similar studies (Hubacher et al., 2012; Naess et al., 2005; Park et al., 2009; Schepers et al., 2006; Tang et al., 2010; van Eijsden et al., 2012; Winkens, Van Heugten, Fasotti, & Wade, 2009) report similar frequencies of fatigue and cognitive impairment to those found in the current study. It is understandable why individuals with severe cognitive problems would not prioritise participating in research and it is acknowledged that fatigue causes individuals to not participate in many events.

With regards to follow-up assessments, depression remained stable and did not significantly increase with the passage of 6 months. Overall the sample seemed to improve in terms of functional mobility, independence in personal self-care activities of daily living and independence in instrumental activities of daily living while anxiety significantly decreased at follow-up.

However, fatigue significantly increased over time for those who did return follow-up assessments. Fatigue has been reported to increase over time (Schepers, Visser-Meily, Ketelaar, & Lindeman, 2006) with a peak around 12 months post-stroke (van de Port, Kwakkel, Schepers, Heinemans, & Lindeman, 2007). A possible explanation is that, in the acute phase, stroke survivors may have other comorbid issues as a result of their stroke, such as side weakness, limited mobility, and compromised speech to which they may attribute their feelings of tiredness and therefore o not report fatigue as a separate problem. The whole medical team also focuses on these aspects and it is possible that the individuals do not acknowledge their fatigue symptoms. Later on, when and if some of the initial primary issues resolve, the participant is in a position to identify secondary factors, such as fatigue which tends to be more apparent when resuming pre-stroke activities. Indeed, the current sample provided evidence to support this notion. Once functional mobility and independence improved, participants scored higher on fatigue. When examining the relationship between follow-up fatigue and baseline cognitive tests, there were no significant correlations; however, the relationship between follow-up fatigue and the discrepancy score between sections A and B of the dot cancellation test at baseline, was close to being significant. This relationship may have been more evident in

people with higher fatigue scores. In addition, if more people had returned follow-up assessments we may have had greater confidence in the evaluation of whether baseline cognitive performance may be associated with fatigue at follow-up. In terms of returned follow-up assessments, 21% of the participants recruited did not provide follow-up questionnaires. Although this is undoubtedly a limiting factor, there was still a good number of individuals who provided data and within the estimates provided by the power calculation. In addition, when analysed separately, the group of people for whom follow-up data was not available, was very similar to the group of people for whom there was follow-up data available. In both groups, the majority of the participants were retired white British males with a partner, living with this partner, and had a right ischaemic lacunar stroke. These similar characteristics indicate that the groups were fairly similar and that including these 55 people at the follow-up analysis would not very likely radically change the outcome of this study.

3.8 Conclusion

Fatigue was not significantly associated with speed of information processing, selective and sustained attention in first ever stroke survivors without depression. As it is evident from previous studies that post-stroke depression and post-stroke fatigue are consistently associated, it may be the case that when including the variable of depression, the relationship between fatigue and cognition is also affected. Therefore, it is of interest to further examine the relationship between fatigue and cognitive impairment in individuals with depression.

Chapter 4: Investigation of the Relationship Between Fatigue and Cognition After Stroke In the Presence of Depression: A Longitudinal Cohort Study (Study 2)

4.1 Abstract

Background: Post-stroke fatigue is very common and is often associated with depression. Study I did not reveal any significant associations between fatigue and cognitive impairment in stroke survivors without depression. **Objective:** To examine the relationship between cognitive impairment and fatigue in first time stroke survivors with depression. **Design:** Longitudinal cohort design. **Settings:** Stroke wards in Nottingham University Hospitals and University Hospitals of Leicester. **Participants:** Stroke patients with no history of dementia, no previous stroke and with depression ($\geq$7 on the Brief Assessment Schedule for Depression Cards), were invited to participate in the study. **Measurements:** Participants were assessed on: Fatigue Severity Scale (fatigue), Dot Cancellation (sustained attention), Victoria Stroop Colour Test (selective attention) and Information Processing Test from the Adult Memory Information Processing Battery. **Results:** A total of 17 participants with depression were recruited from Nottingham and Leicester with time since stroke onset ranging between 6 and 50 days. The results indicated high fatigue levels (71%) and low impairment of attention and speed of information processing (range between 6-18%) at baseline. Fatigue and depression significantly decreased at 6 month follow-up. No significant associations were revealed between either baseline or follow-up fatigue and any of the cognitive tests. **Limitations:** This was a very small sample and most

participants had a lacunar stroke which resulted in low levels of cognitive impairment. No cognitive assessments were conducted at follow-up. **Conclusion:** There was no significant relation between fatigue and measure of attention and speed of information processing. Further studies in a larger sample with multidimensional fatigue and domain specific cognitive measures are needed.

4.2 Introduction

There are many studies that report significant correlations between fatigue and depression after stroke and while there is agreement that there is a relationship between post-stroke fatigue and post-stroke depression, these two have distinct mechanisms (refer to chapter 1). Therefore assessing post-stroke fatigue in individuals with post-stroke depression may mask other significant relationships between fatigue and cognition. The majority of the studies that have investigated fatigue after stroke included stroke patients with comorbid depression. Radman et al., (2012) found that executive dysfunction was associated with fatigue in stroke patients with depression but not in those without depression. In addition, other studies have confirmed a relationship between depression, attention and speed of information processing (Kauhanen et al., 1999; Terroni et al., 2012) which indicates a pattern that may involve fatigue, mood and cognition after stroke. The preceding study excluded participants who scored high on a screening measure for depression in order to determine other factors related to fatigue. This subsidiary study, included a small sample of participants with high depression score in attempt to assess whether the presence of depression would reveal similar

outcome in terms of the lack of significant relationship between fatigue and cognitive impairment.

4.3 Objectives

The aims of this study were to examine: 1) the relationship between sustained attention, selective attention, speed of information processing and fatigue in the acute phase of stroke in the presence of depression; 2) the relationship between sustained attention, selective attention, speed of information processing in the acute phase of stroke and fatigue 6 months after stroke.

4.4 Ethical Approval and Funding

The current study was added as an amendment to the Not-FAST study (REC Reference Number: 13/EM/0187; Protocol Number: 13037; IRAS Project ID: 124341; funded by the Stroke Association; ref: TSA 2012/04) and was added as a subsidiary study to the Cog-FAST (funded by the Vice Chancellor's Scholarship for Research Excellence-European Union; Scholarship Reference Number: RFDX42DB2). The protocol amendment was completed and submitted in February 2014 by the NotFAST study co-ordinator in order to allow Not-FAST to include a sample of individuals with depression. Ethical approval for the amendment was granted in March 2014 (see appendix).

4.5 Methods

4.5.1 Design

A within subjects longitudinal design was used. A measure of fatigue was the dependent variable (1 level; general fatigue) and speed of information, selective attention

and sustained attention as independent variables. Correlations were conducted to determine the relationship between the dependent and the independent variables. The duration of the study was 2 years (6 months per participant).

4.5.2 Settings and Recruitment

The study was multicentre and included two NHS Trust sites in England: Nottingham University Hospitals NHS Trust and University Hospitals of Leicester NHS Trust. Potential participants were identified within 4 weeks of their admission to a hospital following a first stroke, by clinical staff and the Stroke Research Network nurses.

4.5.3 Procedure

The recruitment, baseline and follow-up assessments and time of assessments were identical to those applied in Not-FAST (see chapter 3). The inclusion criteria were modified to include those who scored high on the BASDEC. Due to the fact that in this study all participants had high depression scores (BASDEC) they were all offered to speak with the researcher after the assessment was completed. They were informed that low mood is a very common consequence of stroke and that it is normal for them to feel this way. They were encouraged to talk to their GP and seek counselling from free services; they were encouraged to attend stroke groups and share their experiences with fellow stroke survivors as this may help them. They were once again provided with the researcher's details and were encouraged to contact the researcher if they needed any help finding the right support. If there was a suspicion or fear of suicidality the principal investigator of the study was informed.

4.5.4 Sample Size Estimation

According to Med Calc software, for 80% power at a 0.05 level of significance, a minimum of 13 participants were required per correlation (which is also consistent with literature; DeLisa et al., 2005; Howell, 2009). Therefore, in order to examine the relationship between fatigue and three cognitive tests, 39 participants were required.; in addition, the effect size to be detected was set high (r= .7) in order to detect strong effect size. It is argued that a small sample with a strong effect detected is more reliable than a study with a larger sample that detects a small effect (Fawcett & Garity, 2009). Therefore, the initial target sample for depression was set to a minimum of 39. SPSS version 22 for Windows was used to analyse data.

4.5.5 Statistical Methods

The statistical methods were identical to those used in study 1 (chapter 3). With regards to the dot cancellation, only the main score was used (time taken to complete) due to the small size of sample recruited.

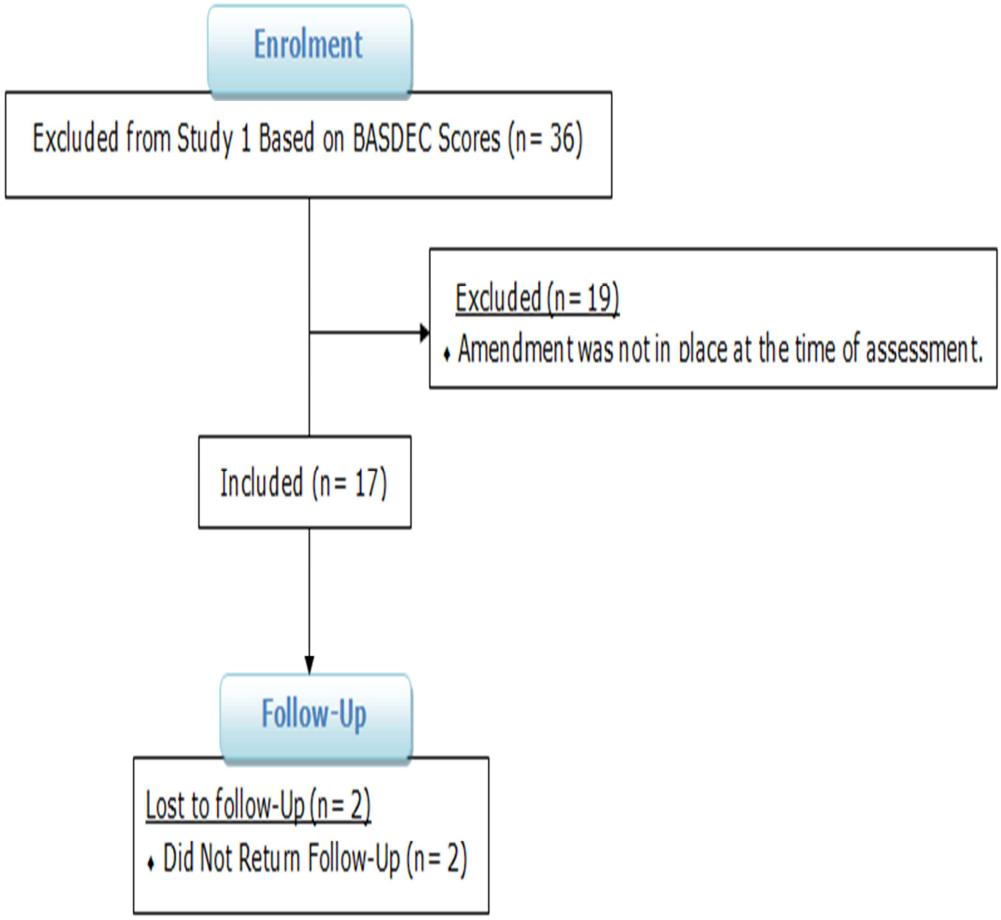
4.6 Results

4.6.1 Recruitment

The Consort (2010) diagram 3 presents the study flow. Thirty-six participants were excluded from study 1 based on their BASDEC score. Of these, nineteen were not included in the current study because the protocol amendment had not been put in place by the time of their assessment. Seventeen participants were included at baseline and 15 participants at

follow-up. Two participants did not return follow-up questionnaires.

Diagram 3: Consort Study Flow Diagram



4.6.2 Demographic Characteristics

Tables 27, 28 and 29 respectively summarise the location of recruitment and assessment, demographic characteristics and education and occupational of participants There were 17 participants with an age range 49-85 years (mean: 74.29; SD: 9.85). Mean time since stroke onset was 25 days (SD: 12.27, range: 6-50 days).

Table 27. Location of Recruitment and Assessment

Location		Number	Percentage
Recruitment Site	Nottingham	9	53%
	Leicester	8	47%
Baseline Assessment	Home	13	77%
	Hospital	4	23%
	Clinic/Other	0	0%

There was a fairly even distribution of participants between sites. The majority of participants were assessed at home.

Table 28. Demographic Characteristics at Baseline

Variable		Number	Percentage
Sex	Men	6	36%
	Women	11	64%
Ethnicity	White British	17	100%
	Mixed	0	0%
	Asian	0	0%
	Black/African	0	0%
	Other	0	0%
Marital Status	Single/Widowed/ Divorced	6	35%
	With Partner/Spouse	11	65%
Living Arrangements	Alone	5	29%
	With Other	12	71%

There was a relatively high proportion of women. All participants were white British, most had a partner and were living with that person.

Table 29. Education and Occupational Characteristics at Baseline

Variable		Number	Percentage
Education	No Qualifications	9	53%
	GCSE Level	1	6%
	A Level	1	6%
	Vocational/Apprenticeship	5	29%
	Higher Degree	1	6%
	Professional Qualifications	0	0%
Employment Status	Retired	12	70%
	Working	3	18%
	Missing	2	12%
Current or Last Occupation	Mangers	1	6%
	Professionals	2	12%
	Technicians & Associate Professionals	0	0%
	Clerical Support Workers	2	12%
	Service & Sales Workers	3	18%
	Skilled Agricultural, Forestry and Fishery Workers	2	11%
	Craft & Related Trades Workers	1	6%
	Plant & Machine Operators and Assemblers	2	12%
	Elementary Occupations	0	0%
	Armed Forces Occupations	0	0%
	Housewife/Unemployed	2	12%
	Missing	4	12%

More than two thirds of the participants were retired from

work.

The medical characteristics are summarised in table 30.

Table 30. Medical Characteristics at Baseline

Variable		n	Percentage
Hemisphere Affected	Right	6	35%
	Left	9	53%
	Both	1	6%
	Missing	1	6%
Stroke Subtype	Ischaemic	15	88%
	Missing	2	12%
Stroke Type	Partial Anterior Circulation	5	29%
	Lacunar	5	29%
	Posterior Circulation	3	18%
	Total Anterior Circulation	0	0%
	Missing	4	24%
Comorbidities	Cancer	2	11%
	Heart Disease	4	24%
	Peripheral Vascular Disease	1	6%
	Respiratory	2	12%
	Diabetes	3	18%
	Transient Ischaemic Attack	1	6%
	Heart Failure	0	0%
	Anaemia	0	0%
	Atrial Fibrillation	3	18%
	Insomnia	2	12%

The majority had suffered unilateral ischaemic and LACS strokes.

The distribution of baseline assessment scores are summarised in tables 31 and 32 and was examined in order to determine whether data were normally distributed in order to determine the most appropriate method of statistical analysis.

Table 31 . Distribution of Scores on Baseline Questionnaires

Measure	n	Percentiles				Mean	S.D.	Skewness	Kurtosis
		25th (low)	50th (Median)	75th (upper)	IQR				
Sheffield Screening Test for Acquired Language Disorders*	17	17.50	19.00	19.50	2	18.47	1.37	-0.99	.97
Brief Assessment Schedule for Depression Cards*	17	7.00	9.00	10.00	3	8.82	1.59	0.32	-.94
Rivermead Mobility Index*	17	6.00	11.00	14.00	8	9.41	4.61	-0.57	-.95
Nottingham Extended Activities of Daily Living*	17	4.50	10.00	19.00	15	12.18	7.31	-0.02	-1.61
Fatigue Severity Scale*	17	3.05	5.55	6.00	2.94	4.77	1.67	-0.81	-0.17
Barthel Index	17	13.50	19.00	20.00	7	16.76	4.40	-1.68	3.19
Beck Anxiety Inventory	17	4.00	11.00	17.00	13	13.59	11.65	1.15	0.35

*Data Normally Distributed

*Note: Some of the participants refused/were unable to complete some of the tests.

Table 32. Distribution of Scores for Baseline Cognitive Assessments

Cognitive Impairment	n	Percentiles				Mean	S.D.	Skewness	Kurtosis
		25th (low)	50th (Median)	75th (upper)	IQR				
DC Time*	16	**428.75**	493.00	**6.16**	187	513.69	130.70	0.342	-0.57
AMIPB Items Attempted*	16	27.00	31.00	55.25	28	37.81	17.63	0.79	-0.36
AMIPB Errors	16	0.25	1.50	6.25	6	3.69	5.12	2.38	6.76
AMIPB % of Errors	16	0.38	6.09	13.47	13	13.82	22.48	2.16	3.71
AMIPB Adjusted Score*	16	29.19	33.50	63.39	34.20	42.42	21.40	0.86	-0.35
AMIPB motor speed*	16	30.00	34.00	41.50	12	34.88	6.56	0.42	-0.89
VST A Time	15	22.00	27.00	38.00	16	38.07	29.24	1.90	2.81
VST A Errors	15	0.00	0.00	0.00	0	0.53	1.35	2.99	9.36
VST B Time*	15	50.00	71.00	98.00	48	73.87	32.16	0.51	0.10
VST B Errors*	15	1.00	3.00	4.00	3	2.87	2.03	0.44	-0.17
VST Interference*	15	15.00	27.00	51.00	36	35.80	29.85	0.83	1.33

*Data Normally Distributed

*Note: Some of the participants refused/were unable to complete some of the tests.

Skewness and kurtosis were examined and it was observed that participants' scores on most questionnaires were normally distributed and on most cognitive tests skewed (<1; Bulmer, 1979; Miles & Shevlin, 2001). However, the sample size was very small and therefore, non-parametric statistical analysis was used for all variables.

Table 33 summarises the frequency of impairment on each domain according to the cut-off scores of each measure:

Table 33: Frequency of Impairment in Each Domain at Baseline

Domain	**Measure**	**Number Above Cut-off Scores (percentage)**
Fatigue	Fatigue Severity Scale	13 (71%) fatigued
Anxiety	Beck Anxiety Inventory	minimal: 7 (41%); mild: 6 (35%); moderate: 1 (6%); severe: 3 (18%)
Speed of Information Processing	Adult Memory Information Processing Battery (Adjusted Score)	2 (12%)
Sustained Attention & Concentration	Dot Cancellation (Time)	1 (6%)
Selective Attention & Concentration	Stroop Victoria Test (Interference)	4 (18%)

The proportion of participants with impairment of attention and concentration was low. The majority of the participants were identified as fatigued and had minimal or mild anxiety in addition to being depressed.

4.6.3 Inferential Statistics

Table 34 summarises the Spearman's correlations that were conducted to determine the relationship between fatigue and cognitive variables.

Table 34: Correlations Between Post-Stroke Fatigue (FSS) and the Cognitive Tests

Correlation with FSS	**n**	**Correlation Coefficient**	**p-Value**
Dot Cancellation Time Taken	16	0.01^{rs}	0.94
Adult Memory Information Processing Battery-Speed of Processing Adjusted Score	16	-0.20^{rs}	0.44
Stroop Victoria Test Interference	15	-0.01^{rs}	0.97

*r_s= Spearman

There were no significant correlations between the level of fatigue and cognitive abilities with small correlation size. As no significant relationships were found, regression analysis was not conducted.

4.6.4 Follow-Up Assessments

Tables 35, 36 and 37 summarise the demographic, education, occupational and medical characteristics of the participants who completed the follow-up assessment.

Seventeen follow-booklets were posted. A total of 15 follow-up assessments were returned (88% response rate). Two participants did not return follow-up assessments. The mean time since stroke onset that the follow-up assessments were completed was 185.40 days (SD: 12.97, Range: 176-208). The mean age of the participants who completed the follow-up assessments was 73.27 years (S.D.: 10.05, range: 49-85). Of the participants who returned the follow-up, 1 (7%) had had a recurrent stroke.

Table 35. Demographic Characteristics at Follow-Up

Variable		**Number**	**Percentage**
Sex	Men	5	33%
	Women	10	67%
Ethnicity	White British	15	100%
	Mixed	0	0%
	Asian	0	0%
	Black/African	0	0%
	Other	0	0%
Marital Status	Single/Widowed/Divorced	6	40%
	With Partner/Spouse	9	60%
Living Arrangements	Alone	5	33%
	With Other	10	67%
	Residential Care	0	0%

There was a relatively high proportion of women. All participants were white British, most had a partner and were living with that person.

Table 36. Education and Occupational Characteristics at Follow-Up

Variable		Number	Percentage
Education	No Qualifications	8	53%
	GCSE Level	1	7%
	A Level	1	7%
	Vocational/Apprenticeship	5	33%
	Higher Degree	0	0%
	Professional Qualifications	0	0%
Occupation	Mangers	1	7%
	Professionals	2	14%
	Technicians & Associate Professionals	0	0%
	Clerical Support Workers	2	13%
	Service & Sales Workers	2	13%
	Skilled Agricultural, Forestry and Fishery Workers	1	7%
	Craft & Related Trades Workers	1	7%
	Plant & Machine Operators and Assemblers	2	13%
	Elementary Occupations	0	0%
	Armed Forces Occupations	0	0%
	Housewife/Unemployed	2	13%
	Missing	2	13%
Employment Status	Retired	10	67%
	Working	3	20%
	Missing	2	13%

The majority of the participants were retired from work.

Table 37. Medical Characteristics at Follow-Up

Variable		Number	Percentage
Hemisphere Affected	Right	5	33%
	Left	8	53%
	Both	1	7%
	Missing	1	7%
Stroke Subtype	Ischemic	14	93%
	Missing	1	7%
Stroke Type	Partial Anterior Circulation	4	26%
	Lacunar	4	27%
	Posterior Circulation	3	20%
	Total Anterior Circulation	0	0%
	Missing	4	27%
Comorbidities	Cancer	2	13%
	Heart Disease	4	27%
	Peripheral Vascular Disease	1	7%
	Respiratory	2	13%
	Diabetes	2	13%
	Transient Ischaemic Attack	1	%
	Heart Failure	0	0%
	Anaemia	0	0%
	Atrial Fibrillation	3	20%
	Insomnia	2	13%

The majority had ischaemic and lacunar strokes.

Table 38 summarises descriptive statistics for the follow-up assessments.

Table 38: Descriptive Statistics for Follow-Up Assessments

Measure	n	Percentiles				Mean	S.D.	Skewness	Kurtosis
		25th (low)	50th (Median)	75th (upper)	IQR				
Brief Assessment Schedule for Depression Cards*	15	2.00	4.00	7.00	5	4.20	2.62	0.02	-1.21
Rivermead Mobility Index*	15	8.00	13.00	14.00	6	11.20	3.42	-0.88	-0.50
Nottingham Extended Activities of Daily Living	15	12.75	20.00	22.00	9	17.43	5.45	-1.28	1.23
Fatigue Severity Scale*	15	4.11	4.77	5.33	1.22	4.40	1.78	-0.83	0.24
Barthel Index	15	17.00	19.00	20.00	3	17.73	3.10	-1.48	1.50
Beck Anxiety Inventory*	15	4.00	13.00	18.00	14	11.80	7.35	0.12	-1.26

* Data Normally Distributed

Skewness and kurtosis were examined and it is observed that participants' scores on most dimensions were normally distributed (<1; Bulmer, 1979; Miles & Shevlin, 2001). However, due to the small sample size, non-parametric analysis was used.

Table 39 summarises the frequency of impairment at follow-up in each variable according to the cut-off scores of each measure.

Table 39: Frequency of Impairment in Each Domain at Follow-Up

Domain	**Measure**	**Number Above Cut-off Scores (percentage)**
Fatigue	Fatigue Severity Scale	12 (80%) fatigued
Anxiety	Beck Anxiety Inventory	minimal: 6 (40%); mild: 4 (27%); moderate: 5 (33%); severe: 0 (0%)
Depression	Brief Assessment Schedule for Depression Cards	2 (12%) depressed

The majority of the participants who returned follow-up assessments were identified as fatigued with minimal anxiety and low depression.

Table 40 summarises the difference between baseline and follow-up assessments for participants who completed the follow-up assessments.

Table 40: Comparison of Baseline and Follow-up Assessments

Measure	Assessment	Number	Mean	S.D.	Min.	Max.	Z-Value	p-Value
Fatigue Severity Scale	Baseline	15	4.91	1.70	1	7	-1.88	0.06
	Follow-Up	15	4.40	1.78	1	7		
Brief Assessment for Depression Cards	Baseline	15	8.87	1.68	7	12	-2.98	≤0.01
	Follow-Up	15	4.20	2.62	0	8		
Beck Anxiety Inventory	Baseline	15	14.80	11.89	2	39	-0.74	0.45
	Follow-Up	15	11.80	7.35	3	25		
Barthel Index	Baseline	15	17.27	4.44	4	20	-0.15	0.87
	Follow-Up	15	17.73	3.10	10	20		
Nottingham Extended Activities of Daily Living	Baseline	15	13.40	6.88	2	22	-2.41	0.01
	Follow-Up	14	17.43	5.45	4	22		
Rivermead Mobility	Baseline	15	10.00	4.58	0	14	-1.41	0.15
	Follow-Up	15	11.20	3.42	4	14		

The tests showed statistically significant differences between baseline and follow-up assessments in some of the variables measured. More specifically: there was an increase of independence in instrumental activities (Nottingham Extended Activities of Daily Living) [Wilcoxon Z (14) = -2.41; $p<.05$] over time whereas there was a decrease in depression (Brief Assessment Schedule for Depression Cards) [Wilcoxon Z (15) = -2.98; $p<.05$]. There was no significant difference in fatigue (Fatigue Severity Scale), functional mobility (Rivermead), anxiety (Beck Anxiety Inventory) and independence in personal self-care activities of daily living (Barthel).

Table 41 summarises the Spearman's correlation coefficients that were conducted to examine the relationship between fatigue at follow-up and cognitive tests at baseline.

Table 41: Correlation Values Between Fatigue at Follow-Up and Cognitive Assessments at Baseline

Correlation with Fatigue Severity Scale	**n**	**Correlation Coefficient**	**p-Value**
Dot Cancellation Time Taken	14	-0.30^{rs}	0.29
Adult Memory Information Processing Battery-Speed of Processing Adjusted Score	15	-0.31^{rs}	0.25
Stroop Victoria Test Interference	14	-0.17^{rs}	0.55

*r_s= Spearman

Fatigue at follow-up was not significantly associated ($p>0.05$) with cognitive scores at baseline. As no significant relationships were found, regression analysis was not conducted.

4.7 Discussion

The results of this study revealed that in those who were depressed there was a low frequency of impairment in attention and concentration, medium fatigue frequency and no significant relationship between fatigue and impairment of attention or speed of information processing with very small correlations. Fatigue, anxiety, functional mobility and independence in personal self-care activities of daily living remained stable over time while there was a decrease of depression and an increase of independence in instrumental activities of daily living over time.

Fatigue was not associated with any of the cognitive components which is consistent with other studies and with the findings from study 1. This means that the presence of depression did not affect the lack of significant relationship between attention, speed of information processing and fatigue. The findings were comparable for people with and without depression. In study 2, participants with depression had slightly higher cognitive impairment and were more fatigued; this is in accordance with what was discussed in chapter 1 with regards to the relationship between cognitive impairment and depression. It seems that the presence of depression was associated with both higher cognitive impairment and fatigue. One very interesting difference however was that participants who had depression, showed a decrease in their fatigue and depression levels over time which is the opposite of study 1 findings, where people who did not have significant levels of depression, increased in fatigue and depression over time. Based on the results of both studies, it looks like there is no significant relationship between fatigue and attention and concentration in the acute phase of stroke regardless of depression levels. Perhaps this

does not apply to stroke survivors in the chronic phase. In addition, it may be that only cognitive components of fatigue are associated with cognitive impairment and that a general fatigue scale such as the Fatigue Severity Scale does not allow such relationships to emerge. It is therefore of interest to examine the reliability of the Fatigue Severity Scale in the samples used in the studies and assess its dimensionality.

The key limitations of this study are similar to the ones discussed in the previous study, including limitations in relation to demographic and medical characteristics, the scales used and the procedure of recruitment and assessments. Likewise, the strengths of this study are also identical to the ones mentioned in the previous study. With regards to the sample size, the target sample of 39 was not achieved as only 17 participants were recruited. This is a limiting factor and the results of the study should be interpreted with caution, as there could a type II error (unable to detect a potential effect/relationship that is present) due to the study being underpowered. Only 17 participants with depression were identified from Nottingham and Leicestershire following the protocol amendment, almost a year. Only these two sites were used to recruit for this study, as the researcher was based in the East Midlands and it was not possible to travel to other sites. In addition, Nottinghamshire recruitment to the NotFAST study was ceased a month earlier than the other sites as they met their target. This left only one site active (Leicester).

One possible explanation for the small sample size is that vulnerable individuals with problems, such as cognitive impairment and depression, anxiety and fatigue are unlikely to consent to participate in a study as discussed previously (Hughes-Morley, Young, Waheed, Small, & Bower, 2015). In addition, the prevalence of depression in the rehabilitation

wards has been reported to be higher than those in the acute wards (Shah, Evans, & King, 2000) and the recruiting nurses mainly recruited from acute wards. Perhaps having included more participants would have facilitated a definitive answer to the study question. Likewise, the fact that two participants did not return follow-up assessments may seem negligible but given the small sample size to begin with, having follow-up data from these two participants may have made a difference regarding this particular correlation. This is consistent with findings from study 1, where again the relationship between follow-up fatigue and baseline difference score between the two sections of the dot cancellation was very close to being significant. It looks like there is a pattern that is consistent in both groups, regardless of depression scores, and that is worth examining further. Perhaps this type of cognitive performance at baseline may be predictive of the experience of fatigue at follow-up but it may be weakened and masked by other factors.

The strength of the study was the fact that stroke survivors with depression were included so that the findings could be compared with those from study 1. Studies rarely analyse people with depression separately and instead simply exclude them. The current study offered the advantage of recruiting depressed stroke survivors, but they were analysed separately. The above findings, are only relevant to first ever stroke survivors with depression. The sample size was very small so only tentative conclusions can be drawn.

4.8 Conclusion

There was no significant relationship between fatigue and measure of attention and speed of information processing in a sample of stroke survivors with depressive symptoms.

Chapter 5: Principal Component Analysis

5.1 Abstract

The Fatigue Severity Scale is very commonly used to measure fatigue in neurological disorders. The reliability of of the scale has been reported to be high in many clinical conditions. A Rasch analysis of the Fatigue Severity Scale supports the unidimensionality of the scale. Following the findings of the previous two studies which did not confirm any significant association between cognition and fatigue, this chapter examined the internal consistency of the scale and its dimensionality. Data was obtained as part of the NotFAST study described in chapter 3. The results indicated that the scale was unidimensional (72.9% cumulative variance) with common variance among the items (>.5) and internal consistency of α= .95. This indicates that the 9-item version of the scale did not compromise the measurement of fatigue across the studies.

5.2 Introduction

The results of the previous studies did not reveal any significant relationships between fatigue and cognitive impairment after stroke, which is consistent with some studies (Schepers et al., 2006; Tang et al., 2010) and inconsistent with others (Hubacher et al., 2012; Radman et al., 2012). While there are several explanations for this, it may be due to using scales with poor psychometric properties such as reliability and sensitivity. Therefore, the next step of this project was to examine the internal consistency of the Fatigue Severity Scale (FSS) as a measure of fatigue in stroke patients and to assess its dimensionality. The FSS comprises 9 items measuring fatigue severity and its impact on daily activities.

Each item is responded on a 7-point Likert scale (1=strongly disagree - 7=strongly agree) (Lerdal & Kottorp, 2011). All responses are summed and divided by number of items (9). The maximum overall score is 7 with higher scores indicating higher levels of fatigue (Neuberger, 2003).

Despite the fact that the scale has been used in stroke research, it appears that only a few studies have examined its psychometric properties in stroke (Lerdal & Kottorp, 2011; Schepers, Visser-Meily, Ketelaar, & Lindeman, 2006; Valko, Bassetti, Bloch, Held, & Baumann, 2008; van de Port, Kwakkel, Schepers, Heinemans, & Lindeman, 2007) (detailed in chapter 1) and only one has reported on the components that it measures. Internal Consistency of the FSS in people with stroke ranges from α = .86 to .96 (Lerdal & Kottorp, 2011; Valko et al., 2008; Schepers et al., 2006; Valko, Bassetti, Bloch, Held, & Baumann, 2008; van de Port et al., 2007). A Rasch analysis (Lerdal & Kottorp, 2011) indicated that items 1 and 2 of the 9 item FSS demonstrated unacceptable high-mean square values and that when these were removed, the scale produced higher internal consitency. Therefore the authors recommended that a 7-item FSS scale (excluding items 1 and 2) would be a more internally consistent scale. The 7-item version of the FSS has also been reported to have higher internal consistency than the 9-item version in studies of patients with chronic neck pain (Takasaki & Treleaven, 2013), HIV/AIDS (Lerdal et al., 2011), multiple sclerosis and stroke (Johansson, Kottorp, Lee, Gay & Lerdal, 2014). Another Rasch analysis, which was conducted on the FSS from people with multiple sclerosis (Mills, Young, Nicholas, Pallant, & Tennant, 2009), indicated that reducing the scale to 5 items, enhanced the unidimensionality of the scale. The authors suggested that items 1 and 2 were not

consistent with responses on the rest of the items; in addition, item 6 was highly associated with age, disability and disease subtype while item 8 was associated with disability.

Unidimensionality of a scale is essential when measuring a complex phenomenon, such as fatigue after stroke. This is because, despite fatigue beeing multifaceted, scales such as the FSS offer a general assessment of fatigue without focusing on any particular area, and without the implication of potential confounders such as cognition (Amtmann et al., 2012). The consistency among the items indicates that the responses reflect a unified model of general fatigue. The fact that some reports recommend shorter versions highlights the possibility that the scale includes unnecessary items, that may be addressing different constructs. Because the FSS was used in the previous studies to assess fatigue, the results may not be representative of actual fatigue due to a potential overlap within the items of the FSS. Therefore, the aim was to assess the factor structure of the scale.

5.3 Objectives

The aim of this chapter was to examine the: 1) internal consistency and 2) factor structure of the FSS in a stroke sample.

5.4 Method

The FSS was administered as a part of the NotFAST and CogFAST (Studies I & II). See method section of study 1 for details (chapter 3). A principal component analysis was conducted on baseline data provided by 284 participants (combined sample from studies 1 & 2). This is within the recommended sample size for component analysis (Comrey & Lee, 1992; MacCallum, Widaman, Zhang, & Hong, 1999).

5.5 Design

The design was an analysis of cross-sectional data collected in studies 1 and 2. Participants recruited for these studies were all assessed on the FSS.

5.6 Criteria Used for the Analyses

SPSS version 22 was used for analyses. Chronbach's α coefficients were calculated to estimate the internal consistency of the 9-item version of the scale. Values greater than .7 were considered to indicate high internal consistency (Hatcher, 2003).

A principal component analysis (PCA) was used to examine the dimensionality of the FSS. PCA is a systematic analysis of the components that make up a construct; the main objective of the PCA is to assess and reduce dimensionality of data while maintaining the highest possible variance which is achieved by linearly reducing a set of data to smaller sets of new distinct and uncorrelated variables (principal components) (Dunteman, 1989; Jolliffe, 1986). Therefore, PCA is recommended in order to assess whether item reduction is essential when using a scale in order to maintain optimal properties. It was used in this study to examine whether item reduction would have been a better choice for the analyses of the previous studies.

The Kaiser-Meyer-Olkin Measure of Sampling Adequacy (KMO) values are usually between 0 and 1 with values closer to 1 indicating that patterns of correlation are compact with reliable factors; values greater than .5 are considered to be compact and factor analysis would yield reliable factors (Kaiser, 1974).

The Bartlett's Test of Sphericity was calculated to

examine the relationship between the variables. For a factor analysis the Bartlett's values need to be significant (< .05). Scree plots were conducted to observe the separation between the vertical and horizontal declines according to the number of components. Commonalities were examined to estimate the proportion of variance for each variable and those above .5 were considered to be consistent.

The Eigenvalues were set >1.00 with the justification that those with <1.00 usually account for less variability than each of the variables independently and are less likely to be retained in the analysis as Eigenvalues <1.00 usually indicates less than 1 variables in the factor (Girden, 2001).

5.7 Results

5.7.1 Descriptive Statistics

The locations of recruitment and assessment are shown in table 42, demographic characteristics of the combined sample are shown in table 43, the education and occupational characteristics are shown in table 44 and the medical characteristics in table 45. The sample comprised those who took part in studies 1 and 2. Two-hundred and eighty-five participants completed the FSS with an age range 24-94 years (mean: 68.20, S.D.: 13.44). Mean time since stroke onset was 23.70 days (S.D.: 13.11, range: 1-61). The mean score on the FSS was 3.60 (S.D.: 1.85; range: 1-7). According to the recommended cut-off score for the FSS (≥4; Valko, Bassetti, Bloch, Held & Baumann, 2008) 125 (44%) of the participants were identified as fatigued.

Table 42. Location of Recruitment and Assessment

Variable		Number	Percentage
Recruitment Site	Nottingham	105	37%
	Leicester	64	23%
	Salford	41	14%
	London	75	26%
Baseline Assessment	Home	177	62%
	Hospital Ward	83	29%
	Clinic/Other	24	9%

Most participants were recruited from Nottingham. The majority of participants were assessed at home.

Table 43. Demographic Characteristics at Baseline

Variable		Number	Percentage
Sex	Men	174	61%
	Women	111	39%
Ethnicity	White British	257	90%
	Mixed (Egyptian/English)	2	1%
	Asian	9	3%
	Black/African	13	5%
	Other	4	1%
Marital Status	Single/Widowed/Divorced	106	37%
	With Partner/Spouse	179	63%
Living Arrangements	Alone	89	31%
	With Other	196	69%

There was a relatively high proportion of men. The majority were white British, had a partner and were living with that person.

Table 44. Education and Occupational Characteristics at Baseline

Variable		Number	Percentage
Education	No Qualifications	68	23%
	GCSE Level	78	28%
	A Level	40	14%
	Vocational/Apprenticeship	35	12%
	Professional Qualifications	14	5%
	Higher Degree	35	13%
	Missing	15	5%
Employment Status	Retired	177	62%
	Working	93	33%
	Unemployed	11	4%
	Missing	4	1%
Current or Last Occupation	Managers	41	14%
	Professionals	64	23%
	Technicians & Associate Professionals	19	7%
	Clerical Support Workers	25	9%
	Service & Sales Workers	43	15%
	Skilled Agricultural, Forestry and Fishery Workers	4	1%
	Craft & Related Trades Workers	23	8%
	Plant & Machine Operators and Assemblers	21	7%
	Elementary Occupations	21	7%
	Armed Forces Occupations	4	2%
	Housewives/Never Worked	11	4%
	Missing	9	3%

Over half the participants were retired from work.

The medical characteristics are summarised in table 45.

Table 45. Medical Characteristics at Baseline

Variable		n	Percentage
Hemisphere Affected	Right	146	51%
	Left	123	43%
	Both	11	4%
	Missing	5	2%
Stroke Type	Ischaemic	258	90%
	Haemorrhagic	24	9%
	Missing	3	1%
Stroke Subtype	Total Anterior Circulation	14	4%
	Partial Anterior Circulation	73	26%
	Lacunar	91	32%
	Posterior Circulation	50	18%
	Missing	57	20%
Comorbidities	Cancer	16	6%
	Heart Disease	29	10%
	Respiratory	35	12%
	Diabetes	43	15%
	Transient Ischaemic Attack	26	9%
	Atrial Fibrillation	56	20%
	Heart Failure	6	2%
	Peripheral Vascular Disease	7	3%
	Anaemia	10	4%
	Insomnia	17	6%

The majority of participants had suffered unilateral ischaemic stroke and either partial anterior circulation or lacunar strokes.

5.7.2 Internal Consistency

Cronbach's α coefficient was α= .95 which indicates high internal consistency. All inter-item correlations were significantly and positively correlated and above .5 which indicates that they measure the same component; the lowest item total correlations were found in items 1 and 2 (.53 and .74 respectively). The item-total statistics values indicated that removing item 2 from the scale would give slightly lower value for overall Cronbach's α coefficients (.95) and removing item 1 would leave the values the same (.953). However, removing both items, the Cronbach's α coefficient was α= .954 which was only slightly higher than using the 9 item version.

5.7.3 Principal Component Analysis

A post-hoc principal component analysis, using pairwise exclusion. The Kaiser-Meyer-Olkin Measure of Sampling Adequacy (KMO) was very good (.92) and above the recommended .5 value. The Bartlett's Test of Sphericity was significant (χ^2 (36) = 2517.1, p < .05).

According to the scree plot, only one component was extracted as there is a clear separation of the horizontal and the vertical declines at number 1 of components.

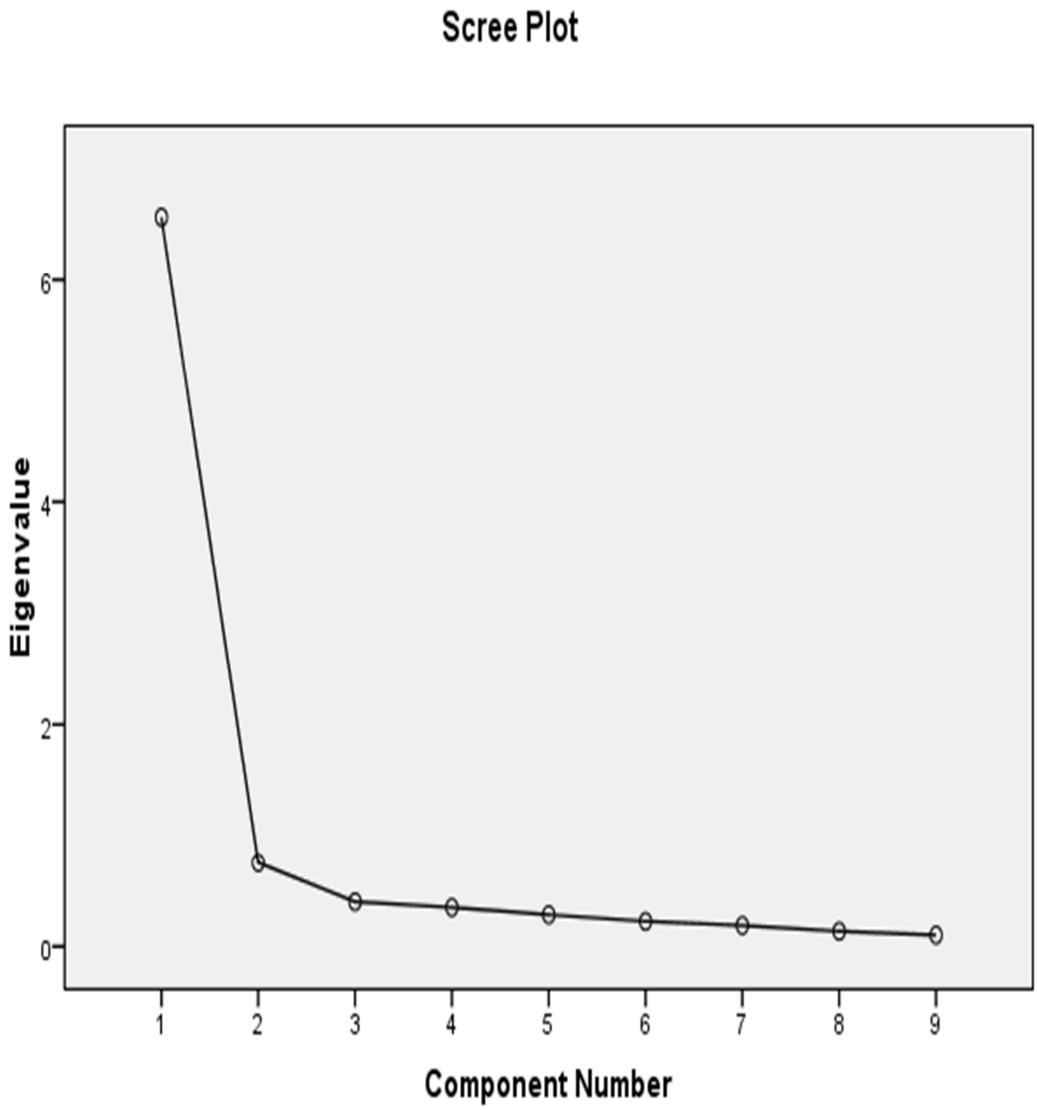


Figure 1 Scree Plot of Factors by Eigenvalues

A shown in table 46, the communalities (proportion of each variable's variance) were all significant and above .5 confirming common variance among the items.

Table 46. Principal Component Analysis

Items	Component -1-
1	.56
2	.59
3	.74
4	.83
5	.79
6	.80
7	.78
8	.71
9	.72

Table 47 summarises the initial Eigenvalues according to each item.

Table 47. Total Variance Explained

Items	Eigenvalues		
	Total	**% of Variance**	**Cumulative %**
1	6.56	72.9	72.9
2	.75	8.3	81.2
3	.40	4.4	85.7
4	.35	3.8	89.6
5	.23	3.1	92.7
6	.22	2.4	95.2
7	.18	2.0	97.3
8	.13	1.5	98.8
9	.10	1.1	100.0

There was only one principal component with Eigenvalues >1.00 (total=6.56) which explains 72.9% of the cumulative variance. This indicates that all 9 items in the FSS

examine fatigue as one component (72.9%) while 27.1% of the variance is explained by unspecified factors.

5.8 Discussion

The analyses indicated that one principal component was underlying the 9 item Fatigue Severity Scale. The scale had high internal consistency (Cronbach's α= .95). Items 1 and 2 produced the lower item total correlation values compared to the other items but when they were removed from the scale the internal consistency did not change. The internal consistency is consistent with previous stroke studies (.86-.96) (Lerdal & Kottorp, 2011; Valko et al., 2008).

Items 1 and 2 produced lower communalities than the rest of the items. It is possible that the lower communality values demonstrated by items 1 and 2 could affect the validity of the scale. Despite these findings, the internal consistency of the 7-item scale was similar to the internal consistency of the 9-item scale as demonstrated by the reliability analysis. The unidimensionality of the 9-item scale was confirmed by the component analysis.

With regards to internal consistency, Chronbach's α coefficient was very high (α= 0.95). Although high internal consistency indicates strong relationship between the items, nearly excellent values (such as α= .95 and above) that indicate complete agreement, are not necessarily desirable as they may reflect redundancy issues (Streiner, 2003). Ideally a scale is based on items that are highly related but there is need for each item to contribute something unique in the overall scale, otherwise the items may be measuring the same thing and are therefore unnecessary. It is generally suggested that more generic constructs are expected to reveal relatively lower coefficients as opposed to more specific constructs

(Peters, 2014).

The FSS produced nearly excellent internal consistency despite measuring such a generic topic as fatigue, it may indicate that there is no distinct contribution for each statement. In addition, Cronbach & Shavelson, (2004) suggested that Cronbach's α is not a sufficient indication of unidimensionality and these two can be independent. Therefore, the unidimensionality of the scale and the high internal consistency combined, despite being seemingly positive may indicate that the scale is actually measuring one component with multiple similar items that do not contribute to the measurement of fatigue and if anything, may even be responsible for small variations which would potentially explain the rest of the 27.1% of the variance that is unexplained by the 9 items. Futhermore, the fact that 72.9% is measured by one component, indicates that there may be other factors that affect the assessment of fatigue; 27.1% of the variance of the scale is explained by other unspecified factors which may have a small effect on scores. For instance, despite the unidimensionality of the scale, the items assess manifestations of fatigue across several aspects (Friedman et al., 2010) and the lack of definition provided by the scale allows for subjective interpretation which may not be consistent with the type of fatigue aimed to be measured. Therefore, although not significant, there seems to be a small proportion of variance that may be explained by other factors such as subjectivity which may compromise assessment.

Although this analysis is in accordance with previous ones (Lerdal & Kottorp, 2011; Valko et al., 2008), and the sample was large, these findings should be generalised with caution. The sample used may not be very represantative of the stroke population as participants have only had mild

strokes and there was a significantly higher proportion of lacunar strokes compared to other studies. Fatigue was at similar levels with those from other studies but the prevalence of cognitive impairment was very low. Perhaps the findings of this analysis may only apply to first mild stroke survivors with medium fatigue and low cognitive impairment scores.

5.9 Conclusion

The results revealed that the 9-item version of the FSS is internally consistent and assesses one factor. It is comparable to the 7-item version. Therefore, it appears that the reduction to the 7-item version of the scale, would not impact significantly on the outcomes of the studies and any suspected implications do not seem to be associated with the psychometric properties of the FSS scale used. However, it is for future studies to further examine the uniqueness and contribution of each of the 9 items as it appears that they measure very similar things.

Chapter 6: Investigation of the Relationship Between Fatigue, Depression and Speed of Information Processing After Stroke Using Cognitive and General Fatigue Scales: A Cross-Sectional Study. (Study 3)

6.1 Abstract

Background: Some studies have reported a relationship between post-stroke fatigue and speed of information processing however this was not supported by the two studies in this thesis. Other studies have used fatigue scales that assess cognitive components of fatigue rather than generic fatigue scales, as was used in studies 1 and 2. **Objective:** The aim of this study was to examine the relationship between speed of information processing and fatigue in stroke, using both a generic and a cognitive fatigue scale. **Design:** Cross-sectional design. **Settings:** Stroke clubs in Nottinghamshire & Lincolnshire. **Participants:** All members of the stroke clubs were invited to join the study. **Measurements:** Participants were assessed on: Fatigue Severity Scale (fatigue), Fatigue Scale for Motor and Cognitive Functions (motor and cognitive fatigue), Brief Assessment Schedule for Depression Cards (depression) and Information Processing Test from the Adult Memory Information Processing Battery. **Results:** Forty-six stroke survivors were included. Time since stroke onset varied from 6 months to 30 years. The majority of participants were identified as fatigued (61% general fatigue; 50% severe cognitive fatigue; 72% severe motor fatigue), not depressed (78%) and not cognitively impaired (74%). No significant associations were found between fatigue, depression and speed of information processing. **Limitations:** Only a limited range of cognitive assessments was used. The lack of significant correlations could either be attributed to the low

levels of speed of information processing impairment of the sample or due to the small sample size or the fact that **Conclusions:** There was no significant relationship between fatigue and speed of information processing. This suggests the results of studies 1 and 2 cannot be attributed to the choice of fatigue scale.

6.2 Introduction

The previous two studies (chapters 3 and 4) did not reveal any significant associations between fatigue and cognitive performance. This applied in both samples of participants who were not depressed and who were depressed.

A systematic review (Lagogianni et al., 2016) found 4 studies that reported a significant relationship between fatigue and cognition post-stroke. Most of these studies used measures of speed of information processing. However these studies mainly used fatigue scales that assess cognitive components of fatigue and measured fatigue as a subjective cognitive complaint (Hubacher et al., 2012; Johansson & Rönnbäck, 2012). Subjective cognitive complaints may be a reflection of mood and confidence rather than cognitive capacity (Lamb et al., 2013; Slavin et al., 2010; Stenfors et al., 2013, 2014). Depression in particular, is frequently associated with fatigue after stroke (Kutlubaev & Mead, 2013; Schepers et al., 2006; Tseng, Billinger, Gajewski, & Kluding, 2010) as well as with cognitive impairment after stroke (Kalaria & Ballard, 2001; Talelli et al., 2004); Radman et al., (2012) have reported that fatigue was associated with impairment in various cognitive domains in people with depression but not in people without depression. Therefore, depression may be a confounding variable that needs to be considered when examining for a relationship between fatigue

and cognitive impairment after stroke.

Studies which used more general fatigue scales, such as the Fatigue Severity Scale, did not reveal any significant associations. The Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) as discussed in previous sections is a commonly used scale of fatigue and it has been used widely in studies of fatigue after stroke. The scale assesses a unified concept of fatigue as opposed to domain specific fatigue scales. As raised in a systematic review by Lagogianni et al., (2016), multidimensional scales of fatigue, although appropriate to measure several aspects of fatigue, may not be appropriate for use in the context of examining their relationship with cognitive impairment, as they may measure cognitive complaints instead of fatigue.

The Fatigue Scale for Motor and Cognitive Functions (FSMC; Penner et al., 2009) assesses motor and cognitive aspects of fatigue. The scale provides a definition of fatigue and the cognitive items are concerned with the impact of fatigue on cognitive domains such as processing speed, memory and attention. A systematic review (Lagogianni et al., 2016) revealed that the FSMC was among the few scales that showed a significant relationship between fatigue and cognitive performance and more particularly between the cognitive subscale and the speed of information processing cognitive test Symbol Digits Modalities Test (SDMT). The FSMC was used because it was the only scale in literature that revealed the most significant correlations with cognitive tests (Hubacher et al., 2012) and differentiates between cognitive and motor components of fatigue. Since this study found significant relationships, this may be due to the use of the FSMC.

The studies conducted previously for this thesis

indicated that post-stroke cognitive impairment in attention and speed of information was not significantly associated with fatigue, as measured by the FSS. However, Speed of information processing has been found to be more highly associated with fatigue than other cognitive components and previous studies have revealed significant correlations between speed of information processing and cognitive fatigue scales (Hubacher et al., 2012; Johansson & Rönnbäck, 2012). In addition, speed of information processing is an underlying component of most cognitive functions (Bugg, Zook, DeLosh, Davalos, & Davis, 2006; Elgamal, Roy, & Sharratt, 2011; Lee et al., 2012 ; McGrath et al., 2011; Rodríguez-Sánchez, Crespo-Facorro, González-Blanch, Perez-Iglesias, & Vázquez-Barquero, 2007; Willmott, Ponsford, Hocking, & Schönberger, 2009; Diamond, Johnson, Kaufman, & Graves, 2008; Kail & Salthouse, 1994; Rosano et al., 2012; Rosano, Brach, Studenski, Longstreth, & Newman, 2007; Su, Wuang, Lin, & Su, 2015; Su et al., 2015) and it is among the most commonly reported cognitive consequences of stroke (Ballard et al., 2003; Barker-Collo, Feigin, Parag, Lawes, & Senior, 2010; Brand et al., 2014; Hochstenbach et al., 1998; Hurford, Charidimou, Fox, Cipolotti, & Werring, 2013; Rasquin, Lodder, & Verhey, 2005).

If cognitive impairment is associated with fatigue after stroke, then speed of information processing is a domain of interest. In addition, based on the previous studies, speed of information processing revealed correlation coefficients which were close to being statistically significant. Therefore, a third study was designed to examine whether the discrepancy in findings was due to the choice of fatigue scales.

6.3 Objectives

The aim was to: 1) assess fatigue in chronic stroke survivors using two fatigue scales, (general and cognitive) and 2) examine their relationship with speed of information processing.

6.4 Ethical Approval and Funding

This study was approved by the faculty of Medicine and Health Sciences Research Ethics Committee, University of Nottingham (reference number: G08122015 SoM RHA; date: 28/01/2016 and was funded by the Vice Chancellor's Scholarship for Research Excellence-European Union; Scholarship Reference Number: RFDX42DB). Further approval was granted by the coordinators of each stroke club included in the study.

6.5 Method

6.5.1 Design

A cross-sectional within subjects design was used. There were two dependent (predictor) variables: fatigue (with three levels: cognitive, motor and general) and mood. The independent variable was speed of information processing, defined as the adjusted score based on the total items attempted on task A and the total items cancelled in task B of the speed of information task. The study used quantitative methods (questionnaires) and correlations were conducted to determine whether there was a relationship between the dependent and the independent variables.

6.5.2 Settings and Recruitment

Participants were recruited from stroke clubs in Nottinghamshire and Lincolnshire. The rationale for recruiting participants from stroke clubs was that we were interested in those who were likely to have high levels of fatigue and cognitive impairment. Previous studies had recruited participants with very low levels of cognitive impairment. By recruiting through stroke clubs we were more likely to include people with impairment of speed of information processing and those with significant fatigue. Potential stroke clubs were identified through web search and were approached by the researcher with a study summary and the university ethical approval. The clubs that agreed to participate were given a poster which advertised the study and an information sheet. The researcher attended the meetings to see whether any of their members expressed interest. Then the researcher spoke to potential participants in person. Those who were interested and available completed the assessments on the day; if there were more people interested and the meeting of the group was completed, an appointment was made for the next meeting and the researcher attended on another occasion. This process was followed for as many times needed until all potential participants were included. Overall study duration was four months (January, 2016-April, 2016) and each assessment took 15-20 minutes per participant.

6.5.3 Participants and Procedure

Inclusion criteria were that the participants were over 18 years old, had had a stroke (single or multiple) and gave consent. Exclusion criteria were that the participant had aphasia or dementia apparent to the group coordinator, such that they were unable to complete the questionnaires. The

participants were given an information sheet and were introduced to the study and given information regarding the study process. They were given the opportunity to have time to think about whether they wanted to join the study or not, and to discuss their concerns or questions with the researcher, the club coordinator or their family. Those who agreed to take part in the study were given a consent form to sign. A copy was given to them as well. It was made clear that their data will be anonymised and treated with confidentiality. All participants were identified by unique study code. They were informed that they could withdraw at any time without it affecting their participation in the group. Participants were assessed either individually or in a small group according to their preference. After giving written consent, participants were asked to fill in a form regarding demographic characteristics (such as: sex, age, ethnicity and marital status) and some questions regarding their stroke (such as: number of strokes, time since last stroke, and side of weakness if any) (see appendices, *Demographic Characteristics*). The assessment included the following questionnaires and cognitive tests:

6.5.4 Measurements

6.5.4.1 Fatigue

Participants completed the *Fatigue Severity Scale* (FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) which is a generic fatigue scale measuring fatigue severity and impact on daily living. Participants with a score ≥ 4 were considered fatigued. For details regarding this scale, please refer to *Unidimensional Fatigue Scales* in chapter 1. It was used for consistency as in the previous two studies it showed that

fatigue was not significantly related to cognitive impairment. Participants with a Fatigue Severity Scale ≥ 4 were considered fatigued. Next, they were asked to complete the *Fatigue Scale for Motor and Cognitive Functions* (FSMC; Penner et al., 2009). This scale was included as previous research (Hubacher et al., 2012) using this scale had found that fatigue was significantly related to cognitive impairment. The scale was initially developed for fatigue assessment in patients with multiple sclerosis. The items are based on other well-known fatigue scales such as the Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989), the Modified Fatigue Impact Scale (MFIS; Paralyzed Veterans of America, 1998) and the Fatigue Assessment Instrument (FAI; Schwartz, Jandorf, & Krupp, 1993) as well as having extra items. It is a two-dimensional scale that differentiates cognitive from motor symptoms of fatigue. It consists of 20 items, 10 of which focus on cognitive symptoms (items: 1, 4, 7, 8, 11, 13, 15, 17, 18, 20) and 10 of which focus on motor symptoms (items: 2, 3, 5, 6, 9, 10, 12, 14, 16, 19). The items are assessed on a 5 point Liker scale (from 'does not apply at all' - 1 point - to 'applies completely' - 5 points). Minimum score is 20 and maximum score is 100. Participants are identified as fatigued or not according to the recommended cut-off scores for the whole scale**:** ≥ 43 mild fatigue; ≥ 53 moderate fatigue; ≥ 63 severe fatigue and the subscales: ≥ 22 mild motor/cognitive fatigue; ≥ 27 moderate motor/cognitive fatigue; ≥ 32 severe motor/cognitive fatigue. The scale takes approximately 5 minutes to complete (Penner et al., 2009).

The initial validation study reported that the internal consistency values for the multiple sclerosis sample was α= .95 for the whole scale, α= .93 for the cognitive subscale and α= .91 for the motor subscale (Penner et al., 2009). In

healthy controls, the scale's internal consistency was: α= .91 for the whole scale, α= .87 for the cognitive subscale and α= .83 for the motor subscale (Penner et al., 2009). The test-retest reliability on patients with multiple sclerosis (4 weeks interval in between assessments) was r= .87 for the total scale, r= .85 for the cognitive subscale and r= .86 for the motor subscale (Penner et al., 2009). A Receiver Operating Characteristic (ROC) analysis revealed 89% sensitivity and 83% specificity for the whole scale, 87% sensitivity and 67% specificity for the cognitive subscale and 89% sensitivity and 86% specificity for the motor subscale in detecting fatigued individuals (compared to the MFIS and the FSS). These values were higher than the sensitivity and specificity values generated for the MFIS (Penner et al., 2009).

One study (Hubacher et al., 2012) has used the FSMC to assess fatigue in stroke survivors therefore evidence regarding psychometric properties in this population is limited. In this study, it was reported that the FSMC had higher sensitivity and specificity values (64% and 71% respectively) for detecting fatigue than the very commonly used FSS and was comparable to the MFIS.

The two fatigue scales were completed in an order determined by random allocation. This was prepared in advance of the study and was intended to minimise order effects.

6.5.4.2 Mood

Depression was a secondary variable and was assessed in order to examine whether participants were significantly depressed and would be used in further analysis to examine its role in potential significant correlations. Therefore, participants were also asked to complete the Brief Assessment

Schedule for Depression Cards scale (BASDEC; Adshead, Cody, & Pitt, 1992) to assess depressive symptoms. Those with score ≥ 7 were identified as depressed. For a detailed description of the scale please refer to methodology of study 1 (chapter 3). This was used for consistency with the other 2 studies.

6.5.4.3 Cognitive Performance

Finally, participants were asked to complete a cognitive task, the information processing test (Task A) from the Adult Memory Information Processing Battery (AMIPB, Coughlan & Hollows, 1985). Speed of Information processing classification was conducted based on the recommended norms according to participants' age. Raw scores were used for correlations. For a detailed description of the test please refer to study 1 methodology (chapter 3). This test was chosen for consistency and because it is a brief test of speed of information processing and can be administered to groups of participants at the same time, as occurred in this study therefore it was easy to administer in busy settings such as stroke clubs.

At the end of the assessment, participants were thanked for their contribution to the study and their willingness to participate. Those who scored high on the depression scale (BASDEC) were offered the opportunity to speak with the researcher in private. They were all informed that low mood is a very common consequence of stroke and that it is normal for them to feel this way. They were encouraged to talk to their GP and seek counselling from free services; they were encouraged to keep attending the stroke groups and share their experiences with fellow stroke survivors as this may help them. They were once again provided with the researcher's details and were encouraged to contact the researcher again if

they needed any help finding the right support. If there was a suspicion or fear of suicidality the principal investigator of the study was informed.

6.5.5 Sample Size Estimation

According to Med Calc software, for 80% power at a 0.05 level of significance, 13 participants were required per correlation. Therefore, in order to examine the relationship between fatigue (two measures), depression and cognitive impairment (one measure) a minimum of 40 participants were required [around 13-15 per correlation (DeLisa et al., 2005; Howell, 2009)]. The effect size that we were interested in detecting was r= .7. This effect size value was chosen in order to detect meaningful effect and not small (potentially attributable to chance) effects.

6.5.6 Statistical Methods

SPSS version 22 for Windows was used to analyse data. Missing values were excluded pairwise to keep most data (Allison, 2001). The descriptive statistics for each variable (including demographic and medical characteristics) were calculated. Skewness and kurtosis were examined to determine the type of analysis to be used. Pearson's correlations were conducted to determine the relationships between the variables.

6.6 Results

6.6.1 Recruitment

Forty-six stroke participants were invited to take part in the study and were assessed for eligibility using the study criteria. All of them were eligible and agreed to take part.

6.6.2 Demographic Characteristics

Location of recruitment and assessment, demographic and medical characteristics of participants are shown in tables 48, 49 and 50 respectively. There were 46 participants with an age range 28-88 years (mean: 67.98; SD: 13.63). Mean time since last stroke onset was 6.11 years (SD: 6.74, range: 6 months-30 years).

Table 48. Location of Recruitment and Assessment

Location		Number	Percentage
Recruitment Site	Lincoln Different Strokes	11	24%
	Gainsborough Stroke Association	7	15%
	Nottingham Stroke Club	16	35%
	Lincoln & District Stroke Club	5	11%
	Scunthorpe & District Stroke Club	1	2%
	Scunthorpe Stroke Association	6	13%

Most participants were recruited from the Nottingham Stroke Club.

Table 49. Demographic Characteristics

Variable		Number	Percentage
Sex	Men	27	59%
	Women	19	41%
Ethnicity	White British	45	98%
	Jamaican	1	2%
	Asian	0	0%
	Black/African	0	0%
	Other	0	0%
Marital Status	Single/Widowed/Divorced	23	50%
	With Partner/Spouse	23	50%

There was a relatively high proportion of men. The majority of participants were white British and half of them were with a partner.

Table 50. Medical Characteristics

Variable		Number	Percentage
Weakness (upper/lower limb/both)	Yes	35	76%
	No	11	24%
Weakness Side	Left	23	50%
	Right	11	24%
	Both	1	2%
Multiple Strokes	Yes	10*	22%
	No	36	78%

*Stroke Number Range: 1-12

The majority of participants had suffered a unilateral stroke, had weakness on their left side and had one stroke incident.

Table 51 provides a summary of the data distribution scores which was examined in order to determine whether data were normally distributed (in order to determine the most appropriate method of statistical analysis).

Table 51. Distribution of Scores on Baseline Questionnaires

Measure	n	Percentiles				Mean	S.D.	Skewness	Kurtosis
		25th (low)	50th (Median)	75th (upper)	IQR				
Brief Assessment Schedule for Depression Cards	46	1.00	3.00	6.00	5	4.22	4.32	1.36	1.52
Fatigue Severity Scale	46	2.77	4.55	5.66	2.89	4.19	1.81	-0.43	-1.13
Fatigue Scale for Motor and Cognitive Functions (Total)*	46	49.25	67.50	79.25	30	62.93	19.92	-0.62	-0.55
Fatigue Scale for Motor and Cognitive Functions (Cognitive)*	46	20.75	32.50	39.25	19	30.26	10.26	-0.38	-0.98
Fatigue Scale for Motor and Cognitive Functions (Motor)*	46	26.00	35.50	40.00	14	32.67	10.19	-0.87	-0.06
Adult Memory Information Processing Battery (Adjusted Score)*	46	24.78	37.87	50.86	26.08	37.85	16.13	0.10	-0.78

Skewness and kurtosis were examined and it was observed that participants' scores on most questionnaires were normally distributed (<1; Bulmer, 1979; Miles & Shevlin, 2001). Therefore parametric statistics were used to analyse even the skewed data for consistency.

Table 52 summarises the percentage of impairment on each variable according to the cut-off scores of each measure:

Table 52: Frequency of Impairment in Each Domain

Domain	**Measure**	**Number Above Cut-Off Scores (Percentage)**
Depression	Brief Assessment Schedule for Depression Cards	10 (22%)
Fatigue	Fatigue Severity Scale	28 (61%)
Fatigue	Fatigue Scale for Motor and Cognitive Functions (Total)	mild: 9 (20%); moderate: 10 (21%); severe : 27 (59%)
Cognitive fatigue	Fatigue Scale for Motor and Cognitive Functions (Cognitive)	mild: 12 (26%); moderate: 11 (24%); severe : 23 (50%)
Motor Fatigue	Fatigue Scale for Motor and Cognitive Functions (Motor)	mild: 7 (15%); moderate: 6 (13%); severe : 33 (72%)
Speed of Information Processing	Adult Memory Information Processing Battery (Adjusted Score)	12 (26%)

The proportion of participants with impairment of speed of information was low. The majority of the participants were identified as fatigued on the Fatigue Severity Scale and as severely fatigued on the Fatigue Scale for Motor and Cognitive Functions Scale. The majority of the participants were not depressed.

6.6.3 Inferential Statistics

Table 53 summarises the Pearson's correlations that were conducted to determine the relationship between fatigue, speed of information processing and depression.

Table 53: Correlations Between Speed of Information Processing, Fatigue and Depression

Correlation with Speed of Information Processing	Number	Correlation Coefficient	P Value
Brief Assessment Schedule for Depression Cards*Adult Memory Information Processing Battery (Adjusted Score)	46	0.02	0.89
Fatigue Scale for Motor & Cognitive Functions (Cognitive)*Adult Memory Information Processing Battery (Adjusted Score)	46	0.20	0.17
Fatigue Scale for Motor & Cognitive Functions (Motor)*Adult Memory Information Processing Battery (Adjusted Score)	46	0.09	0.52
Fatigue Severity Scale* Adult Memory Information Processing Battery (Adjusted Score)	46	-0.03	0.80

There were no significant correlations ($p>0.05$) between the level of fatigue and speed of information processing or between depression and speed of information processing.

6.7 Discussion

The results of the study revealed low frequency of impairment in speed of information, low depression frequency and high fatigue frequency. There was no significant relationship between any kind of fatigue (general, cognitive or motor) and cognitive impairment. In particular, of the four correlations calculated none was statistically significant with very small correlation size. Depression as measured by the Brief Assessment Schedule for Depression Cards, and fatigue

as measured by the Fatigue Severity Scale and the Fatigue Scale for Motor and Cognitive Functions scale and speed of information processing as measured by Adult Memory Information Processing Battery were not significantly associated in the sample examined. It is worth noting that while there were no significant correlations between any of the variables, the size of the correlation between speed of information processing and the cognitive subscale of the FSMC was higher than the rest of the correlations; however this confirms that cognitive fatigue scales seem to be measuring cognitive complaints. The fact that there were no significant associations between fatigue and cognition may be attributed to several factors. To begin with, the sample had very low frequency of speed of information processing impairment. This was despite including chronic stroke patients who were attending stroke clubs. This is consistent with the previous two studies conducted for this project; even though speed of information processing is estimated to be among the most common cognitive consequences of stroke and is expected to cause many problems for stroke survivors (Winkens et al., 2006; Cumming et al., 2013). However, in all three of our studies, stroke participants had very low levels of impairment of speed of information processing. This may be attributed to the test used. However, the speed of information processing test from the Adult Memory Information Processing Battery has been assessed for its utility in measuring processing speed capacity in people with multiple sclerosis and was proven to be reliable to detect major deficits in information processing speed (Vlaar & Wade, 2003) while another study has shown that the test is sensitive enough to distinguish between impaired and intact information processing speed in people with psychiatric disorders such as schizophrenia and bipolar

disorder (Balaban, Atagun, & Ozguven, 2014). However, it may be that the test is only capable of detecting major deficits and not more subtle deficits as this may be the case in stroke. Despite the high negative correlation (r= .81) that was reported by Weldon, (1998) between performance on the test and mood as measured by the Wimbledon Self Report Scale (Coughlan & Storey, 1988) the current study did not reveal any significant relationship between mood and speed of information processing.

With regards to fatigue, the previous studies and the systematic review (Lagogianni et al., 2016) indicated that using the Fatigue Severity Scale as opposed to a more domain specific fatigue scale may have masked the potential relationship between fatigue and cognitive impairment as the scale does not measure cognitive components of fatigue. This study however shows that even when using a cognitive fatigue scale there was no significant relationship between any type of fatigue and speed of information processing. This may be attributed to the fact that there is simply no relationship to be detected. However, it is worth noting that, despite not being significant, the correlation between the cognitive sub-scale of the FSMC and speed of information processing was higher than the correlations between speed of information processing and the motor sub-scale of the FSMC or the FSS and much closer to being significant. Perhaps a larger sample would have allowed a potential relationship to emerge.

Sample characteristics should also be considered when interpreting the results of this study. Participants were self-selected; therefore it is likely that only individuals with a particular interest in the study (such as people who experienced fatigue, or individuals who are not very depressed and motivated enough to join a study) were engaged. This

may explain the high frequency of fatigue and low frequency of depression. Cognitive impairment was much higher than that reported from participants in the previous two studies which indicates that perhaps participants who joined this study were particularly interested in the benefits of the findings as they are probably more affected by their stroke (selection biases). Stroke clubs aren't necessarily very representative of stroke population because they usually consist of people with a greater stroke impact.

Although fatigue may increase with the passage of time, which is in accordance with previous findings of this project and other studies (Hubacher et al., 2012; Schepers et al., 2006; Winkens, Van Heugten, Fasotti, Wade, et al., 2009), it may be that different factors are associated with the experience of fatigue in the acute and the chronic phases. Studies that assessed the relationship between fatigue and cognitive impairment in the chronic phase (Naess, Nyland, Thomassen, Aarseth, & Myhr, 2005; Naess & Nyland, 2013) also did not detect any significant relationship between fatigue and cognition however they used the MMSE which as discussed previously, is not suitable to measure subtle cognitive impairment after stroke.

The only other study that assessed fatigue and cognitive impairment in the chronic phase was the one conducted by Johansson & Rönnbäck (2012), where a significant relationship between mental fatigue and speed of information processing was revealed; however the speed of information processing test that was used was a digit symbol test [Digit Symbol Coding Test (DSCT; Wechsler, 2003)] so again their results cannot be directly compared to the current ones. The DSCT is a test that is used to measure speed of information processing; however several studies in people with

schizophrenia, psychosis and healthy individuals have shown that the performance on the test is not restricted to speed of information processing and it relies on several other abilities such as learning, memory, writing speed, motor skills and sustained attention (Bachman et al., 2010; Cornelis et al., 2014; Crowe et al., 1999; Dickinson, 2008; González-Blanch et al., 2011; Joy, Kaplan, & Fein, 2004; Kreiner & Ryan, 2010; Wechsler, 2003). It is therefore possible that impairment in this test does not necessarily reflect impairment in speed of information processing but also in the aforementioned components.

Hubacher et al., (2012) found a significant relationship between fatigue and speed of information processing; the authors used the FSMC, the MFIS and the FSS to measure fatigue. Their results indicated a significant relationship between the total scores and the cognitive sub-scores of fatigue in the first two scales but not in the FSS. Initially it was suspected that they found a significant relationship because they used the scales that assess cognitive components of fatigue and more specifically the relatively new FSMC (Hubacher et al., 2012; Penner et al., 2009). However, these authors used the SDMT and the PASAT to measure speed of information processing. They found that the SDMT was significantly associated with both the FSMC and the MFIS (total scores and sub-scale scores) while the PASAT was only significantly associated with the FSMC scores. The SDMT is very similar to the DSCT in administration and scoring and therefore measures the same aspects.

The PASAT, is a test of auditory speed of information, working memory and flexibility (Strauss et al., 2006). It has been reported that the administration of PASAT causes frustration which affects participants' performance; in

addition, speech ability and speed can also affect the outcome of the test (Tombaugh, 2006). In addition, a study on people with multiple sclerosis has shown that participants find PASAT very unpleasant compared to other tests such as the SDMT and that those who disliked it were more likely to have lower performance on the test (Walker et al., 2012). It is therefore reasonable to suggest that the two studies with similar design to ours that reported a significant relationship have used cognitive tests that assess multiple components and not just speed of information processing. In addition, verbal short-term memory was the only other component that was associated specifically with the cognitive subscales of the MFIS and the FSMC and not with the motor scales. Although speed of information processing is associated with memory and attention (McGrath et al., 2011; Rodríguez-Sánchez et al., 2007; Willmott et al., 2009), the above tests seem to rely more on these components. Our study used the Information Processing From the Adult Memory Information Processing Battery (AMIPB, Coughlan & Hollows, 1985) which is a more direct test of speed of information processing, is less frustrating and controls for motor speed.

The study had some limitations. The convenience sample recruited was not necessarily very representative of the general stroke population as it was self-selected from stroke clubs. Stroke clubs are usually attended by stroke survivors with longer-term issues due to their stroke and the fact that they were willing to participate in the study may indicate that they were more affected in the variables of interested than the average stroke survivors. In addition, the sample size is not large enough generalize and applicability of the findings needs to be done with caution. Finally, cognitive assessment was limited to one cognitive domain; speed of

information processing. Impairment of attention is very common after stroke and speed of information processing may be only partially involved in the presence of fatigue as it is an overlapping component of other cognitive functions. It is therefore possible that fatigue and speed of information processing were not associated in this occasion because the speed of information processing test used eliminates the assessment of other commonly associated components such as memory.

Despite the limitations, the study also had strengths. This study provides information on two fatigue scales and across three domains of fatigue: motor cognitive and general. The study showed that regardless of the fatigue type, fatigue is not associated with speed of information processing. What distinguishes the study, is the fact that, unlike other studies, it used a tests of speed of information processing that does not rely on memory components.

6.8 Conclusion

There was no significant relationship between fatigue and speed of information processing regardless how fatigue was measured. It is therefore reasonable to suggest that there is either no significant relationship between fatigue and cognitive impairment or that this presumed relationship may lie between fatigue and other cognitive domains such as memory. Future studies may benefit from including memory specific tests to explore this further.

Chapter 7: Critical Appraisal

7.1 Abstract

The literature and systematic reviews identified a lack of robust studies with appropriate fatigue and cognition tests which are sensitive to stroke related impairments. The three studies conducted for the thesis indicated that fatigue after stroke was not significantly associated with speed of information processing, or selective and sustained attention in stroke survivors. This was irrespective of the experience of depression or the fatigue scale used. While these findings are consistent with literature, and there may not be any relationship to detect, it is possible that other types of cognitive impairment are related to fatigue. The findings of the thesis are discussed in this chapter in terms of their limitations, strengths, applicability and the basis they establish for future research.

7.2 Objectives

The aims of this final chapter are to: 1) summarise the findings of the thesis as a whole, 2) explain the link between the studies, 3) reflect on the limitations and strengths of the studies, 4) discuss the application of the findings to clinical practice and 5) suggest future directions for research.

7.3 Summary of Findings

Some research suggests that fatigue is very common and debilitating after stroke (Annoni, Staub, Bogousslavsky, & Brioschi, 2008; Schepers, Visser-Meily, Ketalaar & Lindeman, 2006; Naess, Nyland, Thomassen, Aarseth, & Myhr, 2005; Carlsson, Moller, & Blomstrand, 2004; De Groot et al., 2003; Glader et al., 2002; Ingles et al., 1999; Staub & Bogousslavsky, 2001; Winward, Sackley, Metha, & Rothwell,

2009). Many stroke patients complain about mental fatigue, and refer to their need to take frequent breaks and to slow down when conversing or running errands that require mental effort (Winkens et al., 2006; Barker-Collo et al., 2010; Hochstenbach et al., 1998; Hurford et al., 2013). Cognitive problems such as difficulties with processing information and attention are also common after stroke (Hyndman et al., 2008; McDowd, Filion, Pohl, Richards, & Stiers, 2003; Ballard et al., 2003; Barker-Collo, Feigin, Parag, Lawes, & Senior, 2010; Brand et al., 2014; Hochstenbach et al., 1998; Hurford, Charidimou, Fox, Cipolotti, & Werring, 2013; Rasquin, Lodder, & Verhey, 2005). Mental fatigue may be due to difficulties in attention, such as concentrating for long periods of time, and speed of information processing, that is the rate at which people can think through problems (Chaudhuri & Behan, 2004).

This PhD thesis was designed to examine the relationship between fatigue and cognition after stroke. First, a systematic review was conducted to gather information about all existing literature. The review showed that the majority of the studies that have attempted to examine the relationship between fatigue and cognition after stroke, have used screening tests insensitive to stroke related cognitive problems and did not reveal any significant associations between fatigue and cognition. However, some studies have used domain specific cognitive tests and cognitive fatigue scales and these studies showed that attention and speed of information processing may be associated with fatigue.

Three studies were conducted and all showed that attention and speed of information processing were not associated with fatigue after stroke. The first two studies recruited participants from the NotFAST study (a large scale

study that examined fatigue after first stroke) while the third recruited participants from stroke clubs. In each study fatigue was measured using the Fatigue Severity Scale. Cognitive impairment was assessed in domains of speed of information processing and attention. In addition, a principal component and a reliability analysis were conducted to assess the unidimensionality and internal consistency of the Fatigue severity Scale in the current sample and to compare to those reported in literature. The scale revealed unidimensionality and high internal consistency, in agreement with previous studies (Lerdal & Kottorp, 2011; Valko et al., 2008). In all three studies no significant association was found between attention, speed of information processing and fatigue in either acute or chronic stroke phase. People with depression were examined separately from those without and in both groups, fatigue was not associated with attention or speed of information processing, regardless depression levels. These findings support some previous studies that have examined fatigue in relation to general and domain specific measures of cognitive impairment (Naess et al., 2005; Naess et al., 2013; Kutlubaev et al., 2013; Winkens et al., 2009). It is possible that only mental fatigue is associated with impairment of attention and speed of information processing. However, cognitive symptoms of fatigue which are expressed in the form of perceived cognitive abilities may be due to other psychological and metacognitive factors, such as confidence and perceived capacity (Maaijwee et al., 2014; Slavin et al., 2010; Lamb, Anderson, Saling, & Dewey, 2013; Slavin et al., 2010; Stenfors, Marklund, Magnusson Hanson, Theorell, & Nilsson, 2013, 2014).

Studies in people with other neurological disorders such as multiple sclerosis and traumatic brain injury, have shown

that fatigue is associated with perceived cognitive abilities but not with actual cognitive performance (Johansson, Berglund, & Rönnbäck, 2009; Jougleux-Vie et al., 2014; Kinsinger, Lattie, & Mohr, 2010; Middleton, Denney, Lynch, & Parmenter, 2006) - this however was not the case in the final study of the thesis in which it was found that cognitive fatigue as measured by perceived cognitive complaints, is not associated with speed of information processing and attention in chronic stroke survivors. Therefore, it seems likely that there is no significant relationship between impairment of attention and speed of information processing and fatigue after stroke. Post-stroke fatigue is a multifaceted phenomenon and may be explained by various factors such as health and mobility problems, mood and lesion location (Annoni et al., 2008; De Groot et al., 2003; Stein et al., 1996; Tang et al., 2010; van Eijsden et al., 2012). However, it is possible that mental fatigue may be due to other types of cognitive problems, such as impairment of working or verbal memory. The unique contribution of this piece of work, stems from an integration of findings of all studies conducted, combined with the systematic literature review.

7.4 Limitations

The studies had some limitations that need to be acknowledged. The main limitations are relevant to: low frequency of cognitive impairment, sample sizes, methods of analysis, follow-up assessments and limited cognitive domains assessed. One of the main limitations of the studies is that there were low levels of cognitive impairment. The reason for that is probably the high percentage of people with lacunar strokes in studies 1 and 2 which also indicates that the sample was not very representative of all stroke patients. However,

even in study 3 which recruited people in the chronic phase from stroke clubs there was a low level of impairment. The frequency of cognitive impairment was between 5% and 26%. However, low frequency of cognitive impairment has been reported in other studies (Schepers et al., 2006; van Eisjsden et al., 2012; Kutlubaev et al., 2013) with MMSE scores ranging from 27 to 28. However, this may have occurred because the majority of the studies in this review used brief cognitive screening measures such as the MMSE which, as mentioned in chapter 1, is insensitive to detect cognitive impairments after stroke (Bour et al., 2010; Nys et al., 2005; Radman et al., 2012; Spencer et al., 2013; Strauss et al., 2006; Woodford & George, 2007). Whereas in the studies in this thesis, domain specific tests were used. So perhaps the findings of this study are only applicable to those with mild or no cognitive impairment.

A further point to consider is the fact that the whole thesis focused primarily on associations. As it was mentioned in chapter 1, correlational designs are appropriate when examining the association and the predictive validity of some variables; however, non-linear relationships (U shaped) may also occur between variables and correlations do not detect such relationships. In this thesis, the focus was to assess whether fatigue and cognition after stroke are associated, which were not. However, there is a possibility that, despite the lack of significant p values, the two variables are involved in a curved relationship which would answer the question of whether more cognitive impairment cause more fatigue. It is possible that other study designs may contribute to the understanding of the relationship between fatigue and cognition but were not considered in this project. Perhaps comparing stroke patients with fatigue to those without

fatigue on measures of cognition, or cognitively impaired stroke patients to cognitively intact on measures of fatigue, may have revealed significant differences. However, the method used was able to detect the effect of the degree of fatigue and level of cognitive impairment, which would not have been detected if group comparisons had been used. It is also important to note that the systematic review only considered studies with correlations and may have missed other studies.

Another limitation was the fact that there were no follow-up assessments with regards to cognition. This was because the study was embedded in the NotFAST study, which included only questionnaire follow-up assessments. Doing so would have allowed monitoring the progress of cognitive impairment over time and see if follow-up cognition was associated with follow-up fatigue. It may be that follow-up fatigue differs from fatigue at baseline and that at follow-up cognitive performance is more related to fatigue than at baseline. This however was not confirmed by the third study which included participants who were recruited late after stroke.

Another potential limitation was the fact that in all studies only speed of information processing and attention were considered. Hubacher et al., (2012) found that speed of information processing tests such as the Symbol Digit Modalities Test (SDMT; Smith, 1991) and the Selective Reminding Test (SRT; Buschke & Fuld, 1974) were significantly associated with scores in the cognitive fatigue scales. The SDMT assesses working memory as well and the SRT assesses verbal memory performance. However, other studies (Kutlubaev & Mead, 2013; Schepers et al., 2006) that have used the MMSE which also assesses memory, did not

reveal any significant associations. However, the MMSE only superficially assesses recall (retrieval) memory. Based on these findings it is reasonable to suggest that perhaps working and verbal memory components are more likely to be associated with fatigue after stroke and that if so, these are responsible for any subsequent deterioration in speed of information processing or attention.

Finally, another limitation is the fact that there were small samples for studies 2 and 3. Therefore generalisation of findings should be done with caution; however these findings are in agreement with study 1 and literature (Lagogianni et al., 2016). Despite having a smaller sample, power calculation for study 3 showed that the sample recruited was satisfactory to address the study questions as a more restricted range of measures was used. Depression is a very complex and common complication in the assessment of fatigue and has not been thoroughly discussed in conjunction with cognition before. Excluding people with depression allowed for a more clear understanding of fatigue after stroke without the presence of depression; most studies don't account for that and therefore the majority of the data available comes from populations with comorbid depression. This is why NotFAST decided to exclude people with depression, which consequently also affected the recruitment of depressed individuals for the thesis. The sample for study 2 was too small to be combined with study 1 sample. Data from study 2 was analysed separately from study 1 because study 1 was a part of NotFAST. If the sample sizes had been larger perhaps some relationships would have been detected but as the associations were nowhere near significant it is unlikely that potential relationships were missed.

7.5 Strengths

Despite the limitations discussed above, this project also has strengths. The main strengths are: it provides a systematic review, it assesses people with stroke in both the acute and chronic phases, used domain specific cognitive tests, two fatigue scales and had a large overall sample. To begin with, there was no other systematic review that focused exclusively on the relationship between cognition and fatigue after stroke. The one produced as part of this thesis provided a summary of all the available studies and examined the strengths and weaknesses in their designs. Furthermore, the thesis attempted to examine the potential relationship between speed of information processing, attention and fatigue in both the sub-acute and the chronic phase of stroke.

Another distinctive characteristic of the studies conducted is the fact that they assessed cognitive components on domain specific tests, as opposed to general screening tests that tend to assess multiple and overlapping cognitive components (such as memory and speed of information processing together). The thesis attempted to isolate the domains of interest (attention and speed of information processing) without considering memory components; it is however difficult to exclude working memory as it is an underlying component of most cognitive aspects (including attention and seed of information processing). The tests used in the thesis have not been used before in similar contexts.

The unidimensionality and the internal consistency of the Fatigue Severity Scale was also assessed and consistent with other reports (Lerdal & Kottorp, 2011; Valko et al., 2008). Finally, a large sample was recruited for the first study (268) and overall there is data from 331 individuals in the project which indicates that there was a good sample size. In

addition the thesis examined the usefulness of a cognitive fatigue scale over a more general fatigue scale which has been done before (Hubacher et al., 2012), but has not been discussed in a cohesive manner as in this thesis. The thesis raises a valid, ongoing issue and addressed gaps in literature.

7.6 Application of Findings and Future Directions

The applicability of findings of the thesis is threefold and covers all aspects of research, clinical and theoretical settings. There are several implications for future *research*. Three indicative studies have been produced that consistently revealed the same results. In accordance with other studies (Schepers et al., 2006; Winkens, Van Heugten, Fasotti, Wade, et al., 2009), and in light of the findings from the systematic review (Lagogianni et al., 2016), it is reasonable to suggest that attention and speed of information processing are not associated with fatigue after stroke. Most of the studies focus on speed of information processing and attention because patients' description of fatigue indicates these areas as problematic (Cumming et al., 2013) as mentioned in chapter 1. Those studies that used more extensive and demanding cognitive tests (Hubacher et al., 2012; Johansson & Rönnbäck, 2012) were able to reveal significant correlations with fatigue, but mostly when fatigue was measured on scales that accounted for cognitive components of fatigue such as the FSMC (Penner et al., 2009) and the Mental Fatigue Scale (Johansson, Starmark, Berglund, Rödholm, & Rönnbäck, 2010). Therefore, it is possible that the majority of the existing studies did not reveal similar results because either they used global cognitive assessments or because they did not use cognitive fatigue scales. Therefore, future studies may benefit from including cognitive and general fatigue scales

such as the FSS to examine the differences in their relationship of cognitive impairment.

Furthermore, it seems that cognitive fatigue scales that measure symptoms in the form of subjective cognitive complaints are more likely to produce associations with cognitive tests but this could be merely attributed to the fact that the subjective perception of cognitive impairment may correlate to an extent with objective cognitive performance (van Heugten, Rasquin, Winkens, Beusmans, & Verhey, 2007). While cognitive fatigue scales are more likely to allow significant relationships to show, it is doubtful that they contribute to the understanding of the cognitive mechanisms of fatigue. Therefore future studies could include subjective versus objective domain cognitive tests such as the SDMT or the TMT, and examine the differences in their relationship to general fatigue scales. It is however worth exploring further the role of working memory components in the presence of fatigue as evidence suggests that this may be more likely associated with fatigue. For instance, Hubacher et al., (2012) revealed significant associations between cognitive fatigue scales and speed of information processing tests that rely on working memory components. More studies are needed with measurements that are sensitive to cognitive impairment after stroke, especially working memory related aspects, and with fatigue scales that do not address cognitive components of fatigue, id est. general fatigue scales such as the FSS.

Studies will benefit if they include global (such as the MoCA) and domain specific cognitive tests (such as the SDMT, speed of information processing subtest from the AMIPB and TMT as mentioned in chapter 1) as well as general (FSS) and cognitive fatigue scales (FSMC, MFIS) in acute and chronic stroke survivors to pinpoint the precise cognitive areas that

are associated with fatigue (if any). This will enable a more accurate investigation of the relationship between fatigue and cognitive impairment after stroke. The findings of the current project suggest that depression is not related to the cognitive components measured, however, given the high correlations reported between fatigue and depression (Hubacher et al., 2012; Lerdal et al., 2011; Radman et al., 2012) it would be interesting to examine the role of depression in a potential relationship between working memory and fatigue after stroke. Therefore future studies should take this into consideration and include depression scales (such as the BDI or the BASDEC) in their analyses and interpretations. These findings are likely to trigger a shift in the direction of future research and to mold study designs and choice of instruments.

The long term *research* implication of this thesis is to enhance understanding regarding the cognitive components that are associated with fatigue and to provide a solid ground for future study designs. It has been shown that cognitive rehabilitation interventions may reduce physical and cognitive fatigue symptoms in people with multiple sclerosis (Catalan et al., 2011). Therefore, future studies could examine whether this also applies in people with stroke. I believe that understanding the mechanisms behind the relationship between fatigue and cognition after stroke, may help in developing psychological or multidisciplinary stroke-specific interventions for the management of fatigue.

The *clinical* implication of the findings is that fatigue is likely to be due to factors others than cognitive impairment. The NotFAST study (Drummond et al., 2016) found that mobility and mood were the main determinants of fatigue so perhaps these should be the focus of treatment rather than cognition. There is currently no multidimensional intervention

for fatigue; the findings of this study will inform the design of fatigue interventions indicating that perhaps cognitive rehabilitation is not a priority for fatigue interventions.

The implication for *theory* is that working memory components may be involved in attention and speed of information processing and these may be associated with fatigue. Previous studies have neglected the assessment of working memory impairment in depth. The last study showed that the use of a cognitive fatigue scale alone does not facilitate the detection of a relationship between fatigue and cognition. The cognitive tests that were used in other studies (Hubacher et al., 2012; Johansson & Rönnbäck, 2012) that reported a significant relationship between fatigue and cognition assessed overlapping cognitive components (working memory, sustained attention and speed of information processing). Only one study considered verbal memory (Hubacher et al., 2012) and found significant associations with fatigue scales. Therefore, perhaps certain types of memory when assessed individually may reveal associations with fatigue and future studies could include such tests in their designs.

Evidence of associations between attention impairment, slowed mental speed and post-stroke fatigue could also indicate involvement of working memory (encoding memory) which is an underlying component of the above and supports their maintenance. Working memory is essential in the regulation and maintenance of attention components (Sreenivasan & Jha, 2007) which also appear to be associated with learning and recalling information (Engle, 2002). Speed of information processing and attention seem to be the areas most frequently associated with fatigue as indicated by previous studies (Hubacher et al., 2012; Johansson &

Rönnbäck, 2012; Radman et al., 2012). However, evidence is not robust and further studies are needed to strengthen such theory. Since impairment in mental speed and attention can compromise working memory functioning and/or vice versa (Cowan, 2008; Lamar & Raz, 2007), it seems essential to further investigate the relationship between working memory and fatigue.

There is still need for future well-designed studies to assess the topic in question as it is still unclear as to whether cognitive impairments, other than in the domains of attention and speed of information processing, are associated with fatigue after stroke. It would be helpful if future systematic reviews are designed to evaluate studies with different designs (as the one provided here only focuses on correlations); perhaps studies with different designs can provide extra information about the relationship between fatigue and cognition after stroke and may inform future study designs to better capture such a relationship. Future studies would also benefit from recruiting more representative samples of stroke patients, having larger samples and incorporating follow-up assessments in their designs. Follow up assessments provide information that is important for intervention programs and treatments. So for instance, we can see if the majority of people still suffer, or start suffering at 6 months post stroke and can address what can be done at baseline (early in the acute stroke phase) to prevent that.

In addition, study designs need to be chosen carefully. Cross-sectional studies may be convenient and useful to assess a temporal association between variables; however cross-sectional studies cannot suggest any effect or causation between the variables (Mann, 2003; Sedgwick, 2014). Therefore, apart from longitudinal designs, future studies may

consider examining the topic of interest in terms of mean differences in people with and without fatigue/cognition which has previously been able to show that stroke survivors with fatigue have significantly slower speed of information processing and worse memory than those without (Pihlaja, Uimonen, Mustanoja, Tatlisumak, & Poutiainen, 2014). Finally, time since stroke onset should also be considered as there are mixed results from studies in the sub-acute and the chronic phase of stroke and it is unclear if different factors underline the relationship (if any) between fatigue and cognition soon after stroke or later in the chronic phase.

7.7 Conclusions

The main conclusion of this project overall is that there is no significant relationship between fatigue and speed of information processing or attention after stroke. There seems to be a consensus that the majority of the studies conclude that fatigue and cognition are not associated; so this conclusion is consistent with that of the systematic review.

7.8 Lay Summary (Approved by the Stroke Research Partnership Group)

Fatigue is very common after stroke and many stroke patients complain about being unable to keep up with conversations or cope with everyday tasks due to their fatigue. Fatigue is different from conventional tiredness because it does not get better with rest. Stroke patients describe fatigue in ways which suggest their fatigue may be due to impairments in attention or speed of information processing. Attention refers to the ability to selectively focus on particular stimuli over others. Speed of information processing refers to the amount of time taken to process

information and complete tasks. Previous studies mostly suggest that there is no relationship between fatigue and cognitive impairment after stroke, but a few studies have found a relationship between fatigue and memory, attention and speed of information processing. These studies use tests of specific cognitive abilities rather than measures of global impairment to assess cognition which may be why they came up with different results. They also used fatigue measures which assess reported cognitive effects of fatigue. It is therefore of interest to examine the relationship between fatigue and cognition further with more appropriate tests.

This PhD thesis was designed to examine whether there is any relationship between fatigue and attention and speed of information processing after stroke. The reason that attention and speed of information processing were chosen over other domains is because, attention and speed of information processing are the most common cognitive impairments after stroke and, when stroke patients refer to their fatigue symptoms usually associate them with these cognitive domains (for example: "it takes me longer to understand things" or "I can't keep up with conversations"). In addition, most of the previous studies which found significant relationships between fatigue and cognition associated fatigue with attention and speed of information processing over other cognitive domains. Memory was not included in the study because memory is highly associated with attention and speed of information processing and many memory tests measure speed of information processing and attention. This would make it very difficult to attribute a significant relationship to a distinct cognitive domain. This was also observed in other studies and is perhaps the reason of the understanding of the relationship between fatigue and cognition after stroke. The

thesis was a part of another study (Nottingham Fatigue After Stroke Study-NotFAST) which investigated the relationship between fatigue and other factors, such as depression, anxiety and mobility.

The studies used cognitive tests and fatigue scales which are suitable for people who have had a stroke. People with stroke were identified either through the NHS or through stroke clubs. Three studies were conducted and all showed that fatigue was not associated with speed of information processing or attention. Some of the stroke patients were also depressed but whether they were depressed or not did not make any difference to the findings. However, NotFAST found a relationship between fatigue and: depression, mobility and anxiety.

This means that fatigue, attention and speed of information processing are not associated after stroke regardless of the level of depression. It is therefore very possible that fatigue after stroke is attributed to factors other than cognition such as depression, mobility and anxiety. However, there are other cognitive domains that may be associated with fatigue, such as memory. Memory impairments are also common after stroke and may contribute to the experience of fatigue. Future studies should focus on memory domains and their relationship with fatigue after stroke. The findings indicate that other factors may be more important in the development of fatigue and that cognitive training is not likely to be appropriate to help with the problem caused by fatigue after stroke.

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