MS patients' reports of their cognitive functioning: neuropsychological test performance and influence of depression

Helen Rhianne Jones

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This work has not previously been accepted in substance for any degree and is not concurrently submitted in candidature for any degree.

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ABSTRACT

Background: Cognitive impairment is a leading cause of disability for Multiple Sclerosis (MS) patients. Assessing cognitive impairment on a routine basis can be difficult and there is often a reliance on patients' own reports of their cognition.

Objective: To compare MS patients' reports of their cognitive functioning with their performance on neuropsychological tests and consider the role of depression. A secondary aim was to expand the subjective cognitive measure, The Perceived Deficits Questionnaire (PDQ), to include questions about processing speed and language. This formed the extended PDQ (PDQ-E), and aimed to provide patients with a broader subjective measure to report their cognitive functioning.

Method: 82 MS patients completed a battery of neuropsychological tests to determine cognitive functioning. The PDQ and PDQ-E assessed patients' subjective cognitive reports, and the Beck Depression Inventory-Fast Screen (BDI-FS) measured levels of depression.

Results: A significant difference in PDQ scores was found between patients who were cognitively impaired and unimpaired on neuropsychological tests. A significant relationship between patients' PDQ score and two specific neuropsychological tests (the Stroop and Digit Span) was also found. Depression highly correlated with PDQ scores, but the effect of neuropsychological test performance on PDQ scores was not significantly different for patients who were depressed and not depressed. Expanding the PDQ did not affect what patients reported, as analyses using the PDQ and PDQ-E were comparable. Subjective processing speed questions added to the PDQ (forming PDQ-E) did however appear relevant to patients' concerns.

Conclusion: Patients' reports reflect their performance on neuropsychological tests, but correlate more strongly with depression. Services relying on patients subjective cognitive reports should consider depressive symptoms when determining future intervention, as depressed patients are more likely to report problems with their cognition.

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CHAPTER ONE

INTRODUCTION

1. OVERVIEW OF INTRODUCTION

This introduction provides the background to the present study. Firstly, the focus of the study is described and the importance of research in this area is clarified. This is followed by an introduction to Multiple Sclerosis (MS) including classification, epidemiology and impairment associated with the disease. In addition, the effect MS has on patients' quality of life (QoL), including cognitive impairment, fatigue and depression are discussed. An introduction to a systematic review of literature into how patients' cognitive functioning on neuropsychological tests compares with their subjective cognitive reports is then presented.

1.1 FOCUS OF THE RESEARCH

Cognitive impairment is now recognised as one of the leading causes of disability among patients with MS (Amato, Zipoli & Portaccio, 2006; Rao, 1997). The negative impact of cognitive impairment on employment, relationships, and activities of daily living means that detection and monitoring of its progression is therefore essential (Mitchelle *et al*, 2006). Further, National Health Service guidelines have recommend that "any person with MS complaining of cognitive problems, and any person where this is suspected clinically, should be offered a formal cognitive assessment, coupled with specialist advice on the implications of the results" (NICE, 2003, p23).

Patients functioning on neuropsychological tests are regarded as the most comprehensive assessment of their cognitive functioning (Fischer *et al,* 2001; Mitchelle *et al*, 2006), but whilst these are 'best practice' guidelines, the reality of implementing this in clinical practice is difficult. With no clear pattern of when cognitive impairment presents, and its presence not being required to diagnose MS, clinicians are often left with the uncertainty about knowing *when* cognitive impairment should be assessed, and cognitive difficulties such as slowed processing speed and 'forgetfulness' may be attributed to other symptoms of MS, e.g., fatigue (Rogers & Panegyres, 2007). Comprehensive neuropsychological testing can also be expensive (due to the expertise required for their interpretation) and time consuming, which often limits patients access to routine cognitive assessment.

Therefore, the difficulty associated with assessing cognitive impairment on a routine basis means there is often a reliance on patients to report whether or not they are experiencing problems with their cognition. As further assessment and intervention may be based on patients' reports of their cognition, it is important to distinguish if patients' reports of their cognitive functioning reflect their performance on neuropsychological tests, and if other factors impact on this relationship. For instance, the detrimental effect MS can have on patients' QOL has been well documented (see section 1.4), and there is a likelihood that factors such as depression will influence patients' perceptions of their cognitive abilities, and the subsequent relationship with neuropsychological test performance. The focus of this study aimed to consider these factors by comparing patients' reports of their cognition with their performance on neuropsychological tests and explore the role of depression.

1.2 MULTIPLE SCLEROSIS: EPIDEMIOLOGY, CAUSES & CLASSIFICATIONS

MS is a degenerative disease of the Central Nervous System (CNS) characterised by the production of widespread patches of damage called plaques or lesions in the brain and spinal cord (Rumrill, Kaleta & Battersby, 1996). Plaques are left when myelin, the protective insulation surrounding nerve fibres is destroyed or damaged, a process referred to as demyelination (Engel *et al*, 2007). This axonal loss or damage is detrimental as it results in neurological messages either being slowed down or completely blocked, leading to diminished or loss of neurological functioning (Arnett, 2003).

To some extent, the myelin sheath around the axons can be repaired after the inflammation has resolved, but this will not always take place or will only happen partially, resulting in impaired transmission of signal along the axon. The lost myelin can be replaced with scar tissue in a number of areas within the brain and spinal cord which has given MS its name; "multiple" meaning many, and "sclerosis" meaning scar forming. There is evidence to suggest that the destruction is caused by the body's own immune system (see sub-section 1.3.5), which is why MS is classified as an autoimmune disease (Hafler & Weiner, 1989).

1.2.1 SYMPTOMS AND DIAGNOSIS

There are a broad range of symptoms and impairments associated with MS. In principle, people with MS can experience partial or complete loss of any function controlled by the CNS, and this will depend on which areas of the brain and CNS are affected and how badly they are damaged. Common symptoms include: abnormal fatigue, gait ataxia or weakness, spasticity, balance problems, bladder and bowel dysfunction, numbness in limbs, a loss of vision or visual disturbances, tremors,

sexual dysfunction, cognitive impairment and depression (Amato *et al*, 2006; Chiaravalloti, 2008; Engel *et al*, 2004).

In clinical practice, an accurate diagnosis of MS is often reached through clinical investigation of patients' symptoms, but can sometimes occur following a process of ruling out all other possibilities. This can be a very stressful process for patients to undergo, as even amongst specialist neurologists there may be disagreement about diagnosis (National Institute for Clinical Excellence (NICE), 2003). NICE (2003) recommends The McDonald criteria (McDonald *et al*, 2001) in making an accurate diagnosis of MS, which in summary includes:

1. Objective evidence of two relapses, defined clinically as the sudden appearance or worsening of an MS symptom or symptoms, which lasts for at least 24 hours and up to 1 month.
2. The two lapses must be separated in time (at least one month apart), and evidence of inflammation or damage or both in different areas of the CNS.
3. There must be no other explanation for these relapses or symptoms.

The development of Magnetic Resonance Imaging (MRI) scans have been crucial in providing evidence of MS, as they can facilitate the detection of sclerosis within the brain and spinal cord (NICE, 2003). The examination of cerebrospinal fluid via a lumbar puncture can also facilitate quicker detection, as this identifies oligoclonal bands (or antibodies) within the spinal region which is present in up to 80% of MS patients (Compston & Coles, 2002; NICE, 2003).

1.2.2 CLASSIFICATION OF MS

Once patients receive a diagnosis of MS, they are usually categorised into a disease type based on the history of their symptoms. The categorisation most commonly used is a subset of MS classifications (see Table 1), and patients are usually diagnosed as having one of 3 disease types: Relapse-Remitting (RR), Secondary- Progressive (SP) and Primary-Progressive (PP) (Lubin & Reingold, 1996)

As demonstrated in Table 1, the vast majority of patients, approximately 80%, are diagnosed with RR MS. In this form, patients experience a series of relapses (also known as exacerbations) followed by complete or partial resolution of the symptoms (remissions) until another relapse occurs. Relapses

can last for days, weeks or months and recovery can be slow and gradual or almost immediate. Patients either fully or partially recover from the inflammation caused during relapse.

Approximately 50% of RR patients go on to develop SP MS within 10 years of diagnosis, and this figure increases to 90% by 25-30 years of disease onset. The SP form is characterised by a steady progression of axon loss and subsequent impairment, with minor periods of remission. PP MS affects about 10-20% of patients and is also characterised by a gradual progression of the disease. PP and SP MS are differentiated by the presence of an initial relapsing course in the SP form (Keegan & Noseworthy, 2002; Lubin & Reingold, 1996).

Table 1: Clinical classification of Multiple Sclerosis

Type	**Presentation**	**Prevalence**
Relapsing-remitting (RR)	Clearly defined disease relapses with full recovery or with squeal and residual deficit upon recovery; periods between relapses characterised by a lack of disease progression	Approximately 80% have relapsing-remitting disease at onset
Secondary progressive (SP)	Initial relapsing-remitting course followed by progression with or without occasional relapses, minor remissions and plateaux	Approximately 50% of people with relapsing-remitting MS develop secondary progressive MS during the first 10 years of their illness
Primary progressive (PP)	Disease progression from onset with occasional plateaus and temporary minor improvements allowed.	Approximately 10–15% have primary progressive disease at onset.

The Expanded Disability Status Scale (EDSS; see Table 2) is also a rating system that is frequently used for classifying MS. It is based on the results of neurological examinations and the walking abilities of patients (Kurtzke, 1983), and is commonly used to quantify the degree of functional impairment in MS. It quantifies impairment into 8 functional systems, and allows neurologists to assess the level of disability in each system. Scores range from 0-10, with higher scores denoting more impairment. There are 8 functional systems which include:

- Pyramidal (ability to walk)

- Cerebellar (co-ordination)
- Brainstem (speech and swallowing)
- Sensory (touch and pain)
- Bowel and bladder
- Visual
- Cerebral (ataxia)
- Other (any other neurological findings due to MS)

Table 2: Kurtzke Expanded Disability Status Scale.

Score	Presentation
0.0	Normal neurological examination
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting
7.0	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms retains some self care functions
9.0	Confined to bed; can still communicate and eat.
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10	Death due to MS

FS = Functional System

Despite its utility, the EDSS as a measure of impairment has been criticised for being too narrowly focused on functional systems (Hobart, Freeman & Thompson, 2000). There is undoubtedly an emphasis on the opinion of the neurologist rather than the patient which can sometimes be difficult, as clinicians and patients do not always agree on what aspects of the disease are most important (Rothwell *et al,* 1997). Research has demonstrated that clinicians are typically concerned about the physical manifestations of the disease, where as patients tend to identify fatigue, cognition and emotional problems as the most significant influences on their well-being and QoL (Rothwell *et al*, 1997; Cheng *et al*, 2001). These are discussed in more detail in the quality of life (section 1.4).

1.2.3 EPIDEMIOLOGY & CAUSES OF MS

1.2.3.1 CAUSES

The actual cause of MS is still not quite understood, but environmental, immunological and genetic hypothesis have been generated (Noseworthy *et al*, 2000).

Studies have established a definitive role for genetics as a contributing factor for developing MS. Research has demonstrated that between 5-10% of patients have a relative with the disease, and while unrelated adopted siblings have a 0-2% disease risk, identical twins demonstrate a 25% disease risk (Dyment 2004; Mumford *et al*, 1994). While these genetic links are helpful in understanding MS population clusters, it suggests that MS is not a 'classic' genetic disease i.e., such as that seen in sickle cell anaemia or Huntingdon's Disease, and suggests that it must also be attributable to non-genetic or environmental factors.

Environmental explanations have also been generated, and there is evidence to suggest there is a marked latitudinal difference, whereby the prevalence of MS appears to increase with distance from the equator (Cook *et al*, 1998; Yu *et al*, 1989). The latitudinal effect seems to be most prevalent within North America and in the Southern hemisphere, in particular, in New Zealand and Australia, where incidents of MS are found to be substantially higher in the South than in the North (Fawcett & Skegg, 1988; Skegg *et al*, 1987). Within Western Europe however this latitudinal effect disappears, as correlations vanish when MS prevalence is replaced by incidence rate (Koch-Henriksen & Sorensen, 2010). One explanation that has been proposed for this difference is the effect of solar radiation on the immune system. For example, Kampman, Wilsgaard & Mellgren (2007) demonstrated that people who had more summer outdoor activities in childhood and adolescence had a reduced risk of MS. This is thought to be due to the body producing Vitamin D3 in response to sunlight, and the regulatory role vitamin D plays in immune system reactivity (Kragt *et al*, 2008; Smolders *et al*, 2008).

Population-based studies have also supported this finding, demonstrating that patients with MS have lower levels of vitamin D in comparison to healthy controls (Munger, 2004).

There has also been the generation of the 'hygiene hypothesis' in an attempt to explain the cause of MS and the latitudinal difference in prevalence. Proponents of this argue that MS occurs as a result of reduced exposure to bacteria, virus and parasites in more 'Westernised' societies. They argue that because of the lack of intense infections in industrialised societies caused by improved hygiene, antibiotic use and vaccines, the body's immune system becomes impaired, and subsequently responds inappropriately to innocuous substances (Fleming & Cook, 2006).

Infection is one of the more widely suspected non-genetic risk factors for MS, which proposes that it is caused by myelin-specific overactive antibodies that attack the body's own auto-immune system. Although genetic susceptibility is possible (Ascherio & Munger, 2007), reasons for the over-activation are unknown, but the presence of oligoclonal bands (body's own antibodies) in the brain and cerebral fluid (found in up to 80% of patients) suggests that antibodies migrate to this area and 'attack' the myelin and cause inflammation. One common theory, molecular mimicry, proposes that presentation of foreign antigens that are molecularly similar to self-antigens leads to an autoimmune response (Fujinami 1983; Zabriskie 1986). In other words, viruses involved in the development of autoimmune diseases could possibly display very similar proteins to those found on nerves, making these nerves a target for antibodies. Research has found several viruses to be commonly associated with MS, including: herpes simplex virus (HSV), rubella, measles, mumps, and Epstein Barr virus (EBV) (Ascherio, 2007). Currently, the strongest evidence for the involvement of an infectious agent implicates EBV, as virtually all patients who have MS are infected with EBV (Ascherio, 2007)

1.2.3.2 EPIDEMIOLOGY

MS is one of the most frequent causes of central nervous system disease in young adults and is estimated to affect 85,000 people in the UK, and over 2 million people worldwide (Frank & Elliott, 2000). MS is the leading cause of disability in young and middle aged people in the developing world, and as discussed above, is particularly prevalent in Westernised counties (Cook *et al*, 1998). Life expectancy of people with MS is between 5 and 10 years less than that of unaffected people, and nearly two-thirds of the deaths in people with MS are directly related to the consequences of the disease (Compston & Coles, 2008).

1.2.3.3 GENDER DIFFERENCES IN MS

Studies have shown that MS is twice as common in women as men (Noseworthy *et al*, 2000). This difference is thought to be due, in part, to differences in hormones between the sexes, in particular the female hormone estrogen and testosterone in men. Increased levels of oestrogen during the female menstrual cycle and during the end stages of pregnancy are found to exacerbate symptoms of MS, whilst women during the early stages of pregnancy (low estrogen) experience a significant decrease in relapses (Hughes, 2004; Soldan *et al*, 2003; Voskuhl, 2002).

Testosterone is believed to be a 'protective' factor against MS and may explain why it is less likely to occur in men than women. Men with MS are not found to have lower levels of testosterone than men without MS, but there is evidence to suggest that they have higher levels of the female hormone estradiol (Tomassini, 2005).

1.2.3.4 AGE DIFFERENCES IN MS

MS is usually diagnosed between the age of 20 and 50 years old, and the mean age is approximately 34 years old (Kurtzke *et al*, 1992) although there are gender differences. MS is also found to present itself much later in men (age 30-40) than women (age 18-30), and is thought to be influenced by the natural decline in levels of testosterone in men in their 30's (Voskuhl, 2002).

As the disease is diagnosed primarily in young adults, it is thought to influence personal development and future plans at a time when individuals are starting families and careers. The unpredictable course of the disease means that future disability is difficult to anticipate, and some patients are left with concerns about whether they should start a family (Verdru *et al*, 1994) or tell future partners when starting relationships (Grytten, 2012). These factors have been found to strongly influence patients' QoL, and also impact on their psychological wellbeing (McCabe, 2006).

1.3 QUALITY OF LIFE IN MS

The marked variation in the natural history of MS has been shown to be a difficult factor when identifying major prognostic factors for long-term outcome (Noseworthy *et al*, 2000). This creates an uncommonly stressful illness which often impacts on the QoL of both the patients and their relatives as it is impossible to predict how MS will affect any one person (Lynch, Kroencke & Denney, 2001; Noseworthy *et al*, 2000; Stenager *et al,* 1994). Patients with MS report a lower life satisfaction than people without illness (McCabe, 2006), and when compared to those with several chronic illnesses

including inflammatory bowel disease, rheumatoid arthritis, (Benito-Leon & Martinez-Martin, 2003; Rudick *et al*, 1992), epilepsy and diabetes (Kalda, Ratsep & Lember, 2008; McCabe & McKern, 2002).

Several features of MS may uniquely contribute to low QoL in patients. Firstly, MS affects normal functioning in a diverse number of areas including neurological functioning (motor and sensory disturbances and sexual dysfunction), cognitive impairment, mood disorders (e.g. depression) and fatigue. Secondly, MS is diagnosed primarily in young adults when individuals are undergoing a process of personal development. Thirdly, MS has an unpredictable course which makes future plans unpredictable. The effect of these factors on QoL will be considered and discussed in relation to neurological functioning, cognitive impairment, depression and fatigue.

1.3.1 NEUROLOGICAL FUNCTIONING

Impaired neurological functioning occurs as a result of the demyelination of neurons that is associated with the disease (Arnett, 2003; Hafler & Weiner, 1989). Patients experience motor disturbances such as physical impairment, a loss of muscle control, muscle tremors, and numbness as a result, and are significant symptoms that affect up to 95% of patients at some point in the disease (Ameto, 2001).

As physical impairment increases during the course of the disease, patients often become reliant on physical aids to support and mobilise themselves, and may no longer able to live independently (Somerset, Sharp & Campbell, 2002). Physical impairment is also found to negatively impact on their participation in recreational activities, and patients report that they are no longer able to participate in the activities they once enjoyed (Aronson, 1997). For those that continue to access activities, they may become reliant on support from family/carers to participate. Some patients experience a loss of independence and embarrassment as a result of needing support, which subsequently leads them to avoiding these situations (Hakim *et al*, 2000). This causes many patients to lose contact with friends and family, resulting in them become socially isolated and lonely (Aronson, 1997; Stuifbergen & Rogers, 1997). The functional dependency caused by physical impairment can also limit patients' role within their family, and patients report experiencing a loss of dignity in becoming functionally dependent on their partners (Boeiji *et al*, 2002). There is also a significant amount of shame associated with needing physical assistance at home and in public places, and patients report worrying about others people's attitudes towards them (Ford *et al*, 2001).

In addition to motor disturbances associated with impaired neurological functioning, MS patients also experience bladder and bowel weakness. This is prevalent in approximately 75% of patients during the course of the disease, and is also found to be a result of neurological disturbances (DasGupa & Fowler, 2003; Chia *et al*, 1995). Patient report a significant amount of embarrassment and shame as a result of their incontinence and becoming reliant on partners to support them with this, which also impacts on their engagement with recreational activities and relationship with their partner (DasGupa & Fowler, 2003).

Sexual problems, although less researched, are also found to occur as a result of impaired neurological functioning in MS (Kersten *et al*, 2000). This can have a detrimental effect on patients self esteem and sexual relationships; particularly as these difficulties may occur at a time when patients may be initiating sexual relationships with partners (Nortvedt *et al*, 2001). This can have a marked reduction in the QoL of patients (even among those with otherwise low disability), and because it is a symptom of MS that services do not usually focus on, patients frequently have limited resources available to support them with this (Kersten *et al*, 2000).

1.3.2 COGNITIVE IMPAIRMENT

Cognitive impairment is thought to occur as a result of demylenation of the brain's white matter which has been associated with MS (Bagert *et al*, 2002). This is estimated to effect between 54% and 65% of patients across all stages of the disease (Amato *et al,* 2005; Amato *et al*, 2006).
Impaired memory functioning is reported to be the most common cognitive domain affected (Maurelli *et al*, 1992; Rao *et al*, 1993), followed by processing speed and executive functioning (Arnett *et al,* 1997; Rao *et al*, 1991a), language, and spatial perception (Rao *et al,* 1991a; van den Burg *et al,* 1987).

Longitudinal studies have demonstrated that cognitive deterioration appears to increase from 10-35% over time, with patients who display cognitive impairment at baseline being significantly more likely to become further impaired (Bernardin *et al*, 1993; Kujula *et al*, 1997; Amato *et al,* 2001).
Memory, learning and abstract reasoning have been found to be the first areas affected, with short term memory and attention occurring later on during the course of the disease (Amato *et al*, 2001).
The prevalence and measurement of cognitive impairment is addressed in more detail within the systematic review (section 2.5).

Also, there is a large amount of evidence to suggest that cognitive difficulties negatively impact on patients' quality of life; affecting employment, social relationships and engagement in social activities, even when compared to those with similar levels of physical disability (Benedict *et al*, 2005; Glanz *et al*, 2010; Rao *et al*, 1991b).

Patients with high levels of cognitive impairment are less likely to work outside the home, more likely to require assistance with activities of daily living, and more likely to have limited social support (Rao *et al*, 1991; Roessler *et al*, 2001). Cognitive impairment has been found to be more predictive of unemployment than any other symptom associated with MS (Benedict *et al*, 2005), and is believed to contribute to early retirement in as many as 80% of individuals with MS (Gronning *et al*, 1990; Roessler & Rumrill, 1995). This has both social and financial implications for patients and their families, and can also result in patients becoming more socially isolated within their homes. Some studies have also raised concerns about patients driving ability (Shawaryn *et al*, 2002; Schultheis *et al*, 2002). Compared with control subjects, MS patients are found to perform significantly worse on computerised tasks of driving skills, and show higher rates of simulated motor vehicle crashes (Schultheis *et al*, 2002). Findings such as these could further restrict patients' independence, as although physical aids can be put in place to facilitate patients driving, their cognitive difficulties may mean that they still depend on their care givers. Overall, these findings also demonstrate the detrimental effect cognitive impairment can have on patients' lives, and supports why a valid and reliable assessment of patients' cognitive functioning in essential.

1.3.3 DEPRESSION

Depression is a common symptom associated with MS, with lifetime prevalence estimates ranging from 47% to 54% of patients being affected (Fischer *et al.*, 1994; Solari *et al,* 2004). Further, suicide rates are also estimated to be 7.5 times that of the general population (Sadovnick *et al*, 1996), and assessment is therefore crucial for MS patients psychological well being. What complicates this however, it that several criteria for depression are also common MS symptoms, e.g. fatigue, psychomotor retardation, decreased concentration, and insomnia/ hypersomnia. This issue of measurement and prevalence of depression is addressed in more detail within the systematic review which comes later on in this chapter (see section 2.8).

MS patients are thought to develop depression as a consequence of the multiple symptoms associated with the disease; particularly as it has no possibility of cure and symptoms become progressively worse over time (Wallin *et al*, 2006). In addition to the neurological deficits, MS is

frequently associated with losses in vocational status, social roles, and participation abilities, which undoubtedly can have a negative impact on psychological well-being (Mohr & Cox, 2001). Individual presentations in the nature of MS (i.e. symptoms and disease progression) means there is also a large amount of uncertainty associated with the disease, which is understandably difficult for patients to cope with (Mitchell *et al,* 2006). As a result of the impairments associated with MS, approximately one third of patients experience a decrease in their standard of living and the majority of patients lose their job. Unemployment, loss of role, and living near the poverty level are all factors for depression within the general population (Turner & Turner, 2004), and it is unsurprising therefore that these are also associated with a lower QoL in MS patients (Aronson, 1997).

Also, the unpredictable course of MS makes it difficult to make future plans or anticipate future disability, and most patients are left feeling like they have very little control over the disease (Benito-Leon *et al*, 2003). Patients often think that the worst possible option is inevitable, and become understandably concerned about requiring institutionalised care such as a nursing home as they become more impaired (Benito-Leon *et al*, 2003). Because of the physical and cognitive difficulties associated with the disease, there is often a change in the relationship MS patients have with their partners (Mitchell *et al,* 2006). Factors such as difficulties joining in family activities, a reliance on partners as care givers as well as sexual dysfunction can result in a deterioration of the relationship patients have with their partner, and can be a major psychological consequence of MS (Mohr, 1999).

In addition to the psychological causes of depression, neurological changes caused by brain lesions associated with the disease are also thought to predispose patients to changes in their mood. Some MRI studies have demonstrated that patients with lesions located in the frontal and temporal lobes (associated with emotional regulation) are more likely to display depressive symptoms (Pujol *et al*, 1997; Mohr *et al*, 2003), although this association has not been reported by all studies (Clark *et al*, 1992; Millefiorini *et al*, 1992).

1.3.4 FATIGUE

Fatigue is recognised as one of the most commonly reported symptoms of MS, with 65-97% of MS patients reporting significant fatigue (Bakshi *et al*, 2000; Krupp *et al*, 1988), and 15-40% describing fatigue as their most disabling symptom (Bergamaschi *et al*, 1997; Fisk *et al*, 1994). Fatigue has been defined as “an abnormal sense of tiredness or lack of energy, out of proportion to the degree of effort or level of disability that significantly interferes with routine physical or intellectual

functioning" (Weinshenker *et al*, 1992 p.118). Thus, MS related fatigue is an unusual and abnormal form of fatigue that differs from the fatigue experienced by healthy individuals after exertion (Weinshenker *et al*, 1992).

The fatigue MS patients experience is believed to contribute to associated levels of morbidity by limiting energy and endurance and by adversely affecting mood and ability to cope with accompanying symptoms (Ritvo *et al*, 1996; Schwartz *et al*, 1996). Fatigue has been found to directly influence patients' engagement in social activities and employment, resulting in patients subsequently withdrawing from them (Ritvo *et al*, 1996). Unfortunately, this process is self perpetuating, as withdrawal from these activities causes patients to have reduced muscle strength and fitness, further adding to the likelihood of them disengaging in these activities in the future (Kent-Braun *et al*, 1994).

In addition to the effect of fatigue on physical impairment, fatigue is also found to affect patients' cognitive abilities, in particular speed of processing; a domain which has been linked to the ability to maintain employment (Clayton *et al*, 1999). Fatigue has also been associated with higher levels of depression in MS patients regardless of their physical ability or type of MS (i.e. relapse-remitting or progressive type), and is believed to be a result of both psychological (as above), and neurological causes (Bakshi *et al*, 2012)

1.3.5 SUMMARY

MS is a chronic and progressive neurological disease of the CNS, and is the leading cause of disability in young and middle-aged people in the developing world. Patients typically present with neurological impairment which include symptoms such as motor disturbances, bowel and bladder weakness and sexual dysfunction, cognitive impairment, emotional difficulties and fatigue. The combination of a progressive and unpredictable disease process, with no possibility of cure, creates an uncommonly stressful illness for patients to cope with. MS is found to develop at a time when patients are undergoing a process of personal and social development which can influence future life plans such as career progression, developing relationships and having children, which are detrimental to patients psychological well being and QOL. Throughout the course of MS, patients report that motor dysfunction, cognitive impairment, depression and fatigue significantly affect their ability to work, engage in meaningful activities without support and develop and maintain relationships with friends, family and partners. However, whilst patients levels of fatigue and motor disturbances such as physical impairment are routinely assessed by MS services, cognitive

impairment and depression are less likely to be assessed or monitored over time (Amato *et al*, 2006; Christodoulou *et al*, 2009; Mitchell *et al*, 2006). Having outlined the detrimental effect cognitive impairment can have on patients' QOL, this chapter now focuses on the measurement of cognitive impairment in MS, including subjective measures used for patients to report their cognition, and the effect of depression on determining whether further cognitive assessment is needed.

1.4 INTRODUCTION TO SYSTEMATIC REVIEW

Cognitive impairment is a symptom frequently associated with MS, occurring in approximately 40-70% of patients across the disease course (McIntosh-Michaelis *et al*, 1991; Rao *et al*, 2001). It can present at different stages of the disease, and has not been found to correlate with other significant symptoms of MS such as physical disability or disease duration. Indeed, both appear to be poor predictors of the degree of cognitive impairment in MS (Brassington & Marsh, 1998; Ron *et al*, 1991)

Further, patients with MS-related cognitive impairment are less likely to be employed, engage in fewer social activities, report greater difficulty in performing household tasks, benefit less from rehabilitation therapies, and exhibit more psychopathology than cognitively intact patients with MS (Langdon & Thompson, 1999; Rao *et al*, 1991). As already discussed, this has a detrimental effect on patients QoL and psychological well-being, and highlights the importance of detecting cognitive impairment in MS.

Unfortunately however, with no clear pattern of when cognitive impairment presents, and it not being required to diagnose MS, clinicians' are often left with uncertainty about *when* cognitive impairment should be assessed. The limited time and resources available to clinicians means that formal testing is not routinely carried out (Rao, 1995), and cognitive difficulties such as slowed processing speed and 'forgetfulness' may be attributed to other symptoms of MS e.g., fatigue (Rogers & Panegyres, 2007). The difficulty associated with assessing cognitive impairment on a routine basis means there is often a reliance on patients to report whether or not they are experiencing problems with their cognition.

As further assessment and intervention may be based on patients' reports of their cognition, it is important to evaluate whether patients reports reflect their performance on neuropsychological tests. Moreover, it is also important to identify if factors other than cognitive functioning are influencing patients cognitive reports, and if this is subsequently distorts the relationship with neuropsychological test performance.

The aim of this systematic review therefore was to consider existing literature that has compared patients' reports of their cognitive functioning with their performance on neuropsychological tests, and consider the extent to which depression may impact on this relationship.

CHAPTER TWO

SYSTEMATIC REVIEW

2. OVERVIEW OF SYSTEMATIC REVIEW

This chapter presents a systematic review of the literature into how patients' cognitive functioning on neuropsychological tests compares with their subjective cognitive reports. The effect of depression on patients' subjective cognitive reports and their neuropsychological test performance is also discussed. The chapter begins with describing the process of reviewing relevant articles and papers included in the review. This is followed by a detailed evaluation of the findings. The limitations of papers are then considered and implications for future research discussed. Leading on from the systematic review, this chapter is followed by an outline of the current study's aims and research hypotheses.

2.1 REVIEWING OF PAPERS

Databases and individual journals were searched and included: PsychINFO, Science Direct, The Journal of Multiple Sclerosis, PubMed, The Journal of Neurological Sciences, the Cochrane Database of Systematic Reviews, and the journal, Neurology. The following terms were used: subjective cogniti* impairment AND MS; objective cogniti* impairment AND MS; patient/self reports of cogniti* AND MS; Neuropsychological cognit* impairment AND/OR dysfunction in MS.

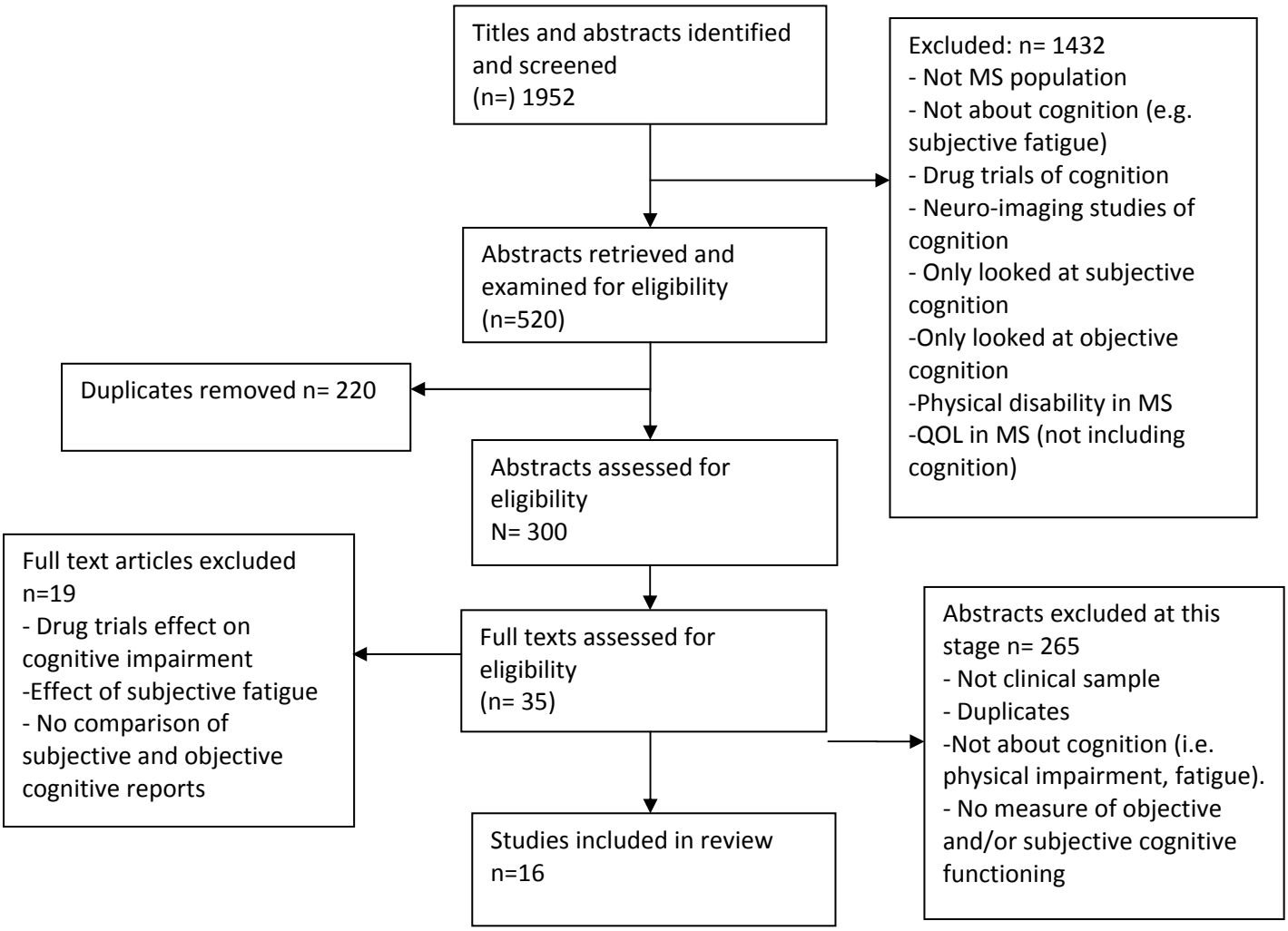
In reviewing the articles, the following exclusion and inclusion criteria was applied in order to generate articles that reported this relationship, and also if they looked at the effect of depression. Papers were included if they:

- Were English language publications
- Included participants that had received a diagnosis of MS
- Compared objective cognitive functioning on neuropsychological tests with patients reports of their cognition
- Included a measure of depression
- Were published pre-1990

Papers were excluded if they failed to meet these criteria. As demonstrated in Figure 1, the application of the inclusion and exclusion criteria yielded a total of 1952 articles. Articles were reviewed by title and abstract for potential relevance to this topic, and when the title and abstract

did not clearly indicate the degree of relevance to the topic, the article itself was reviewed. Of the full texts reviewed, 16 were eligible to be included in the systematic review. Bibliographies of topic-appropriate articles were also examined to discover additional references not identified in the primary search.

Figure 1: Flow Chart of studies included in the systematic review



2.2 PAPERS INCLUDED IN SYSTEMATIC REVIEW

A total of 16 articles were considered to meet the inclusion criteria and were reviewed in detail. A summary of all of the articles included in the review are presented in Appendix 1. The articles were reviewed and discussed in detail according to: the study design; aims and objectives; definition of cognitive impairment; types and prevalence of cognitive impairment identified; neuropsychological measures used; patients reports of their cognition; measures used to identify patients reports of cognitive impairment; the relationship between patients reports of their cognition and their performance on neuropsychological tests; and depression and its effect on patients cognition (measured and reported). Limitations of the existing research and a summary highlighting implications for future research and clinical practice were also included in the review.

2.3 AIMS OF THE STUDIES

Five studies proposed that their study aim was to examine the relationship between patients' subjective reports of their cognition and their performance on a battery of neuropsychological tests (Deloire *et al*, 2006; Krch *et al,* 2010; Maor *et al,* 2001; Marrie *et al,* 2005; Middleton *et al*, 2006). Three studies reported that they were also exploring the effect of depression on this relationship, (Goverover *et al,* 2005; Lovera *et al,* 2006; Randolph, Arnett & Freske, 2004), and one study also explored the role of depressive attitudes (Randolph, Arnett & Freske, 2004).

Three of the studies examined the development, follow up, and reviewing of a subjective neuropsychological screening questionnaire, the MS Neurological Questionnaire (MSNQ; Carone *et al*, 2005; Benedict *et al,* 2003; Benedict *et al,* 2004), and another reviewed a subjective measure of QoL and emotional well-being in an MS population (Gold *et al*, 2003). One other study looked at the prevalence of normative dissociative experiences such as "highway hypnosis" (i.e. losing awareness while driving, then suddenly discovering some distance has been travelled) on MS patients perceptions of their cognitive functioning (Bruce *et al,* 2010).

The review included three longitudinal studies, all of which aimed to evaluate treatment interventions over time (Christodoulou *et al,* 2005; Julian *et al,* 2007; Kinsinger *et al*, 2010). Kinsinger, Lattie & Mohr, (2010), assessed the effectiveness of two psychological interventions for depression on patients' mood, their cognitive functioning, and perceptions of their cognitive functioning. Julian *et al,* (2007) looked at the effect of psychological and pharmacological treatments for improving mood, and Christodoulou *et al,* (2005) evaluated the effect of the drug Donepezil for improving cognition.

2.4 STUDY DESIGN

As can be seen from the table in Appendix 1, 13 studies were cross sectional designs and 3 were longitudinal designs. 13 of the studies used correlations to explore the relationship between patients' reports of their cognition and their performance on neuropsychological tests, one used a factorial design, and two studies explored the predictive value of level of cognitive impairment on patients' reports of their cognition (Julian *et al*, 2007; Marrie *et al*, 2005).

Of the 13 cross sectional studies, 5 included a control group (Benedict *et al,* 2004; Bruce *et al*, 2010; Deloire *et al*, 2006; Carone *et al,* 2005; Middleton *et al*, 2006), generally these tended to be much smaller in comparison to patient sample sizes. Control groups ranged from being less than 30% of the sample size (e.g. Deloire *et al,* 2006) to less than 85% of the sample size (e.g. Carone *et al*, 2005). Of the five studies that used a control group, two matched controls with the age and education of patients (Bruce *et al*, 2010; Carone *et al,* 2005), two matched age, sex and education (Benedict *et al,* 2004; Deloire *et al*, 2006), and one used a convenience sample that was not demographically matched (Middleton *et al*, 2006).

The three longitudinal studies assessed patients at two time points (Christodoulou *et al,* 2005; Julian *et al,* 2007; Kinsinger, Lattie & Mohr, 2010). Two of them did this at 16 weeks (Julian *et al*, 2005; Kinsinger *et al*, 2010) and one at 24 weeks (Christodoulou *et al*, 2005). One longitudinal study was a Randomised Controlled Trial (Kinsinger *et al*, 2010), and two were experimental treatment trials (Christodoulou *et al,* 2005; Julian *et al*, 2007).

2.5 SAMPLES INCLUDED IN STUDIES

On reviewing the studies, it was evident that studies differed in the process for recruiting participants, and the demographic (e.g. gender, age) and disease characteristics of patients (e.g. MS classification, disease duration).

2.5.1 SAMPLE SIZE

Samples ranged from 26 (Goverover *et al*, 2005) to 221 patients (Middleton *et al*, 2006). Four of the studies included informants (Benedict *et al*, 2003; Benedict *et al*, 2004; Carone *et al*, 2005; Goverover *et al*, 2005). Informant samples ranged from 26 (Goverover *et al*, 2005) to 102 (Benedict *et al*, 2003).

2.5.2 RECRUITMENT

Thirteen studies recruited samples from MS clinics. One cross sectional study (Goverover *et al*, 2005) and one longitudinal study recruited from both MS clinics and in the community (Kinsinger *et al*, 2010).

Twelve studies recruited patients at random during their clinical appointments. Four studies required patients to be referred into them (Carone *et al,* 2005; Christodoulou *et al*, 2005; Lovera *et al*, 2006; Marrie *et al*, 2005). Two of these required patients to be reporting problems with their cognition (Lovera *et al*, 2006; Marrie *et al*, 2005). Carone *et al,* (2005) included patients who were reporting euphoria, and Christodoulou *et al* (2005) required patients to be displaying mild cognitive impairment on any single cognitive test.

2.5.3 AGE

The age range of patients was only reported by seven studies (Benedict *et al,* 2003; Bruce *et al*, 2010; Chrisotdoulou *et al,* 2005; Goverover *et al,* 2005; Krch *et al*, 2010; Marrie *et al,* 2005 Middleton *et al*, 2006). Mean ages of participants were reported to range from 37-50 across these studies, but most included patients with a mean age between 42-46 years old. Age was considerably larger in some studies than others (i.e. 20-55 years old, Middleton *et al*, 2006; 38-57 years old Krch *et al*, 2010).

2.5.4 DISEASE DURATION

Disease duration ranged between 2-11 years across the studies. Only one study focused on impaired cognitive functioning in early diagnosed MS patients (mean duration two years, Deloire *et al*, 2006). 11 studies included patients with a mean disease duration of between 8-11 years, and five did not provide the range or mean disease duration of patients (Benedict *et al,* 2004; Christodoulou *et al,* 2005; Kinsinger *et al*, 2010; Lovera *et al;* 2006; Marrie *et al,* 2005).

2.5.5 GENDER

There was a marked difference in the male to female ratio in the majority of studies, with the number of females consistently outweighing the number of males. This ranged from participants being 68-90% female, with only two studies reporting a 60-40% ratio (Chrisotdoulou *et al,* 2005; Maor *et al*, 2001). This discrepancy is likely to reflect the prevalence of MS in women compared to men (2:1 ratio).

2.5.6 FUNCTIONAL IMPAIRMENT

Functional impairment was a terminology that was used to refer to patients' physical ability. 10 studies used the EDSS to measure functional impairment (Benedict *et al,* 2003; Benedict *et al,* 2004; Bruce *et al,* 2010; Carone *et al,* 2005; Christodoulou *et al,* 2005; Deloire *et al*, 2006; Gold *et al*, 2005; Maor *et al,* 2001; Middleton *et al*, 2006; Randolph, Arnette & Freske, 2004) and four studies used the Ambulation Index (AI; Hauser *et al,* 1983) (Goverover *et al*, 2005; Julian *et al*, 2007;Krch *et al*, 2010; Lovera *et al*, 2006). Kinsinger, Lattie & Mohr, (2010) used the Guys Neurological Disability Scale (Sharrack & Hughes, 1999) and Marrie *et al,* (2005) used the Multiple Sclerosis Functional Composite (Fischer *et al,* 1999).

Only one study did not include a measure of functional impairment (Lovera *et al,* 2006). 13 studies reported mean functional impairment to fall between the mild-moderate range (no aid required for walking), and 2 reported the mean level of impairment to be severe (require wheelchair for mobility) (Maor *et al,* 2001; Randolph Arnette & Freske, 2004).

2.5.7 EDUCATION

Average years of education were consistent across the studies and ranged from 14.5 – 16 years. Three of the studies did not report education history (Gold *et al*, 2003; Lovera *et al,* 2006; Maor *et al,* 2001).

2.5.8 CATEGORISATION OF MS

MS subtype i.e., Relapse Remitting (RR), Primary Progressive (PP), Secondary Progressive (SP) was reported by 12 studies. Four studies did not report patients' MS categorisation (Christodoulou *et al*, 2005; Goverover *et al*, 2005; Julian *et al,* 2007; Maor *et al,* 2001). There was a larger number of RR type MS patients included in the studies, and this ranged from 48% (Gold *et al*, 2005) to 88% (Benedict *et al,* 2003) of the entire sample. Only seven studies included patients with SP MS (Carone *et al,* 2005; Gold *et al*, 2005; Kinsinger *et al*, 2010; Krch *et al,* 2010; Lovera *et al,* 2006; Middleton *et al*, 2006; Randolph et al, 2004).

2.6 PERFORMANCE ON NEUROPSYCHOLOGICAL TESTS

2.6.1 NEUROPSYCHOLOGICAL TESTS USED

All of the studies used standard neuropsychological tests to measure patients' cognitive functioning. Tests are reported according to the specific cognitive domains they assess.

2.6.1.1 MEMORY

Fifteen studies included a measure of memory (only one did not; Gold *et al,* 2003). Tasks were primarily verbal learning tasks which required participants to remember and recall lists of words. Thirteen studies included a verbal memory task, and the remaining three used an auditory memory task (Bruce *et al,* 2010, Goverover *et al,* 2005; Randolph *et al*, 2004).

The California Verbal Learning Test version II (CVLT-II; Delis *et al,* 2000) was the most common measure of verbal memory and was used by seven studies (Benedict *et al*, 2003; Benedict *et al*, 2004; Carone *et al,* 2005; Krch *et al,* 2010; Kinsinger *et al*, 2010; Lovera *et al*, 2006; Middleton *et al,* 2006;). The Selective Reminding Test, which forms part of the Rao's Brief Repeatable Battery (Rao, 1990) was the second most common measure of memory used, and was used by 3 studies (Christodoulou *et al*, 2005; Deloire *et al*, 2006; Middleton *et al,* 2006).

Two studies used the Wechsler Memory Scale-III (WMS-III; Wechsler, 1997) (Goverover *et al*, 2005; Marrie *et al,* 2005), one of which also included memory subtests from the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997) i.e. digit span, arithmetic and letter number sequencing task (Marrie *et al,* 2005). Julian *et al*, (2007) also used a digit span task from the WMS-III, as well as the Rey Auditory Verbal Learning Test (Rey, 1964).

Other measures used included the Spatial Recall Test (Rao, 1990) used by Christodoulou *et al,* (2005), and the Auditory Verbal Learning test (Taylor, 1959) which was used by Bruce *et al*, (2010). Krch *et al,* (2010) included three measures of memory, the CVLT-II, the Open Trail-Selective Reminding Test (Chiaravalloti *et al,* 2009), and Prose Memory from the Memory Assessment Scales (Williams, 1991).

2.6.1.2 PROCESSING SPEED

Thirteen studies included a measure of processing speed, with the exception of Kinnsinger et al, 2010; Maor *et al*, 2001; Randolph Arnett & Freske, 2004. The Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977) and the Symbol Digit Modalities Test (SDMT; Smith, 1991) were the most utilised measures of processing speed. Five studies used solely the Paced Auditory Serial Test (PASAT; Gronwall, 1977) (Benedict *et al,* 2003; Carone *et al*, 2005; Deloire *et al,* 2006; Goverover *et al,* 2005; Middleton *et al,* 2006) and 4 used the SDMT (Benedict *et al,* 2004; Christodoulou *et al*, 2005; Lovera *et al,* 2006; Bruce *et al,* 2010). Three studies used both of these measures (Benedict *et al*, 2004; Deloire *et al,* 2006; Lovera *et al*, 2006), and two studies (Gold *et al*, 2005; Julian *et al*, 2007) used the letter-number sequencing subtest from the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997).

2.6.1.3 EXECUTIVE FUNCTIONING

Twelve studies included a measure of executive functioning. The Wisconsin Card Sorting Test (WCST; Nelson, 1976) was used by five of the studies (Benedict *et al,* 2003; Benedict *et al,* 2004; Bruce *et al* 2010; Carone *et al,* 2005; Goverover *et al,* 2005) and was the most common measure of executive functioning. The Stroop task was the second most common measure of executive functioning and was included in 4 studies (Bruce *et al* 2010; Deloire *et al* 2006; Julian *et al,* 2007; Lovera *et al,* 2006), one of which also included the WCST (Bruce *et al* 2010). Two studied used The Tower of Hanoi (Douglas, 1985) (Christodoulou *et al,* 2005; Randolph *et al*, 2004), and Middleton *et al*, (2006) used a similar task to The Tower of Hanoi; The Tower of London (Shallice, 1982). Benedict *et al* (2003) used the Trail Making Test (Arnett & Labovitz, 1995) and Marrie *et al*, (2005) used the perceptual organisation tasks i.e. picture completion, block design and matrix reasoning from the WAIS-III (Wechsler, 1997).

2.6.1.4 LANGUAGE

Eleven of the sixteen studies included a measure of language abilities. The measures most commonly used were word generation tasks which required patients to generate as many words as possible in a given time period. The Controlled Oral Word Association Test (COWAT) was the most popular word generation task and was used by nine of the studies (Benedict *et al*, 2004; Carone *et al*, 2005; Christodoulou *et al*, 2005; Deloire *et al*, 2006; Goverover *et al,* 2005; Julian *et al*, 2007; Kinsinger *et al*, 2010; Lovera *et al*, 2006; Middleton *et al*, 2006). Benedict *et al*, (2003) used the Boston Naming test (Kaplan, 1983), and Marrie *et al*, (2005) used verbal subtests from the WAIS-III (Wechsler, 1997) i.e. vocabulary, similarities, information, and comprehension.

2.6.1.5 ATTENTION

Only three studies included a measure of attention (Kinsinger *et al*, 2010; Marrie *et al*, 2005; Maor *et al*, 2001). The Digit Span task from the WAIS-III was used by 2 studies and provided a measure of both working memory and attention (Julian *et al*, 2007; Marrie *et al,* 2005), and one study used a measure of attention from the Neurobehavioral Cognitive Status Examination (NCSE, Maor *et al,* 2001).

2.6.1.6 SPATIAL ORIENTATION

Three of the 16 studies assessed spatial orientation (Benedict *et al*, 2003; Benedict *et al*, 2004; Caron *et al*, 2005), all of which used the Judgment of Line Orientation Test (Benton *et al*, 1994).

2.6.2 IMPAIRMENT ON NEUROPSYCHOLOGICAL TESTS

Six studies reported that 35-56% of patients were cognitively impaired (Benedict *et al*, 2004; Caron *et al,* 2005; Deloir *et al,* 2006; Gold *et al,* 2003; Marrie *et al*, 2005; Maor *et al,* 2001), and Randolph *et al*, (2004) reported that 12% of patients were cognitively impaired. Two studies provided qualitative descriptions of patients mean level of cognitive functioning, one of which reported 'moderate' cognitive impairment (Christodoulou *et al*, 2005) and the other reported 'borderline-impaired' cognitive impairment (Randolph *et al*, 2004). Apart from findings by Randolph *et al* (2004), the level of cognitive impairment reported was consistent with longitudinal research demonstrating that 40-60% of MS patients are affected by cognitive impairment (Amato *et al*, 2006).

Ten studies reported the domains which were the most commonly impaired and six studies did not (Benedict *et al*, 2003; Benedict *et al,* 2004; Julian *et al,* 2007; Kinsinger *et al*, 2010; Krch *et al,* 2010; Marrie *et al*, 2005). Four studies reported memory to be the most commonly impaired cognitive domain (Carone *et al*, 2005; Christodoulou *et al*, 2005; Middleton *et al,* 2006; Randolph *et al*, 2004) and five reported processing speed (Bruce *et al*, 2010; Deloire *et al*, 2006; Goverover *et al*, 2005; Gold *et al*, 2005; Lovera *et al*, 2006). Two studies reported attention and concentration to be the most common type of impairment (Christodoulou *et al*, 2005; Maor *et al,* 2001), although Maor *et al,* (2001) did not include a measure of information processing or memory which may account for this.

2.7 DEFINITION OF COGNITIVE IMPAIRMENT

The studies reviewed utilised a range of definitions for 'cognitive impairment'. Seven studies did not provide information about how cognitive impairment was defined (Bruce *et al*, 2010; Goverover *et al*, 2005; Julian *et al*, 2007; Kirch *et al*, 2010; Kinsinger *et al*, 2010; Middleton *et al*, 2006; Randolph *et al*, 2004).

Two studies required patients to be displaying mild impairment (scored less than 0.5 standard deviations below the standard norm) on any single cognitive measure to meet the eligibility criteria for the study (Christodoulou *et al*, 2005; Lovera *et al*, 2006). Other studies defined cognitive impairment as a score <5th percentile on one (Chiaravalloti *et al*, 2005; Marrie *et al*, 2005), two (Deloire *et al*, 2006), or three (Carone *et al,* 2005) neuropsychological tests. Gold *et al* (2003) defined cognitive impairment as 2.5 standard deviations below the norm (matched for age and education) on a single neuropsychological measure (Gold *et al*, 2003).

Benedict *et al*, (2003) calculated a mean standard score across a battery of six cognitive tests, and patients were defined as cognitively impaired if their mean standard score was < 5th percentile. Maor *et al*, (2001) defined impairment as a 'decreased score in one domain of the NCSE', but did not report what this score was.

Benedict *et al* (2004) used the most stringent definition of impairment, which included: a) a mean z score <-1.5 (<5th percentile for age equivalent) across all four attention and memory measures; or b) the presence of one severe (a z score < -2, <2nd percentile) and two mild (z score < -1.5) deficits, or two severe deficits, across all cognitive measures

2.8 SUBJECTIVE REPORTS OF COGNITIVE FUNCTIONING

2.8.1 SUBJECTIVE COGNITIVE MEASURES

The Perceived Defects Questionnaire (PDQ; Sullivan, Edgley, & Dehoux, 1990) was the single most commonly used subjective cognitive measure to assess patients' cognitive reports. It includes questions about subjective memory, concentration and attention, and was used by four studies in the review (Marrie *et al*, 2005; Lovera *et al*, 2006; Kinsinger *et al*, 2010; Christodoulou *et al*, 2005).

Three studies used the MS Neuropsychological Screening Questionnaire (Carone *et al*, 2005; Benedict *et al*, 2003; Benedict *et al*, 2004). This measure is completed by both patients and informants, and includes questions on attention and speed of processing, memory, other cognitive

ability (primarily language) and personality, and behaviour. The MS Quality of Life -54 (MSQOL-54; Vickrey *et al*, 1995) was also used by 3 studies (Julian *et al*, 2007; Krch *et al*, 2010; Deloire *et al*, 2006), one of which (Deloire *et al*, 2006), used a French adaption of this scale; the SEP-59 (Vernay *et al*, 2001). The measure includes 4 questions about whether or not patients had experienced difficulties with their memory, attention, concentration and thinking, and whether family/friends have noticed them experiencing any cognitive problems.

Two studies used the Memory Functioning Questionnaire (Gilewski *et al*, 1990) (Krch *et al*, 2010; Randolph *et al*, 2004), and Bruce *et al*, (2010) used The Prospective and Retrospective Memory Questionnaire (Crawford *et al*, 2003). Both measures ask patients to report any difficulties they experience with their memory. Middleton *et al*, (2006) used The Cognitive Failures Questionnaire (Broadbent *et al*, 1982). This asks respondents to rate any difficulties they have been experiencing with their memory, attention, and motor functions. In addition to this measure, participants were also asked to rate how well they thought they had done on the neuropsychological tests, immediately after completing them.

Goverover *et al*, (2005) used The Frontal Systems Behaviour Scale (Grace & Malloy, 2001). This is primarily a self awareness measure which assesses executive dysfunction, disinhibition and apathy. Gold *et al* (2003) used the Hamburg Quality of Life Questionnaire in MS (Gold *et al*, 2001) which includes two questions about cognition. One question asks patients to rate whether or not they experience any memory problems, and the other asks if they have difficulty remembering new information.

Benedict *et al* (2003) was the only study to use two subjective cognitive measures. One of these was the MS Neuropsychological Screening Questionnaire (Benedict *et al,* 2003), and the other was The Cognitive Failures Questionnaire (Broadbent *et al*, 1982).

2.8.2 PREVELANCE OF SUBJECTIVE COGNITIVE IMPAIRMENT

Each study reported using a 'cut off' criterion to define patients as 'subjectively impaired'. This was based on criterion set by the subjective cognitive measure used, and in two studies, by how well patients' reports correlated with informant reports (Carone *et al*, 2005; Goverover *et al*, 2005). Only two studies provided the percentage number of patients that were subjectively impaired according to the study's criterion. This ranged from 22% (Deloire *et al*, 2006) to 51% (Maor *et al*, 2001) in the studies reviewed.

Marrie *et al* (2005) found that patients reported less problems with their cognition the older they were i.e. younger patients reported significant problems with their cognition and older patients (>55 years old) reported very few problems with their cognition. No other study found that patients' reports of their cognition varied according to their age, or indeed any other demographic characteristic (including gender, years in education or marital status).

2.9 DEPRESSION

2.9.1 MEASURE OF DEPRESSION

The Beck Depression Inventory-II (BDI-II; Beck, Steer & Brown, 1996) was used by 7 of the 16 studies in the review (Benedict *et al*, 2003; Carone *et al*, 2005; Goverover *et al*, 2005; Julian *et al*, 2007; Kinsinger *et al*, 2010; Randolph, *et al*, 2010). Three studies used the Centre for Epidemiological Studies-Depression Scale (CES-D; Radloff, 1977) (Middleton *et al*, 2006; Maor *et al*, 2001; Benedict *et al*, 2004), two of which also used the Beck Depression Inventory-Fast Screen (BDI-FS; Beck, Steer & Brown, 2000) (Benedict *et al*, 2004; Bruce *et al*, 2010). The BDI-FS is a short questionnaire specifically designed to assess depressive symptoms in medical populations, and has also been validated within the MS population (Benedict 2003b).

Krch *et al,* (2010) used The Chicago Multiscale Depression Inventory (Nyenhuis *et al*, 1998), and Lovera *et al*, (2006) used the Beck Depression Inventory-Amended (Beck *et al*, 1988). Two studies used the Mongomery and Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) (Christodoulou *et al*, 2005; Deloire *et al*, 2006).Two studies used a measure of anxiety and depression (Gold *et al*, 2005; Marrie *et al*, 2005). Gold *et al*, (2005) used The Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983), and Marrie *et al*, (2005) used the Mental Health Inventory (Veit & Ware, 1983).

Only two studies used a measure of depression that did not include questions about the somatic symptoms associated with MS e.g. fatigue, psychomotor retardation, decreased concentration and insomnia/hypersomnia (Benedict *et al*, 2004; Bruce *et al*, 2010). Measures such as the BDI, BDI-A, CES-D and MADRS which were used by 12 studies, all include questions about sleep disturbance, concentration and fatigue.

2.9.2 PREVALENCE OF DEPRESSION

Prevalence of depression was reported by seven studies and ranged from 27%-61% of patients affected (Benedict *et al*, 2004; Gold *et al*, 2003; Krch *et al*, 2010; Kinsinger *et al*, 2010; Lovera *et al*, 2006; Maor *et al*, 2001; Randolph *et al*, 2004). The five studies that included a control group also reported that patients were significantly more depressed than controls ($F=8.8$, $p<.0001$; Lovera *et al*, 2006; Carone *et al*, 2005).

2.10 PATIENTS' SUBJECTIVE REPORTS OF THEIR COGNITIVE FUNCTIONING AND PERFORMANCE ON NEUROPSYCHOLOGICAL TESTS

The main focus of this review was to highlight existing research that has compared patients' subjective reports of their cognition and their performance on neuropsychological tests. All of the studies included in this review did this. Thirteen studies used simple correlations, one used a factorial design (e.g. ANOVA; Carone *et al*, 2005), one used multiple regression (Julian *et al*, 2007), and another implemented a goodness of fit regression model (Hosmer-Lemeshow Goodness of fit test) to explore this (Marrie *et al*, 2005).

Seven of the 13 studies that used simple correlations reported a significant relationship between patients' subjective reports of their cognition and their objective performance on neuropsychological tests (Benedict *et al*, 2004; Deloire *et al*, 2006; Goverover *et al*, 2005; Krch *et al*, 2010; Middleton *et al*, 2006; Kinsinger *et al*, 2010; Randolph *et al*, 2004). Of these seven studies, three reported a significant negative correlation between patients *total* scores on the neuropsychological tests and their *total* score on the subjective cognitive measure, ranging from small $r= -0.23$, $p<0.01$ (Kinsinger *et al*, 2010) to large $r=-0.63$, $p<0.01$ (Goverover *et al*, 2005). This denotes that patients' reports were related to their functioning on neuropsychological tests, as patients who obtained low scores on neuropsychological tests (poor functioning), reported more problems with their cognition on subjective measures (Benedict *et al*, 2004; Goverover *et al*, 2005; Kinsinger *et al*, 2010).

Three other studies reported a significant negative correlation between a *single* cognitive measure (from a battery of tests used) and *one* part or single question on a subjective cognitive measure (Krch *et al*, 2010; Deloire *et al*, 2006; Randolph *et al*, 2004). For example, Krch *et al*, (2010) found that patients reports of their subjective memory were related to their performance on trial 1 of a list learning task ($r=- 0.51$, $p<0.001$), but were not related to any other cognitive measure or subjective question.

Middleton *et al* (2006) did not find a relationship between patients' reports of their cognitive functioning and their performance on neuropsychological tests (r= -0.11, p=0.10). They did however report a significant negative correlation between patients performance on the neuropsychological tests, and ratings of their performance on the tests immediately after completing them (r= 0.66, p=0.001) i.e. as performance improved then ratings of performance was reduced.

The remaining five (out of 13) studies using simple correlations found no significant relationship between patients reports of their cognitive functioning and their performance on neuropsychological tests (Benedict *et al*, 2003; Bruce *et al*, 2010; Christodoulou *et al*, 2005; Gold *et al*, 2003; Lovera *et al*, 2006). Non significant correlations ranged from r=-0.01, p>0.05 (Christodoulou *et al*, 2005) to r=0.13, p>0.05 (Gold *et al*, 2003)

Carone *et al* (2005) looked at differences between patients' reports of their cognition and their performance on neuropsychological tests by firstly comparing self reports with reports from informants. Patients were classified into 'under estimators', 'accurate estimators' and 'over estimators' based on how well their reports correlated with informants, and this was then compared with their performance on neuropsychological tests. A significant difference on neuropsychological tests scores were found between patients who under, over, and accurately estimated their cognitive functioning [F(2,95)=4.0, p=0.02]. Post hoc tests using Student Newman-Keuls demonstrated that 'accurate estimators' and 'under estimators' performed better on neuropsychological tests (higher scores), and patients who 'overestimated' their abilities obtained the lowest scores on the cognitive tests.

Marrie *et al* (2005) also looked at differences between patients' reports of their cognition and their performance on neuropsychological tests. Patients were split into 'subjectively impaired' and subjectively unimpaired' based on their subjective reports of their cognition and compared with their performance on neuropsychological tests. No significant differences were found (F values not reported, p=0.09 to p=0.70). However, a goodness of fit regression model revealed a non-linear relationship (Hosmer Lemeshow p-value = 0.54, c-index =0.91) between patients reports of their cognition and their performance on a processing speed task. Marrie *et al* (2005) reported that when functioning on this task was above average (as defined by one standard deviation above the norm) patients reported minimal problems with their cognition, but those with slight declines (a decrease in functioning one standard deviation below the norm, insufficient to meet the criteria for

'impairment') reported the most subjective problems with their cognition. For patients who were the most impaired on the cognitive tests (two or more standard deviations below the norm) they were also less likely to subjectively report problems with their cognition.

Two studies used regression analysis to estimate the predictive value of neuropsychological test performance on patients' reports of their cognitive functioning (Julian *et al*, 2007; Maor *et al*, 2001). Both studies reported that patients' performance on the cognitive tests significantly predicted their subjective reports of cognitive functioning (R^2=0.07, p=0.02, Maor *et al*, 2001; R^2=0.08, p<0.01, Julian *et al*, 2007).

2.11 DEPRESSION, SUBJECTIVE COGNITIVE REPORTS AND NEUROPSYCHOLOGICAL TEST PERFORMANCE

As per inclusion criteria, all of the studies looked at the effect of depression on patients subjective reports of their cognitive functioning. Some also looked at the effect of depression on patients' performance on neuropsychological tests, and others as a factor affecting a relationship between patients' subjective reports and their performance on neuropsychological tests.

2.11.1 DEPRESSION AND SUBJECTIVE COGNITIVE REPORTS

Twelve studies reported a significant relationship between patients' reports of their cognitive functioning and levels of depression. These were reported as both positive and negative correlations. A positive correlation denotes that as symptoms of depression increase, patients' report more problems with their cognition, and negative correlations suggests that as symptoms of depression increase, the lower patients reports their cognitive functioning to be. Positive correlations ranged from r= 0.44, p<0.01 (Gold *et al*, 2005) to r=0.59, p<0.001 (Goverover *et al*, 2005), and negative correlations ranged from r= -0.37, p<0.01 (Maor *et al*, 2001) to r= -0.43, p<0.01 (Deloire *et al*, 2006). Therefore, correlations were moderate to high for positive relationships and moderate for negative relationships.

Two studies using regression analysis found that in predicting patients reports of their cognition, depression predicted an additional 14% (R^2 =0.14, p<0.01; Julian *et al*, 2007) to 17.7% (R^2=-0.17, p<0.05; Maor *et al*, 2001) of the variance, above and beyond which could be accounted for by patients performance on neuropsychological tests (which predicted between 4% and 8% of the variance; Maor *et al*, 2001; Julian *et al*, 2007).

Carone *et al* (2005) looked at significant differences in depression among patients who under and overestimated their cognitive abilities, and found that patients who were depressed were more likely to underestimate their cognitive functioning than patients who were not depressed [$F(2,48) = 3.7$, $p<0.05$]. Marrie *et al* (2005) also looked at differences in depression between patients who were 'subjectively impaired' and 'unimpaired' on a self report cognitive measure, and found that patients who were subjectively 'impaired' reported higher levels of depression (statistic not reported)

2.11.2 DEPRESSION AND NEUROPSYCHOLOGICAL TEST PERFORMANCE

Six studies looked at the effect of depression on neuropsychological test performance (Benedict *et al*, 2003; Bruce *et al* 2010; Christodoulou *et al*, 2005; Lovera *et al*, 2006; Maor *et al*, 2001; Middleton *et al*, 2006). Five of these reported that there was no significant relationship (Middleton *et al*, 2006; Benedict *et al*, 2003; Bruce *et al* 2010; Christodoulou *et al*, 2005; Lovera *et al*, 2006), and non significant correlations ranged from $r= 0.03$, $p>0.05$ (Bruce *et al*, 2010) to $r=-0.24$, $p>0.05$ (Christodoulou *et al*, 2005) . Maor *et al* (2001) reported a weak, negative correlation between one test from a neuropsychological measure (the NCSE) and depression ($r=-0.19$, $p<0.05$), which suggests that patients who performed poorly on this measure were more likely to be depressed.

2.11.3 EFFECT OF DEPRESSION ON SUBJECTIVE COGNITIVE REPORTS AND NEUROPSYCHOLOGICAL TEST PERFORMANCE

Five studies looked at the effect of depression on patients subjective cognitive reports and their performance on neuropsychological tests (Carone *et al*, 2005; Julian *et al*, 2007; Krch *et al*, 2010; Kinsinger *et al*, 2010; Middleton *et al*, 2006). Two of these were longitudinal treatment trials for depression. Kinsinger *et al* (2010) was one of these studies and found following treatment for depression, the relationship between patients' cognitive reports and their functioning on neuropsychological tests improved but was not significant ($r=-0.23$, $p <0.01$ to $r=-0.37$, $p<0.001$). Julian *et al* (2007) was the second longitudinal study, and found that among patients who 'responded' to treatment for depression, depression was no longer a significant predictor of patients' cognitive reports, and their performance on neuropsychological tests became significantly more predictive of patients reports of their cognitive functioning ($R^2=0.39$, $p<0.01$). Among 'non-responders' to treatment, depression remained the only significant predictor of patients cognitive reports ($R^2=0.13$, $p<0.05$) and performance on neuropsychological tests was no longer predictive ($R^2=0.01$, $p=0.55$). They suggest that a change in depressive states may influence the relationship between performance on neuropsychological tests and patients cognitive reports. Specifically,

improvements in depression following treatment are associated with an increased association between performance on neuropsychological tests and patients cognitive reports.

As discussed above, Carone *et al* (2005) looked at significant differences in patients who underestimated and overestimated their cognitive functioning, and found that patients who were depressed were significantly more likely to underestimate their functioning [$F(2,48) = 3.7$, $p<0.05$]. They suggest that depression negatively influences patients' perceptions of their cognitive ability, resulting in a larger difference between what patients report their cognitive functioning to be and their neuropsychological test scores.

Middleton *et al* (2006) also explored the role of depression on patients reports of their cognitive functioning and their performance on neuropsychological tests, and found that depression was a significant predictor variable in this relationship ($b=0.54$; $t=8.08$; $p<0.001$). Krch *et al* (2010) was the only study to report that depression did not significantly affect the relationship between patients' cognitive reports and their performance on neuropsychological tests. They found that although depression was related to patients cognitive reports ($r=0.42$, $p=0.001$), when depression was controlled through partial correlations, the correlation between patients cognitive reports and neuropsychological test performance remained significant and positive ($r=0.34$, $p=0.009$).

2.12 SUMMARY OF SYSTEMATIC REVIEW

A systematic review of the existing literature identified 16 studies that compared patients' reports of cognitive functioning with their performance on neuropsychological tests. All of these studies included a measure of depression and this was considered in the analyses. Thirteen of the studies were cross sectional, and three were longitudinal.

2.12.1 DESCRIPTIVE FINDINGS

Participants were mainly recruited from MS clinics, apart from two studies that recruited from clinics and the community (Goverover *et al*, 2005; Kinsinger *et al*, 2010). Most patients were recruited at random, but some studies required patients to be either reporting cognitive problems (Lovera *et al*, 2006; Marrie *et al*, 2005), or displaying mild cognitive impairment to participate (Christodoulou *et al*, 2005). The mean ages of participants ranged between 37-50 years old across the studies, although the majority of studies reported the mean age of participants to be in their 40's. Disease duration ranged from 8-11 years in all but one study, as this study only included newly diagnosed MS patients (disease duration < 2 years, Deloire *et al*, 2006). Consistent with the prevalence of MS, females

outweighed males in all of the studies, with some studies reporting up to 90% females (e.g. Bruce *et al*, 2010). Patients' mean level of functional impairment was found to fall within the mild-moderate functional range in 14 studies, and severe functional impairment in two studies (Maor *et al,* 2001; Randolph *et al*, 2004). This is consistent with the larger number of RR type MS patients that participated in the studies (48% Gold *et al*, 2005 to 88% Benedict *et al,* 2003 of entire sample) and the lower level of impairment associated with this MS sub-type.

2.12.2 COGNITIVE FUNCTIONING

Studies included in the review used neuropsychological tests to measure cognitive functioning. Memory was the most commonly assessed domain with 15 studies including a measure of memory, with the exception of Gold *et al*, (2003). Thirteen studies included a measure of processing speed and 12 included a measure of executive functioning. This finding is encouraging given that these domains are found to be the most commonly impaired cognitive domains in MS patients (Amato *et al*, 2001). Language was assessed by 11 studies, which was surprising given that language functions have received less attention than other aspects of cognitive decline in MS (Drew *et al*, 2008). Only three studies included a measure of spatial orientation (Benedict *et al*, 2003; Benedict *et al*, 2004; Carone *et al*, 2005).

Six studies reported that 35-56% of patients were cognitively impaired (Benedict *et al*, 2004; Crone *et al*, 2005; Deloir *et al*, 2006; Gold *et al*, 2003; Maor *et al*, 2001; Marrie *et al*, 2005), and one study reported that 12% of patients were cognitively impaired (Randolph *et al*, 2004). Findings from these studies are consistent with longitudinal research which has demonstrated that between 40-60% of MS patients are affected by cognitive impairment (Amato, Zipoli & Portaccio, 2006). Memory and processing speed were the domains patients were the most impaired on, although the specific domains were not reported by six studies (Benedict *et al*, 2003; Benedict *et al,* 2004; Julian *et al,* 2007; Krch *et al,* 2010; Kinsinger *et al*, 2010; Marrie *et al*, 2005).

2.12.3 SUBJECTIVE COGNITIVE REPORTS

Patients' reports of their cognitive functioning were assessed by subjective cognitive measures. These were completed by patients, and three studies also included an informant's report of patients cognitive functioning (Benedict *et al*, 2003; Benedict *et al*, 2004; Carone *et al*, 2005). Unlike the neuropsychological tests, subjective measures were not reported to be selected according to which, or how many cognitive domains they measured, and therefore varied across the studies. Subjective cognitive measures included questions about at least one cognitive domain found to be impaired in

MS, although there was no consistency in the number questions that were used to assess 'subjective cognitive impairment'.

Patients were asked to report their memory functioning in 15 studies and this was the most commonly assessed subjective cognitive domain (Goverover *et al*, 2005 did not asses memory). Seven studies asked patients to report their subjective executive functioning abilities (e.g. Marrie *et al*, 2005), and three studies asked patients report any difficulties with their processing speed (e.g. Carone *et al*, 2005). Five studies included a subjective measure of attention (e.g. Marrie *et al*, 2005), and three studies asked patients to report their subjective language abilities (Benedict *et al*, 2003; Benedict *et al*, 2004; Carone *et al*, 2005).

Two studies provided the percentage number of patients that were 'impaired' according to the subjective cognitive measures criterion. This ranged from 22% (Deloire *et al*, 2006) to 51% of the study's population (Maor *et al*, 2001). Only one study found that found that patients' reports of their cognitive functioning varied according to patients' age, or indeed any other demographic or MS characteristic (Marrie *et al*, 2005).

2.12.4 DEPRESSION

Studies used a number of commonly used measures to assess depression e.g. BDI-II, CES-D, most of which are designed to be used in mental health services as opposed to medical settings (Wallin *et al*, 2006). Only two studies included a measure of depression that did not assess the somatic symptoms associated with MS (Benedict *et al*, 2004; Bruce *et al*, 2010). Prevalence of depression ranged from 27%-61% of patients affected (Benedict *et al*, 2004; Gold *et al*, 2003; Krch *et al*, 2010; Kinsinger *et al*, 2010; Lovera *et al*, 2006; Maor *et al*, 2001; Randolph *et al*, 2004).

2.12.5 PATIENTS SUBJECTIVE COGNITIVE REPORTS AND THEIR PERFORMANCE ON NEUROPSYCHOLOGICAL TESTS

Seven studies reported that there was a significant relationship between patients' subjective reports of their cognition and their performance on neuropsychological tests (Goverover *et al*, 2005; Benedict *et al*, 2004; Deloire *et al*, 2006; Randolph *et al*, 2004; Krch *et al*, 2010; Middleton *et al*, 2006; Kinsinger *et al*, 2010). Three of these reported a significant negative correlation (Goverover *et al*, 2005; Benedict *et al*, 2004; Kinsinger *et al*, 2010), which denotes that lower scores on neuropsychological tests (poor functioning), correlated with more subjective reports of cognitive problems. Three other studies reported negative correlations, but these existed between a single

cognitive measure (from a battery of neuropsychological tests) and one part (or question) from a subjective cognitive measure (Deloire *et al*, 2006; Krch *et al*, 2010; Randolph *et al*, 2004), and it is questionable whether performance on one measure provides a comprehensive assessment of cognitive functioning. Middleton *et al* (2006) also reported that patients' reports were related to their performance, but significant results were only found between test performance and how well patients thought they had done on the test immediately after completing it.

Carone *et al* (2005) found a significant difference in neuropsychological test performance between patients who under, over, and accurately estimated their cognitive functioning, but Marrie *et al*, (2005) did not find any significant differences. Marrie *et al* (2005) did however find a non-linear relationship between patients' reports of their cognition and their performance on a processing speed task. Thus patients who were experiencing mildly impaired processing speed (not enough to make criteria for impairment) reported the most problems with their cognition, and those who were cognitively impaired or in the upper extremity of functioning reported the least problems.

The two studies using regression analysis also reported a relationship between neuropsychological test performance and patients' reports of their functioning. They reported that patients' performance on the cognitive tests significantly predicted their reports of cognitive functioning, although as discussed below, this was relatively weak (Julian *et al*, 2007; Maor *et al*, 2001). Six studies using simple correlations found no significant relationship between patients reports of their cognitive functioning and their performance on neuropsychological tests (Benedict *et al*, 2003; Benedict *et al*, 2004; Bruce *et al*, 2010; Christodoulou *et al*, 2005; Gold *et al*, 2003; Lovera *et al*, 2006).

2.12.6 THE IMPACT OF DEPRESSION ON PATIENTS SUBJECTIVE REPORTS AND THEIR PERFORMANCE ON NEUROPSYCHOLOGICAL TESTS

Depression was consistently reported to affect patients' subjective reports of their cognitive functioning. Twelve studies reported significant positive correlations, which suggests that as patients' subjective cognitive reports increased (poor cognitive functioning), their levels of depression also increased. Two studies reported that depression predicted significantly more of the variance than neuropsychological tests performance (14% to 17.7% Julian *et al*, 2007; Maor *et al*, 2001).Patients who were depressed were also more likely to underestimate their cognitive ability than patients who were not depressed (Carone *et al*, 2005), and patients who were 'subjectively

impaired' according to their cognitive reports were also more likely to be depressed (Marrie *et al*, 2005).

Five studies looked at the role of depression in the relationship between patients' subjective reports and their performance on neuropsychological tests (Carone *et al*, 2005; Julian *et al*, 2007; Kinsinger *et al*, 2010 Krch *et al*, 2010; Middleton *et al*, 2006). Two of these were longitudinal (Julian *et al*, 2007; Kinsinger *et al*, 2010). Julian *et al*, (2007) found that following a change in levels of depression (after Psychological treatment) patients' subjective cognitive reports were more reflective of their performance on neuropsychological tests, but Kinsinger *et al*, (2010) found no significant change in patients' subjective cognitive reports. Carone *et al* (2005) reported that depression significantly affected the relationship between patients' cognitive reports and their performance on neuropsychological tests, and Middleton *et al* (2006) found that depression was a significant predictor variable in the relationship between patients' cognitive reports and their neuropsychological test performance. Krch *et al* (2010) was the only study that reported that depression did not significantly affect the relationship between patients' reports of their cognition and their performance on a neuropsychological test.

Six studies looked at the effect of depression on neuropsychological test performance (Benedict *et al*, 2003; Bruce *et al* 2010; Christodoulou *et al*, 2005; Lovera *et al*, 2006; Maor *et al*, 2001; Middleton *et al*, 2006). Five of these reported that there was no significant relationship (Benedict *et al*, 2003; Bruce *et al* 2010; Christodoulou *et al*, 2005; Lovera *et al*, 2006; Middleton *et al*, 2006). Maor *et al* (2001) reported a weak, negative correlation between one test from a neuropsychological measure (the Neurobehavioral Cognitive Status Examination; NCSE) and depression.

2.13 LIMITATIONS OF STUDIES

When interpreting the findings from the systematic review there are a number of limitations that should be considered.

2.13.1 FINDINGS

Although studies reported significant correlations between patients subjective cognitive reports and their neuropsychological test performance, these were relatively weak e.g. Kinsinger, Lattie & Mohr (2010) $r=-.23$, $p<0.001$ (Cohen, 1988). Goverover *et al* (2005) reported the highest correlations between patients subjective cognitive reports and their neuropsychological test performance, ($r=-0.47$ to $r=-0.63$, $p>0.01$), but this study only included 26 patients and the large significant

relationship in this study may be due to a lack of statistical power. Studies reporting the predictive values of neuropsychological tests performance on subjective cognitive reports were also very small (7.4%, Maor *et al*, 2001; 8% Julian *et al*, 2007) and should be considered when interpreting the results.

2.13.2 SAMPLING

2.13.2.1 LEVEL OF FUNCTIONAL IMPAIRMENT

Five studies in the review only included patients with mild physical impairment, some of which were in the early stages of the disease and were newly diagnosed (Benedict *et al*, 2003; Bruce *et al*, 2010; Deloire *et al*, 2006; Goverover *et al*, 2005; Krch *et al*, 2010). Two of these studies reported no significant relationship between patients cognitive reports and their performance on neuropsychological tests (Benedict *et al*, 2003; Bruce *et al*, 2010), and two found a significant relationships between one cognitive test and one question from a subjective cognitive measure (Deloire *et al*, 2006; Krch *et al*, 2010). It is possible that patients in these studies may have been in the initial stages of coming to terms with their diagnosis, or thinking about how it may impact on their life, which may have influenced their subjective cognitive reports.

2.13.2.1 REFERRAL INTO THE STUDIES

Some studies required patients to be reporting or displaying cognitive impairment in order to participate in the study, which may have also influenced their findings. Two studies that reported no significant relationship between patients cognitive reports and their performance on neuropsychological tests required patients to be displaying mild cognitive impairment (Christodoulou *et al*, 2005), or reporting problems with their cognition (Lovera *et al*, 2006) to participate. Therefore, even when recruiting patients who are reporting problems with their cognition, no relationship was found. Patients were also referred into studies for experiencing difficulties with their mood. For example, Carone *et al* (2005) found a significant difference in levels of depression between patients who overestimated and underestimated their cognitive functioning, but may have found different results if patients were randomly recruited.

2.13.3 MEASUREMENT

2.13.3.1 NEUROPSYCHOLOGICAL TESTS

Three studies reporting significant correlations between patients' cognitive reports and their performance on neuropsychological tests failed to include a measure of processing speed (Julian *et al*, 2007; Krch *et al*, 2010; Maor *et al*, 2001). This domain is one of the most commonly impaired

cognitive domains in MS patients, and failure to measure this may not have provided a comprehensive assessment of patients cognitive functioning.

Gold *et al* (2003) included a large sample of patients in their study (n=196), but only included a single neuropsychological test (processing speed). Whilst this cognitive domain is found to be commonly impaired in MS, it is questionable whether *one* test provides an accurate assessment of patients' cognitive functioning, and may explain why no significant relationship with patients' subjective cognitive reports was found.

Kinsinger, Lattie & Mohr (2010), administered neuropsychological tests by telephone and found a significant relationship between patients' cognitive reports and their performance on neuropsychological tests. This has potential implications for interpreting the results of this study as there is no way of knowing if participants were following procedures correctly or were using memory aids to help them i.e. writing things down, and they could also not include any visual tasks. There is no way of knowing therefore if patients would have performed as well on the neuropsychological tests if they were administered during a clinical appointment, face-to-face.

Only three studies assessed all of the cognitive domains found to be impaired in MS and reported mixed findings (Benedict *et al*, 2003; Benedict *et al*, 2004; Carone *et al*, 2005). Carone *et al*, (2005) reported a significant difference in patients' cognitive reports between those who were impaired and unimpaired on neuropsychological tests. Benedict *et al* (2004) reported a negative correlation between patients reports and their performance on neuropsychological tests (i.e. patients reported more problems as their impairment increased), and Benedict *et al* (2003) found no significant relationship.

2.13.3.2 COGNITIVE IMPAIRMENT

There was an inconsistency in the definition of cognitive 'impairment' between studies, which highlighted existing difficulties in deciding what should be classified as cognitively impaired in MS. Although studies quantified scores into z-scores which allowed comparison against the population mean, the use of different measurement criteria meant that participants may have been defined as 'impaired' in one study, and 'unimpaired' in another. For example, Benedict *et al* (2004) was found to be a good quality study in the review as it included a subjective measure that assessed a number of domains, included objective measures that assessed all of the cognitive domains found to be impaired in MS, and included a large sample of patients at varying stages of the disease. However,

this study implemented a more stringent criterion for impairment in comparison to other studies in the review, which made comparison difficult. For instance, in comparison to Marrie *et al* (2005) who defined impairment as impaired on one cognitive test (score < 5th percentile), Benedict *et al* defined impairment as impaired functioning across all six cognitive domains assessed, and patients who would have been classified as 'impaired' in other studies would be classified as 'unimpaired' according to this criterion.

2.13.3.3 SUBJECTIVE COGNITIVE REPORTS

When patients were asked to report their cognitive functioning, measures used were often limited in the number of domains they included. Four studies included a subjective cognitive measure that was a QOL measure, and was therefore limited in both the number of cognitive domains and questions it asked (Deloire *et al*, 2006; Gold *et al*, 2003; Julian *et al*, 2007; Maor *et al*, 2001).Three other studies used a measure that only included questions about subjective memory (Bruce *et al*, 2010; Middleton *et al*, 2006; Randolph *et al*, 2004), and it is possible that limiting questions to one cognitive domain did not provide patients with an opportunity to report difficulties they may be experiencing in other areas (i.e. processing speed, problem solving). These studies found no significant relationship found between scores on these subjective measures and patients functioning on neuropsychological tests, and it is possible that a relationship may have been found if a broader subjective measure was used.

Two studies also determined the 'accuracy' of patients' cognitive reports by comparing them with informant reports (Carone *et al*, 2005; Goverover *et al*, 2005). Thus, patients' actual cognitive reports were not compared with their neuropsychological tests scores, and may account for the non-significant finding by Carone *et al*, (2005). Goverover *et al* (2005) did however found a positive correlation between better 'self awareness' (based on how well reports matched with informants) and better cognitive functioning, but only included a small number of patients in their study (n=26) and was therefore underpowered.

2.13.3.4 DEPRESSION

When interpreting the results of these studies it is important to consider that only two studies included a measure of depression that was sensitive to MS symptomatology (Benedict *et al*, 2004; Bruce *et al*, 2010). This needs to be considered when interpreting the results of the five studies that explored the role of depression on patients subjective cognitive reports and their neuropsychological test performance, as none of these studies included a depression measure sensitive to MS

symptomatology (Carone *et al*, 2005; Julian *et al*, 2007; Kinsinger *et al*, 2010 Krch *et al*, 2010; Middleton *et al*, 2006).

2.14 CONCLUSION

There is evidence to suggest that patients' reports of their cognition relate to their performance on neuropsychological tests, and that depression can be an influential variable in this relationship. Whilst significant results were found, there were some mixed findings, and a number of study limitations were identified. These included: the size of the sample and level of functional impairment; referral into the study for reporting problems with cognition or mood; the inconsistent definition of 'cognitive impairment'; the number of neuropsychological tests used to measure cognition; subjective cognitive measures that were limited to questions about one cognitive domain; and a measure of depression that was sensitive to MS symptompology.

Two studies were identified as being of better quality, and may therefore be more representative of patients' reports of their cognition and their performance on neuropsychological tests (Benedict *et al*, 2004; Marrie *et al*, 2005). A number of strengths were identified in these studies, which include a large sample size of MS patients who varied in level of impairment, utilising a battery of neuropsychological tests that assessed all of the cognitive domains found to be impaired in MS, and use of a subjective measure that asked questions about more than one subjective cognitive domain.

Benedict *et al* (2004) reported that there was a significant negative correlation between patients' reports of their cognition and their performance on neuropsychological tests, in particular, tests that assessed processing speed, memory and spatial orientation. This suggests that as patients became more impaired on these tests, they reported more problems with their cognition. Marrie *et al* (2005) found that there was a non-linear relationship between patients' reports of their cognition and their performance on a processing speed task. They demonstrated that patients who were mildly impaired on the processing speed task (not enough to meet criteria for impairment) reported the most problems with their cognition, and both those who showed no sign of impairment and patients who were significantly impaired, reported very few problems with their cognition.

Both Benedict *et al* (2004) and Marrie *et al* (2005) reported that depression was positively correlated with patients' reports of their cognitive functioning. Thus as patients reports increased on the subjective measures (denoting poor impairment) symptoms of depression also increased. Although

neither of these studies looked at the influence of depression on the relationship between patients' cognitive reports and their neuropsychological test performance.

However, these studies did have their limitations and these were considered when interpreting their findings. Firstly, patients were referred into the study by Marrie *et al* (2005) for reporting cognitive impairment. Secondly, Marrie *et al* (2005) used a measure of depression that included questions about the somatic symptoms associated with MS (fatigue, insomnia etc). Thirdly, Benedict *et al* (2004) implemented a very strict criteria for cognitive impairment, and patients who may have been defined as 'unimpaired' on this study, would have been defined as 'impaired' in other studies included in the review. And finally, whilst these studies also included a subjective measure that included questions about more than one cognitive domain, questions were still limited, and may have failed to provide a comprehensive opportunity for patients to report their cognition. Whilst these studies reported a significant relationship, it must also be considered that Benedict *et al* (2004) reported *weak* to *moderate* correlations on 5 (out of 7) neuropsychological tests (r=0.37 to r=-0.45, p=0.05), and Marrie *et al* (2005) only reported a significant relationship between *one* neuropsychological test (processing speed) and patients subjective reports. It can be concluded therefore that whilst these studies found a relationship between patients' subjective cognitive reports and their neuropsychological test performance, this was relatively weak. It is possible that if the limitations of these studies were considered in future research, that this may improve the relationship between patients' subjective cognitive reports and their performance on neuropsychological tests.

2.15 IMPLICATIONS FOR FUTURE RESEARCH

Given the limitations of these studies and those included in the review, there are a number of considerations that could be taken in order to improve our knowledge in this area. Firstly, a sufficient sample of patients should be included in the study that is representative of MS patients e.g., varies in their level of functional impairment, disease duration, and patients should be selected at random as opposed to being referred to the study. Only including patients who are reporting problems with their cognition or who are demonstrating a level of cognitive impairment may be less representative of patients coming to routine clinical appointments.

Secondly, neuropsychological tests should be implemented to assess all of the cognitive domains found to be impaired in MS i.e. processing speed, memory, executive functioning, language and spatial orientation, as this may provide a more comprehensive assessment of patients functioning on

these tests. Furthermore, when considering what is 'cognitive impairment' on these tests, a criterion of impairment should be implemented that is consistent with the neuropsychological test criteria (i.e. a z-score <5th percentile).

Thirdly, patients should be provided with a subjective measure that includes questions about all of the cognitive domains impaired in MS (as above), so that patients reports of their cognitive functioning are not limited by the questions they are asked by e.g. only including a subjective measure of memory. Subjective questions should also be administered to patients before they complete neuropsychological tests, in order to limit patients' perceived performance on these tests on their subjective reports.

And finally, a measure of depression should be implemented that does not include the somatic symptoms of MS i.e., fatigue, insomnia/ hypersomnia, psychomotor retardation and decreased concentration. These are common symptoms of MS and are therefore likely to influence patients reported level of depression.

CHAPTER THREE

AIMS AND HYPOTHESES

3. STUDY AIMS AND HYPOTHESES

3.1 STUDY AIM ONE

The main aim of this study was to compare patients' subjective cognitive reports with their performance on neuropsychological tests and consider the role of depression. The study intended to do this by:

- Implementing a battery of neuropsychological tests that assessed *all* of the domains found to be impaired in MS;
- Applying a criterion of cognitive impairment that is consistent with neurological test criteria for impairment (i.e. a score less than the 5th percentile), so that cognitive impairment can be classified appropriately;
- Providing an opportunity for patients to report their level of cognitive functioning on a measure that is not limiting in the number of subjective areas in contains, e.g., not just memory;
- Using a measure of depression that is sensitive to the somatic symptoms associated with MS, so that the effect of depression on patients' reports can be appropriately considered.

3.1.2 SPECIFIC HYPOTHESES

1. Patients who are impaired on neuropsychological tests will report more problems with their cognition
2. Patients who are depressed will report more subjective problems with their cognition
3. The effect of neuropsychological test performance on patients subjective cognitive reports will be different for those who are depressed and not depressed

3.2 STUDY AIM TWO

In order to provide patients with an opportunity to report their level of cognitive functioning on a subjective measure that was less limiting in the cognitive areas which it assesses; as they are ALL limited in the number of questions they contain. The Perceived Deficits Questionnaire (PDQ). This measure was highlighted in the review as the most commonly used subjective measure of patients' cognitive reports, but fails to include questions about subjective processing speed and language

(domains commonly impaired in MS). Study aim 2 therefore was to provide a broader subjective cognitive measure for patients to report their cognition. This was an exploratory analysis and no specific hypotheses were therefore made.

CHAPTER FOUR

METHODOLOGY

4. INTRODUCTION

This chapter will describe the methods used for this research study, and considers the design, sample, measures used, procedure, and ethical considerations.

4.1 DESIGN

The study employed a cross-sectional design to compare patients' subjective cognitive reports with their performance on neuropsychological tests. Depression was also considered as a factor when comparing these two variables. The study used standard neuropsychological tests, a self-report cognitive measure to assess patient reports, and a psychometric measure of depression.

4.2 POWER ANALYSIS

There have been a number of published studies that have compared patients' subjective cognitive reports with their performance on neuropsychological tests. Christodoulou *et al* (2005) was one of these studies and was included in the systematic review. In this study 53 participants completed the Perceived Deficits Questionnaire (PDQ) as a measure of patients' cognitive reports and the Symbols Digits Modalities Test (SDMT) to assess processing speed (neuropsychological test). The study found that the PDQ correlated with the SDMT at rates of $r = 0.46$, $p<0.05$, which is classified as a medium effect size according to Cohen (Cohen, 1988).

Using standard parameters of $\alpha = 0.05$ for an 80% chance of power being detected, a power analysis for a factorial design identified that 40 participants were needed per group. Participants were split based on whether they were cognitively impaired or unimpaired on a neuropsychological test; this resulted in 2 groups. In order to obtain the appropriate power, this study therefore aimed for a sample size of no less than 80 participants (Cohen, 1988, p.83).

4.3 PARTICIPANTS

The participants comprised of 82 MS patients who were receiving a service from a South Wales Centre for neuroinflammatory diseases. This centre is a major tertiary referral centre for neurology and provides a network of MS clinics for approximately 1500 patients. All participants had received a diagnosis of MS as defined by the McDonald (McDonald, 2000) or Poser criteria (Poser, 1983). Additional inclusion criteria for participation included patients that were:

- Aged 18 or over
- Fluent in English
- Able to provide informed consent to take part in the study

Patients were excluded from the study if they:

- Were unable to consent to participate
- Had a current or past neurological disorder other than MS
- Had a current psychiatric disorder other than depression
- Had a current substance abuse problem

The clinical team were asked to apply this criterion when identifying potential participants during clinical contact. Patients excluded based on this criterion were therefore not made available to the researcher.

4.4 MEASURES

Measures were classified into two types. The first type were those that were based on patients' self reports, and were classified as subjective measures. The second type were neuropsychological measures aimed at objectively assessing cognitive functioning. As highlighted in the review, these measures are routinely used in both research and clinical practice with MS populations.

4.4.1 SUBJECTIVE MEASURES

Following their identification within the systematic review, subjective measures were explored with the lead Neuropsychologist at the Centre for Neuro- Inflammatory diseases, and a Consultant Clinical Psychologist. A subjective cognitive measure was selected based on its validity and reliability within the literature, and use within clinical practice. Subjective measures of mood were also highlighted from the review and discussed, and a measure was selected based on its use within the literature, and that was understood to be sensitive to symptoms associated with MS.

4.4.1.1 THE PERCEIVED DEFICITS QUESTIONNAIRE (PDQ)

Participants' cognitive reports were measured by the PDQ (Sullivan, Edgley & Dehoux, 1990; Appendix 2). The PDQ was identified in the systematic review as the most commonly used measure of subjective cognitive functioning. It is a 20 item Likert based questionnaire that assesses perceived cognitive problems, and also forms part of a larger quality of life instrument; the MS Quality of Life Inventory (MSQLI; Fischer *et al*, 1999). The PDQ consists of questions that assess subjective memory (prospective and retrospective), attention, and planning, and participants are asked to indicate how frequently they experience each of the difficulties on a 5-point scale ranging from 0 (never) to 4 (almost always). Total scores range from 0 to 80, *with higher scores denoting more reported problems with patients' cognition*. Patients were defined as 'subjectively impaired' if they reported a PDQ score >40, a score more than 2 standard deviations greater than that previously reported in healthy populations (Sullivan, Edgley & Dehoux, 1990).

In an attempt to provide patients with a broader measure to report their cognition, questions about language and processing speed; domains commonly impaired in MS, were added to the PDQ to form the Extended PDQ or PDQ-E. These questions were developed in conjunction with the Neuropsychologist at the Centre for Neuro-inflammatory Diseases, and were based on clinical experience of what patients report during routine appointments. The PDQ-E consisted of 28 items (Appendix 2), and a score of >56 (i.e. half the maximum score) was used to define 'subjective cognitive impairment' on this measure.

4.4.1.2 THE BECK-DEPRESSION INVENTORY-FAST SCREEN (BDI-FS)

The BDI-FS (Beck *et al*, 2000) was identified from the review as a valid measure of clinically significant levels of depression in medical patients. It consists of 7-items which assesses dysphoria, suicidal ideation, and cognitive related symptoms on a three point scale. Scores range from 0 to 21, with higher scores indicating more depressive symptomatology. A score of $\geq$4 was used to define clinically significant levels of depression (Beck *et al*, 2000). The measure was selected based on its demonstrated validity within MS populations, and because it has omitted questions about the somatic symptoms associated with MS (e.g. insomnia, fatigue, poor concentration).

4.4.1.3 THE EXPANDED DISABILITY STATUS SCALE (EDSS)

The EDSS is the most widely used measure in MS research and clinical practise. It is usually completed by clinicians, and is used to determine the functional abilities of patients with MS. Scores on the EDSS are usually based on the results of neurological examinations and the walking abilities of

patients (Kurtzke, 1983). The most recent EDSS scores were obtained from the services patient database following patients consent to the study.

A self report version of this measure was also administered and formed part of the subjective measures (Appendix 3). This self report scale has been found to correlate highly with clinician rated EDSS within the same MS population (intraclass correlation coefficients of 0.69 to 0.89; Ingram *et al*, 2010). It required participants to select from a series of statements describing walking abilities and use of aids, and provides patients with a score ranging from less than 4 to 8, with a higher score signifying higher levels of disability. Statements are based on how far patients can walk at *their best*, and provide distances in Yards. For those patients who may not be familiar with this measurement of distance e.g. 550 yards, the questionnaire makes reference to well-recognised local landmarks to aid decisions.

The EDSS self report measure does not allow patients to score an EDSS score of below 4 (minimal impairment), as these scores are usually determined by a neurological examination. In order to determine scores for participants who scored less than 4, a review of patient records was conducted. The mean EDSS score was calculated from a total of 2399 neurological examinations of MS patients who obtained a score of less than 4 and who were not currently in relapse. The mean score recorded was 2.16, and as such, any value < 4 on the self report EDSS was entered as 2.16 in the analysis.

4.4.1.4 THE FATIGUE SEVERITY SCALE (FSS)

The Fatigue Severity Scale (FSS) was used as a measure of fatigue due to broad use within MS populations (Appendix 4). It has been reported to have acceptable internal consistency (Krupp, 1989), and in a recent review, was found to be the most discriminative fatigue scale within MS (Flachenecke, 2002). It consists of a 9-item questionnaire, and participants are required to use a 7-point Likert scale ranging from 1 (‘completely disagree’) to 7 (‘completely agree’), to rate their response. The mean score of the 9 items was used as the ‘FSS score’ and categorise the severity of participants’ fatigue. In recent literature, fatigue has been set as a FSS score $\geq$ 5 (Johansson *et al*, 2008; Lerdal *et al*, 2007; Tellez *et al*, 2005) and this was used to define clinically significant levels of fatigue.

4.4.2 NEUROPSYCHOLOGICAL TESTS

Neuropsychological tests were also identified from the systematic review and through discussions with Specialist Neuropsychologist at the service. Neuropsychological tests were selected to assess the specific cognitive domains found to be impaired in MS, namely: memory; processing speed; executive functioning; visual perception and; language. The burden the tests would place on patients to complete i.e. how stressful they may be to complete and the length of time needed to complete each task were also considered.

4.4.2.1 MEMORY

4.4.2.1.1 THE CALIFORNIA VERBAL LEARNING TEST VERSION II (CVLT-II)

The CVLT-II (Delis *et al*, 2000) is a measure of verbal learning and memory, and was identified in the systematic review as the most widely used measures of memory within the MS population. It is a multiple-trial list-learning task, and requires patients to remember, recall and recognise two word lists over immediate and delayed memory trials. In the first 5 trials patients were asked to recall words from 'List A' immediately after they were presented with the list. List A is composed of 16 words, four from each of four semantic categories (furniture, vegetables, animals, and ways of travelling), and each word from a semantic category is presented consecutively. A 16-word inference list, 'List B' was then presented for one trial, and introduced two additional categories: musical instruments and parts of a house. Following this, patients were required to recall words from List A in a free recall and cued recall trial. A 20 minute delay then occurred before participants were required to recall words from List A again. The CVLT-II has been found to have high internal consistency (r=0.80 to 0.89) for the immediate recall tasks, and adequate internal consistency for the long delay task (r=0.70 to 0.79; Delis *et al*, 2000).

4.4.2.1.2 DIGITS FORWARD AND BACKWARD

The Digit Span task is a subtest that forms part of the Wechsler Adult Intelligence Scale fourth Edition (WAIS-IV; Wechsler, 2008). It is a measure of auditory attention and working memory and comprises of two parts; a forward and backward task. Each segment (forward and backward) consists of seven pairs of random number sequences, and required participants to repeat the string of digits in the same order in, or backwards to the researcher. Participants are required to repeat all of the numbers in the correct order for each segment. This measure has been found to have high internal consistency (sub scales range from r=0.80 to 0.89).

4.4.2.2 PROCESSING SPEED

4.4.2.2.1 THE SYMBOL DIGIT MODALITIES TEST (SDMT)

The SDMT (Smith, 1991) was used as a measure of information processing speed. The test has two forms: the oral (where respondents call out their response); and the written (where respondents write their response). Performance on both versions have been found to correlate well (r=0.78, Smith, 1991; r=0.88, Ponsford & Kinsella, 1992). The oral version of this test was used so that those who may be experiencing physical or sensory difficulties would not be disadvantaged. During the task a coding key was presented to participants that consisted of nine abstract symbols, each paired with a number. Participants were provided with a list of symbols and required to use the key to complete the task. Participants were given 90 seconds to call out the number corresponding to each symbol as fast as possible while the examiner recorded their responses. Scores were derived from the number of correctly completed abstract symbols.

4.4.2.3 LANGUAGE

4.4.2.3.1 ANIMAL FLUENCY TEST

The Animal fluency test (Lezak, 1995) was used as a measure of language functioning. The test emphasised category association through the requirement to spontaneously produce words belonging to a defined semantic grouping. Word generation tasks such as this have been identified as the most common measure of language abilities in the MS population. It is a 60 second task within which the participant was asked to name as many animals as they could call to mind. Participants are not pre-warned about the task, and therefore evaluated on their spontaneous production of words under restricted search conditions. Norms for this task were obtained from a study by Tombaugh *et al*, (1999) and were used to score the number of animals participants generated.

4.4.2.4 EXECUTIVE FUNCTIONING

4.4.2.4.1 STROOP TASK

The Stroop task was selected as it places demands on executive functioning, including selective attention and cognitive flexibility (Stroop, 1935). The version used in this study was taken from the Delis-Kaplan Executive Functioning System D-KEFS (Delis *et al*, 2001) and was a timed task (therefore also assessing speeded processing). The Stroop task as part of the DKEFS has been found to have adequate internal consistency in a normative sample (r=0.70 to 0.79; Delis *et al*, 2001). As part of this task patients were presented with a page containing 50 colour words (red, green and blue), whereby each colour word was printed in an incongruent ink colour e.g. the word blue was printed

in the ink colour red. Participants were instructed to name the *ink* colour of the 50-items as fast as they could without making any errors. The researcher timed this task and this was recorded as their raw score.

4.4.2.5 SPATIAL ORIENTATION

4.4.2.5.1 BENTON JUDGEMENT OF LINE ORIENTATION TEST

The Benton Judgement of Line Orientation Test was used as a measure of spatial orientation. Although not commonly assessed in the MS literature, this was the only measure of spatial orientation included in studies in the review, and is frequently used in clinical settings. The test consists of line segments of varying spatial orientation which must be matched with a set of longer lines on a response card. Due to the length of this test, the short form was used to ease completion for participants. The short form consists of 15 items and, as would be expected given the decrease in the number of items, the internal consistency is lower, however is still considered to be adequate (r=0.69 to 0.75; Vanderploeg *et al*, 1997; Winegarden *et al*, 1998). Normative data from the short form of the test were obtained from Woodward *et al*, (1998), and participants' scores were calculated according to this.

4.5 PROCEDURE

4.5.1 CLINICAL GOVERNANCE

Research and Development approval was obtained from Cardiff and Vale and Gwent Local Health Board Research and Development Offices (R&D; Appendix 5), and the South East Wales Research Ethics Committee (LREC; Appendix 6). Permission to complete the research was also obtained from service managers and clinical staff at the Neuroinflammatory Service.

As part of the process of designing the study, the researcher met with the Specialist Neuropsychologist at the Service to review the research protocol, participant information sheet, consent form and proposed research procedure. The researcher also met with members of the clinical team, including MS nurses to discuss the purpose of the research, and the practicalities of completing the project i.e. clinical space and accessibility of patients at clinics. Inclusion and exclusion criteria were developed and discussed with the clinical team before the study began.

4.5.2 ETHICS

Ethical approval was obtained from R&D and LREC before completing the study (see above procedure). The main ethical issues that arose were:

4.5.2.1 CONTACTING PATIENTS

Patients were not contacted by the lead researcher, and were only told about the study during clinical contact. The direct care staff were the only ones that had access to patients' personal information, and had the responsibility for screening potential participants. Only once patients had provided consent to the study were their details made available to the lead researcher.

4.5.2.2 CONSENT

Patients were provided with a patient information sheet which explained the study in lay person's terms. The lead Clinician's contact details were also provided so that patients could discuss the information further if they wanted to. Patients were provided with an opportunity to ask questions when they met with the researcher, and were reminded that they were free to withdraw at any time. The researcher also assessed whether or not patients understood what they were consenting too by checking patients understood the information.

4.5.2.3 ASKING PATIENTS TO REPORT THEIR COGNITIVE FUNCTIONING

It was anticipated that this may evoke an emotional response from some patients who may be concerned about their cognitive functioning. These questions form part of the standard clinical review of MS patients, and patients who clinicians thought would find participating too distressing were not included in the study. The researcher was also mindful of any participants who showed distress when participating.

4.5.2.4 STORING PERSONAL INFORMATION

All participants were assigned an identification number which was used in the analysis to ensure that no identifying information could be obtained from the data. Participants' personal details were stored in a separate database to their scores on the standard measures, and all identifying information was stored within the MS service secure database. Consent forms were stored in a locked filling cabinet on NHS premises, and questionnaires were only identifiable via ID numbers. These were also stored in a locked filling cabinet on NHS premises and were kept separate from the consent forms.

4.6 RECRUITMENT

Following R&D and LREC approval, clinical staff were provided with information packs, copies of inclusion and exclusion criteria and pre-paid envelopes. The information pack contained a Patient Information Sheet (Appendix 7), covering letter (Appendix 8), and a tick box question (Appendix 9) stating whether they would like to participate or not. Patients who were interested in participating were asked to complete the tick box question and provide their name, address and contact number. The tick box question was then returned to clinical staff at that time or by post. Clinical staff informed the lead researcher of patients interested in participating and passed on the completed tick box form.

Following this, the lead researcher contacted patients via telephone to arrange a suitable time and place to carry out the assessment. Participants were offered an appointment at a convenient NHS outpatients centre within health boards as close to their home as possible. The lead researcher was also available in weekly clinics for those that wanted to take part on the day of their clinical appointment.

On meeting participants, the session began with an opportunity for participants to ask any questions, and for the researcher to assess whether the participant had understood what had been conveyed to them. Those that fully understood what they were consenting too completed the consent form (Appendix 10).

The first task involved the completion of the subjective measures and demographic questions including age, sex, date of birth, marital status and education. Subjective measures were administered before the neuropsychological tests so that patients' reports were not influenced by their perceived performance on the tests. Participants were then informed that they would be asked questions about 'thinking' difficulties, their physical disability, fatigue and mood. It was reiterated to participants that the study was interested in patients who did and didn't experience these difficulties, and to answer the questions as accurate as possible.

Participants worked through the subjective measures which took approximately 20 – 30 minutes to complete. Participants were asked if they would like to complete this alone or with the help of the lead researcher. After the questionnaire was completed, the researcher checked through the questionnaire and identified any missing questions patients may have not fully understood.

The second stage of the study required participants to complete a series of neuropsychological tests. Participants were reassured before completing that these were standard cognitive tests which had been designed to stretch their cognitive abilities, and they might therefore find some tasks difficult to complete. Patients were also told that it would take approximately 30 minutes to complete the tasks and that they could ask to stop at anytime; although no participants asked for a break.

Throughout the assessment, all attempts were made to remain sensitive to any symptoms of distress or upset by the participant. In order to minimise this, all participants were reminded that participation was entirely voluntary and that they were not obliged to answer any of the questions. As per the consent form, participants were also informed that they were free to withdraw from the study at any time without reason. Those who did not want to participate were also reassured that this would not affect future treatment or relationships with the clinical team

The measures were completed in a predetermined order which is presented in Table 3 below. This ensured that all tests were completed in the same order, and that a 20 minute delay occurred before the final task of the CVLT-II was completed.

Table 3: Order neuropsychological tests administered.

Order	**Measure**
1.	The California Verbal Learning Test Version II (CVLT-II) – immediate recall, cued recall
2.	The Symbol Digit Modalities Test (SDMT)
3.	Digits forward and Backward
4.	Animal fluency test
5.	Stroop task
6.	Benton Judgement of Line Orientation Test
7.	The California Verbal Learning Test Version II (CVLT-II) – long delay free recall

On completion, participants were thanked and given the opportunity to ask any questions. Patients were reminded that the results of their assessment would be collated with other patients' and form part of a research project. Although individual results were not fed back to participants, they were asked if they would like a copy of the main findings from the study once completed. Participants were advised that if they had any concerns about their cognition they should discuss this with the clinical team during their appointment.

4.7 DATA ANALYSIS

Data was analysed using the Statistical Package for Social Sciences software (SPSS) version 18. Descriptive analyses about demographic and illness characteristics were initially conducted. This examined whether the study's sample was consistent with those reported by studies included in the review, and also if patients' characteristics were consistent with an MS population. This included age, sex, and years of education as well as level of functional impairment (EDSS score), type of MS, disease duration, and level of fatigue.

In order to ease comparison between neuropsychological tests and to standardise the data, scores were converted into age and gender adjusted z-scores using published normative data for each test. Cognitive impairment was defined as a z-score of $\leq$ -1.5 standard deviations below the norm (a score < 5^{th} percentile) on any neuropsychological test, and patients were classified as being 'cognitively unimpaired' or 'cognitively impaired' based on this criterion. Descriptive statistics were utilised to identify the number of participants that were cognitively impaired on neuropsychological tests and whether this differed according to each cognitive domain assessed i.e. memory, processing speed, executive functioning, language and visual perception. Level of fatigue, depression and subjective cognitive impairment (PDQ score) were also calculated. This provided a means of calculating the number and percentage of patients who were depressed, fatigued, and level of subjective cognitive impairment.

During this process data was screened via frequency tables and visual inspection. This identified that depression (BDI-FS) and fatigue (FSS) were not normally distributed. Analyses using these variables were therefore performed using non-parametric methods. Histograms and box plots were also used to identify outliers and these were then checked to confirm that data had been entered correctly and measures correctly scored. All results were feasible. Outliers were retained for the parametric analysis as they were deemed to be feasible results (it was anticipated that some participants may report extreme reports e.g. high depressive symptoms).

A t-test analysis was initially used to test hypotheses one in order to identify differences in PDQ scores between patients who were cognitively impaired and unimpaired on neuropsychological tests. Following this, Pearson's product moment correlations were used to identify any significant relationships between patients' PDQ scores and their performance on each neuropsychological test, and a one tailed test was used due to the hypothesised relationship. Due to the multiple comparisons that were made during this analyses, a conservative threshold of $p \leq 0.01$ was used.

Following this, correlations between the levels of depression on the BDI-FS and PDQ scores were performed as it was hypothesised that depression would have a significant positive relationship with PDQ scores. A one tail level of significance was therefore used. A two-way factorial analysis of variance (ANOVA) was then performed to identify the main and interactional effect of performance on neuropsychological tests and depression on PDQ scores. Patients were split into 'depressed' or 'not depressed' (based on BDI-FS score) and cognitively 'impaired' or 'unimpaired' (z-score $\leq$-1.5) and these were entered as the independent variables in the analyses. Patients' PDQ score were entered as the dependent variable and age was entered as a covariate after descriptive analysis identified it as an influential variable on the dependent variable (PDQ score).

As above, the second aim of this study was to explore extending the PDQ to include questions about subjective processing speed and language so that patients could be provided with a boarder subjective measure to report their cognitive functioning. The analyses outlined above were therefore repeated; however patients' reports of their cognitive functioning on the PDQ-E were also entered into the analyses. Although this was exploratory analyses, one tailed tests were used due to the hypotheses made in study aim one.

CHAPTER FIVE

RESULTS

5. OVERVIEW OF CHAPTER

This chapter begins by describing the sample including demographic information (e.g., age, sex, and years of education), disease characteristics, the prevalence of cognitive impairment on neuropsychological tests, levels of depression, and reports of subjective cognitive impairment. This is then followed by the results of the data analyses used to answer study aim one, which was to compare patients' reports of their cognitive functioning with their performance on a battery of neuropsychological tests. The analyses used to answer each research hypotheses are then outlined, which included:

- Patients who are impaired on neuropsychological tests will report more problems with their cognition;
- Patients who are depressed will report more subjective problems with their cognition;
- The effect of neuropsychological test performance on patients' subjective cognitive reports will be different for those who are depressed and not depressed.

This is then followed by the analyses for the second study aim, which was to expand the subjective cognitive measure, The PDQ, to form the PDQ-E. Prevalence of subjective cognitive impairment on the PDQ-E is reported, as is the effect of depression on patients PDQ-E scores. This is followed by exploratory analysis into comparing patients' subjective cognitive reports (on the PDQ-E) with their performance on neuropsychological tests, and analysis into whether this is different for patients who are depressed and not depressed.

5.1 DESCRIPTION OF THE SAMPLE

Table 4 includes a summary of the sample characteristics that are discussed below.

5.1.1 AGE AND GENDER

Participants were aged between 31 and 75, and the mean age was 51.6 (SD 9.05). 40% of the participants were male (n=33), and 60% (n=49) were female.

5.1.2 MARITAL STATUS

The majority of participants described themselves as 'married' or were co-habiting (73%, n=60). 13% (n=11) of patients were single, 11% were divorced (n=9), and 2% (n=2) were widowed.

5.1.3 EDUCATION AND EMPLOYMENT

The majority of participants were retired (45%, n=37) or 'unable to work' because of their condition (15%; n=12). 26% of patients described themselves as employed. This was predominantly full time (24%, n=20) and 2% (n =2) worked part time. 13% (n =11) were 'not working', which included a stay at home parent (n=1) and patients who were unemployed (n=10).

38% (n=31) obtained qualifications at a degree level. 33% (n=27) had stayed in education up to 15 years of age, and 20% (n=17) had completed education up to 18 years of age. 9% (n=7) of patients had left school before the age of 15 obtaining no qualifications.

5.1.4 EXPANDED DISABILITY STATUS SCALE (EDSS)

EDSS scores were obtained from the MS service patient database. Patients' functional impairment, as assessed by a member of the clinical team using the EDSS, was obtained from a patient database. This information was unobtainable for 14 patients (Table 4). For those patients whose clinician rated EDSS scores were missing, self report EDSS scores were used. This self report measure has been found to correlate with clinician derived EDSS scores within the same service (intraclass correlation coefficients of 0.69 to 0.89), and was therefore consider appropriate to use (Ingram *et al*, 2010).

As demonstrated in Figure 2 (Appendix 11), EDSS scores ranged from 2.16 to 8.5, and the mean EDSS score was 5.18 (sd = 1.95). Therefore, patients ranged from having no symptoms of physical impairment to requiring a wheelchair for mobility, but on average showed moderate to severe impairment. Patients who's EDSS score was unobtainable from the patients database and whom subjectively rated themselves as an EDSS of <4 were entered as 2.16 in the analyses (as a neurologist is needed to assess EDSS scores <4). It should be considered however, that it is highly unlikely that *all* patients will be functioning at an EDSS of 2.16, and are more likely to be evenly distributed below an EDSS score of 4.

5.1.5 TYPE OF MS

The type of MS patients had been diagnosed with was also attained from the service patient database. There was a larger proportion of patients with Relapse Remitting (n=35, 43%) and Secondary Progressive MS (n=37, 45%). Only three patients (3.7%) were diagnosed with the Primary Progressive disease type. The type of MS patients had been diagnosed with was unobtainable for seven patients (see Table 4).

5.1.6 DISEASE DURATION

Disease duration was calculated by subtracting the date participants were diagnosed with MS (obtained from the patient database) from the date they consented to the study. Information about disease duration was unobtainable for 13 participants (Table 4). Disease duration ranged from 3.07 years to 43.30 years, and mean duration was 18.33 years (n=69; sd = 9.95).

5.1.7 FATIGUE

Participants' scores ranged from 1 to 7, and the mean fatigue score was 5 (SD 1.6) (Table 4). 80% (n=66) of patients reported that fatigue significantly impacted on their daily functioning. This can be seen in Figure 3 (Appendix 12), which demonstrates a larger proportion of patients reporting higher levels of fatigue.

Table 4: Characteristics of participants

Variable	Number	Mean (Standard Deviation)	Range	Percentages
Gender:				
Male	33			40%
Female	49			60%
Total	82			100%
Age:				
Total	82	51.6 (9.05)	31 - 75	100%
Marital Status:				
Married/civil partner	60			73%
Single	11			13%
Divorced	9			11%
Widowed	2			2%
Total	82			100%
Education:				
Pre- 15 years old	7			9%
Up to 15 years old	27			33%
Up to 18 years old	17			20%
Degree or higher	31			38%
Total	82			100%
Employment:				
Employed full time	20			24%
Employed part time	2			2%
Unable to work	12			15%
Retired	37			45%
Unemployed	11			13%
Total	82			100%
EDSS Scores:				
Total	82 (14 from self report EDSS)	5.18 (1.95)	2.16 - 8.5	100%
Type of MS:				
Relapsing remitting	35			43%
Primary progress.	3			3.7%
Secondary progress	37			45%
Total	75			91.5%
Disease Duration:				
Total	69	18.33 (9.95)	3.07 - 43.30	84%
Fatigue:				
Total	82	5	1-7	100%

5.1.8 COGNITIVE IMPAIRMENT

Cognitive impairment was defined as a z-score ≤- 1.5 standard deviations below the mean score (taken from published normative data) on one or more neuropsychological test. Using this criteria, 54% (n=44) of patients were cognitively impaired, and 46% (n=38) were unimpaired.

Table 5 demonstrates the number and percentage of patients impaired on each neuropsychological test. It shows a larger number of patients impaired on one or two neuropsychological tests and very few patients impaired on all tests.

Table 5: Number of neuropsychological tests impaired on

Number of tests impaired on	**Frequency**
0	46% (n=38)
1	21% (n=17)
2	17% (n=14)
3	7% (n=6)
4	1% (n=1)
5	2% (n=2)
6	5% (n=4)

(Total sample size n=82)

The number and percentage of patients impaired on each neuropsychological test are reported in Table 6. The table also includes which cognitive domain each test assesses.

Table 6: Number of patients impaired and unimpaired on each neuropsychological test

Measure (cognitive domain)	**Impaired**	**Unimpaired**
SDMT (Processing Speed)	37% (n=30)	63% (n=52)
CVLT (Verbal learning)	29% (n=24)	71% (n=58)
Stroop (Executive Functioning)	28% (n=23)	72% (n=59)
Semantic Fluency (Language)	12% (n=10)	88% (n=72)
Benton line (Spatial Perception)	11% (n=9)	89% (n=73)
Digit span (Working Memory)	6% (n=5)	94% (n=77)

Percentages rounded up if >0.05 (Total sample size n=82)

Table 6 demonstrated that of the 54% (n=44) of patients who met the criteria for cognitive impairment, 37% (n=30) were impaired on the processing speed task. 29% (n=24) of participants were impaired on the memory (CVLT) task, and 28% (n=23) were impaired on the executive functioning task (Stroop). Language (Semantic fluency) and spatial perception (Benton) were the cognitive domains patients were least impaired on, with less than 15% (n=11) of patients impaired on these tests. Only 6% (n=5) of patients were impaired on the working memory task (digit span).

5.1.9 SUBJECTIVE COGNITIVE REPORTS

Scores on the subjective cognitive measure, the PDQ, ranged from 3 to 76 (max score of 80) with higher PDQ scores signifying patients reporting *more* problems with their cognition (i.e., denoting poor cognitive functioning). The mean PDQ score was 35 (sd = 16.5), which is marginally below the cut off for 'subjective impairment' (a PDQ score >40). 43% (n=35) of participants were 'subjectively impaired' on the PDQ, and 57% (n=47) were subjectively unimpaired. Mean scores for each domain are presented in Table 7 and demonstrate that patients reported more problems with their subjective attention and retrospective memory, followed by subjective planning and prospective memory.

Table 7: Mean scores of subjective cognitive domains on the PDQ

Cognitive domain	**Mean score (standard deviation)**	**Range**
Attention (PDQ)	9.5 (4.55)	0-20
Retrospective memory (PDQ)	9.2 (4.87)	0-17
Planning (PDQ)	8.9 (4.54)	0-19
Prospective memory (PDQ)	7.7 (3.96)	0-20

Pearson's correlations were used to identify if, similarly to Marrie *et al* (2005) a relationship existed between patients' subjective cognitive reports and age. A significant negative correlation was found (r= -0.33, p=0.001), demonstrating that as patients became older; they reported less problems with their cognition. In order to identify if this could also be due to the length of time patients had been diagnosed with MS i.e., as there will be longer disease duration in older patients, analyses were also carried out between disease duration and PDQ score. A significant negative correlation was also found (r=-0.26, p=0.05), which suggests that the longer patients were diagnosed with MS, the less cognitive problems they reported.

5.1.10 DEPRESSION

Participants scores on the BDI-FS ranged from 0-20 and the mean score was 4.8 (sd = 4.1). 43% (n=35) of participants met the criteria for clinically significant levels of depression (a score $\geq$4). 16% (n=13) of participants had 'moderate' symptoms of depression (a score $\geq$ 9), and 6% (n=5) met the criteria for 'severe' depression (a score $\geq$ 13). One participant with severe depressive symptoms also stated that they had suicidal intentions but had no immediate plans. The lead researcher contacted Mental Health Services and arranged appropriate support for this participant. The team at the MS Service were also made aware of this.

Preliminary analyses were performed to explore normality, linearity, homoscedasticity and identify any outliers on patients' BDI-FS scores. Preliminary analysis identified that scores were not normally distributed and further analyses were carried out to identify if this distribution was significantly different to a normal distribution. This analyses is included in Appendix 13.

5.2 STUDY AIM ONE: COMPARE PATIENTS' SUBJECTIVE COGNITIVE REPORTS WITH THEIR PERFORMANCE ON NEUROPSYCHOLOGICAL TESTS AND CONSIDER THE ROLE OF DEPRESSION

5.2.1 HYPOTHESIS ONE: PATIENTS WHO ARE IMPAIRED ON NEUROPSYCHOLOGICAL TESTS WILL SUBJECTIVELY REPORT MORE PROBLEMS WITH THEIR COGNITION

Consistent with previous research, findings from this study found that 54% of patients were cognitively impaired on neuropsychological tests, and 43% of patients subjectively reported significant problems with their cognition.

In order to explore hypothesis one, an independent t-test was used to compare patients' subjective reports on the PDQ with their neuropsychological test performance. Patients' PDQ scores were entered as the dependent variable and 'impairment' on neuropsychological tests was entered as the independent variable. A one-tailed test was used due to predictions made prior to the analysis.

A significant difference in mean PDQ scores for patients who were cognitively impaired and unimpaired on neuropsychological tests was found ($t(82)=-2.03$, $p=0.02$). Mean scores are reported in Table 8 below. As higher scores on the PDQ relate to patients subjectively reporting *more* cognitive problems, results demonstrated that patients who were impaired on neuropsychological tests reported more problems with their cognition. However, although this difference was

significant, the magnitude of this difference was calculated ($r^2 = t^2/t^2+df$) to be -0.05, which is considered to be very small effect size (Cohen, 1988).

Table 8: Scores for subjective cognitive measure The PDQ

Cognitive Impairment (number)	**Mean PDQ Score**	**Standard Deviation (PDQ Score)**	**Range (PDQ Score)**
Not impaired (n=38)	31.24	16.24	3-64
Impaired (n=44)	38.55	16.22	7-76

Pearson's product moment correlations were used to investigate if significant relationships existed between individual neuropsychological tests and total PDQ scores. Studies that were found to be of better quality in the systematic review reported a significant relationship between patients' cognitive reports and neuropsychological test performance, and a prediction was made that a similar finding would be found in this study. Whilst it was acknowledged that type I errors could occur as a result of multiple comparisons, a Bonferroni Correction was not used as this test is highly conservative and may miss significant relationships (Bland, 1996). In order to minimise the chances of type I and type II errors, a more conservative threshold of $p \leq 0.01$ was selected. A one-tailed test was used due to the predicted relationship.

As Table 9 illustrates, using a threshold of $p \leq 0.01$, a significant negative relationship was found between the PDQ and an executive functioning task (the Stroop task), and the PDQ and working memory (the digit span task). A significant negative correlation between these tests and total PDQ score suggests that as patients level of cognitive impairment increased (lower z score), they reported *more* problems with their cognition (higher PDQ score). Using a p-value ≤ 0.01, no other neuropsychological tests correlated with patients total PDQ score.

Table 9: Correlations between scores on the PDQ and neuropsychological tests

Neuropsychological test	Correlations with PDQ standard scores
Stroop (Executive Functioning)	r= -0.36 p=0.001**
The Symbol Digit Modalities Test (SDMT) (Processing Speed)	r= -0.23 p=0.02
Digit Span (Working Memory)	r= -0.26 p=0.01*
Animal fluency test (Language)	r= -0.14 p=0.10
The California Verbal Learning Test Version II (CVLT-II) (Verbal Learning and Memory)	r= -0.12 p=0.14
Benton Judgement of Line Orientation Test (Spatial Orientation)	r= -0.01 p=0.46

*p≤ 0.01; **p≤0.001 (numbers rounded when >0.05)

Analyses were then carried out to examine whether other relationships existed between individual neuropsychological tests and domain specific questions on the PDQ. Pearson's correlation analyses were used to compare subjective memory (retrospective and prospective), attention, and executive function on the PDQ with each neuropsychological test. A one-tailed test was used, and a conservative threshold of p≤0.01 due to the multiple comparisons.

As demonstrated in Table 10, significant negative correlations were again found between the Stroop task (executive functioning) and individual subjective domains (r=-0.28, p=0.005 to -0.36, p=0.001). This was the only neuropsychological test that correlated with all subjective domains on the PDQ. The Digit Span task (working memory) negatively correlated with three subjective domains; prospective memory (r= -0.29, p=0.004), attention (r= -0.28, p=0.006), and executive functioning/planning (r=-0.27, p=0.008), and the SDMT (processing speed) negatively correlated with subjective retrospective memory (r=-0.27, p=0.007).

Table 10: Correlations between neuropsychological tests and subjective domains on the PDQ.

PDQ domains	Cognitive Domain (Neuropsychological Test)					
	Memory (CVLT)	**Processing Speed (SDMT)**	**Semantic Language (Word List)**	**Executive Functioning (Stroop)**	**Memory (Digit Span)**	**Visual Perception (Benton)**
Retrospective memory	r= -0.13 p=.12	r= -0.27* p=0.007	r= -0.17 p=0.06	r= -0.36** p=0.001	r= -0.12 p=0.14	r= -0.12 p=0.14
Prospective Memory	r= -0.14 p=0.11	r= -0.15 p=0.08	r= -0.07 p=0.28	r= -0.28* p=0.005	r= -0.29* p=0.004	r= -0.08 p=0.24
Attention	r= -0.12 p=0.15	r= -0.21 p=0.03	r= -0.13 p=0.13	r= -0.32** p=0.001	r= -0.28* p=0.006	r= -0.04 p=0.37
Executive functioning/planning	r= -0.06 p=0.30	r= -0.20 p=0.04	r=-0.16 p=0.08	r= -0.35** p=0.001	r= -0.27* p=0.008	r=0.16 p=0.07

*p≤0 .01; **p≤0.001 (figures rounded when >0.05)

5.2.1.1 SUMMARY OF HYPOTHESIS ONE

There was a significant difference in PDQ scores between patients who were impaired and unimpaired on neuropsychological tests. Patients impaired on neuropsychological tests were found to report more problems with their cognition than those who were unimpaired. This is consistent with research hypotheses one i.e., that patients who are impaired on neuropsychological tests will report more problems with their cognition.

Further correlation analyses between the PDQ and neuropsychological tests highlighted that the executive functioning (the Stroop task) and working memory test (digit span task) were the only tests that negatively correlated with patients' subjective cognitive reports (total PDQ score). When the PDQ was broken down into individual subjective domains (i.e., subjective memory, attention and executive functioning), the measure of processing speed (the SDMT) also correlated with subjective prospective memory, but no other subjective domains.

5.2.2 HYPOTHESIS TWO: PATIENTS WHO ARE DEPRESSED WILL REPORT MORE PROBLEMS WITH THEIR COGNITION

The systematic review highlighted that studies have consistently found a positive relationship between symptoms of depression and patients' reports of their cognition, that is, as patients become more depressed, they report more problems with their cognition. Consistent with these findings, it was anticipated that a positive relationship would also be found in this study. A one tailed level of significance was therefore used.

Due to scores on the BDI-FS violating the parametric assumptions of normality, a Spearman's correlation was used to investigate the relationship between patients' subjective cognitive reports on the PDQ and symptoms of depression on the BDI-FS.

As hypothesised, a significant positive correlation was found between the PDQ and BDI-FS ($r=0.42$, $p=0.000012$). Thus, as patients level of depression increased, so did the number of cognitive problems reported.

5.2.2.1 SUMMARY OF HYPOTHESIS TWO

A significant positive correlation was found between levels of depression on the BDI-FS and patients' cognitive reports on the PDQ. This demonstrated that as patients became more depressed, they reported more problems with their cognition. This finding is consistent with the research hypothesis.

5.2.3 HYPOTHESIS THREE: THE EFFECT OF NEUROPSYCHOLOGICAL TEST PERFORMANCE ON PATIENTS' SUBJECTIVE COGNITIVE REPORTS WILL BE DIFFERENT FOR THOSE WHO ARE DEPRESSED AND NOT DEPRESSED

A two-way factorial analysis of variance (ANOVA) was used to test hypothesis three, by measuring whether a combination of depression and performance on neuropsychological tests predicted reports of cognitive functioning on the PDQ. Patients were split into 'depressed' or 'not depressed' based on BDI-FS criterion and 'cognitively impaired' or 'cognitively unimpaired' if they had z score $\leq$ -1.5 on one or more neuropsychological test. These were entered as the independent variables in the analyses. Patients' reports of their cognitive functioning on the PDQ were entered as the dependent variable.

Age was entered as a covariate, as descriptive analyses identified it as an influential variable on the dependent variable (PDQ score). A Bonferroni confidence interval adjustment was selected and a one-tailed test was used due to the hypothesised relationship. Levene's Test of Equality of Error Variances was >0.05 which suggests that the variance of the dependent variable (PDQ score) was equal across the two independent variables; depression and cognitive impairment.

As demonstrated in Table 11, there was no significant main effect of level of cognitive impairment on PDQ scores ($F(1, 78) = 2.51$, $p=0.11$). This finding is inconsistent with findings from hypothesis 1 (i.e., a significant difference in PDQ scores between patients who were impaired and unimpaired on neuropsychological tests, and significant correlations between the Stroop, Digit Span and PDQ score).

Consistent with hypothesis 2, a significant main effect of depression on PDQ scores was found ($F(1, 78) = 16.60$, $p=0.000001$), demonstrating that patients who were depressed reported more problems with their cognition.

The ANOVA analyses also revealed that there was no significant interactional effect between depression and cognitive impairment on PDQ scores ($F(1, 78)=0.68$, $p=0.41$). This demonstrates that the effect of neuropsychological test performance on patients' cognitive reports was not significantly different for patients who were depressed and not depressed. Hypothesis 3 was therefore rejected. The results of these analyses are reported in Table 11 and Figure 4.

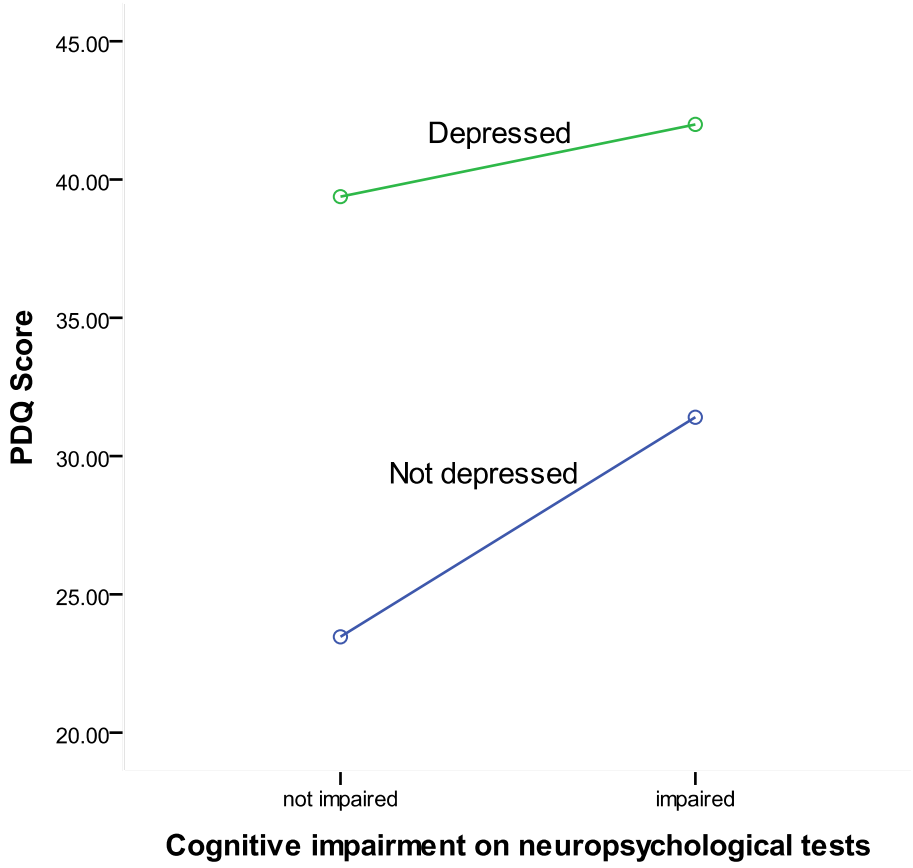
Table 11: ANOVA analyses. Dependent variable: Total PDQ

Source (Independent Variables & Covariate)	**Sum of Squares**	**Degrees of freedom**	**Mean Square**	**F**	**Significance**
Age (covariate)	1029.23	1	1029.233	4.99	0.03*
Cognitive impairment	518.61	1	518.61	2.51	0.11
Depression	3425.06	1	3425.06	16.60	0.00001**
Cognitive impairment*Depression	141.34	1	141.34	0.68	0.41

*$p \leq 0.01$; **$p \leq 0.001$ (Figures rounded when >0.05)

Visual inspection of profile plots in Figure 4 demonstrate findings from the ANOVA. Firstly, although not found to be significant in the ANOVA analysis, it reveals that patients impaired on neuropsychological tests report more problems with their cognition (higher PDQ score). Secondly, it shows that depressed patients have higher PDQ scores regardless of whether they are cognitively impaired or unimpaired on neuropsychological tests. And finally, although not significantly different, it reveals that the difference in PDQ scores between those impaired and unimpaired on neuropsychological tests is smaller in depressed patients than in not depressed patients.

Figure 4: Interaction between PDQ and cognitive impairment on PDQ scores



5.2.3.1 SUMMARY OF HYPOTHESIS THREE

Analysis confirmed that depression had a significant main effect on patients' subjective cognitive reports, but cognitive functioning on neuropsychological tests (i.e. impaired or unimpaired) did not. The interaction between depression and cognitive impairment was not significant, which suggests

that the effect of neuropsychological test performance on patients' cognitive reports is not significantly different for patients who are depressed and not depressed.

5.3 STUDY AIM TWO: PROVIDE PATIENTS WITH A BROADER SUBJECTIVE COGNITIVE MEASURE TO REPORT THEIR COGNITIVE FUNCTIONING

The PDQ was highlighted in the review as the most commonly used subjective measure of patients' cognitive reports, but fails to include questions about subjective processing speed and language; domains commonly impaired in MS. Therefore, study aim two was included these questions in an attempt to provide patients with a broader subjective measure for patients to report their cognitive functioning. The analyses outlined in study aim one was repeated with the expanded subjective cognitive measure, the PDQ-E, as exploratory analysis. Unless otherwise stated, one tailed tests were used due to the predictions made in study aim one.

5.3.1 SUBJECTIVE COGNITIVE REPORTS ON THE PDQ-E

Scores on the PDQ-E ranged from 5 to 108 (max score of 112), and the mean score was 50 (sd = 23). This is somewhat higher than the mean PDQ score (mean score of 35).

A score >40 (out of a possible 80) on the PDQ is used to define subjective cognitive impairment (Sullivan, Edgley & Dehoux, 1990), and a similar criterion (i.e. half the total score) was used for the PDQ-E. Patients who obtained a score of >56 were therefore defined as 'subjectively impaired' on the PDQ-E. Using this criteria, there were no differences in the percentage of patients 'impaired' on the PDQ and PDQ-E (both 43%).

Table 12 presents the mean scores for the subjective processing speed and language questions included in the PDQ-E. The mean PDQ scores for attention, retrospective memory, prospective memory and planning have also been included to aid comparisons. As higher scores relate to patients subjectively reporting *more* problems with their cognition, mean scores demonstrated that the questions about processing speed added to the PDQ (to form the PDQ-E) and appear relevant to patients cognitive reports; as mean scores for this domain are higher than some of those included in the PDQ.

Table 12: Mean scores for domains included in the PDQ-E

Cognitive domain	Mean score
Processing Speed (PDQ-E)	8.5
Language (PDQ-E)	6.8
Attention (PDQ)	9.5
Retrospective memory (PDQ)	9.2
Planning (PDQ)	8.9
Prospective memory (PDQ)	7.7

(Figures rounded when >0.05)

Consistent with findings using the PDQ, Pearson's correlations identified a significant negative correlation between age and subjective reports on the PDQ-E. This demonstrated that as patients became older, they reported less problems with their cognition ($r=-0.32$, $p=0.004$). Similarly, correlations were repeated to explore whether this relationship existed between disease duration and PDQ-E, and a significant negative correlation was found ($r=-0.25$, $p=0.04$). Thus, as demonstrated with the PDQ, as time increased (i.e., patients became older & disease duration was longer) they reported less problems with their cognition.

5.3.2 COMPARE PATIENTS SUBJECTIVE COGNITIVE REPORTS (ON THE PDQ-E) WITH THEIR PERFORMANCE ON NEUROPSYCHOLOGICAL TESTS

The main aim of this study was to compare patients' subjective cognitive reports with their performance on neuropsychological tests and consider the role of depression. The analyses used in study aim 1 were repeated, but patients' cognitive reports on the PDQ-E were entered into the analyses (as opposed to their PDQ scores in study aim one).

Analyses were initially used to compare patients' subjective reports of their cognition (on the PDQ-E) with their performance on neuropsychological tests. An independent t-test revealed that there was a significant difference in PDQ-E scores between patients who were cognitively impaired and unimpaired on neuropsychological tests ($t(82) = -2.01$, $p=0.02$), which indicate similar findings to those using the PDQ ($t(82) = -2.03$, $p=0.02$).

Correlational analyses were then repeated with the PDQ-E to assess whether the additional questions added to the PDQ would affect the relationship between patient's subjective cognitive

reports and their performance on neuropsychological tests. A one-tailed test was used due to the predicted relationship in study aim 1. Correlations between the individual neuropsychological tests and total PDQ-E scores are presented in Table 13 below. Due to the multiple comparisons that were made, a threshold of $p \leq 0.01$ was used.

Table 13: Correlations between scores on the PDQ-E and neuropsychological tests

Neuropsychological test	**Correlations with PDQ-E scores**
Stroop (Executive Functioning)	r= -0.35 p=0.001**
The Symbol Digit Modalities Test (SDMT) (Processing Speed)	r= -0.22 p=0.02
Digit Span (Working Memory)	r= -0.26 p=0.01*
Animal fluency test (Language)	r= -0.15 p=0.09
The California Verbal Learning Test Version II (CVLT-II) (Verbal Learning and Memory)	r= -0.12 p=0.14
Benton Judgement of Line Orientation Test (Spatial Orientation)	r= -0.11 p=0.16

**$p \leq 0.001$; *$p \leq 0.01$ (Figures rounded when >0.05)

As Table 13 illustrates, using a threshold of $p \leq 0.01$, a significant relationship was found between and the PDQ-E and the executive functioning task (the Stroop), and the PDQ-E and working memory (digit span task). A significant negative correlation between these tests and total PDQ score suggests that as patients level of cognitive impairment increased (lower z score), they reported *more* problems with their cognition (higher scores on the PDQ). Using a p-value of 0.01, no other neuropsychological tests correlated with patients PDQ scores. The Stroop task and Digit span were also the only tests that correlated with patients cognitive reports on the PDQ (see Table 9)

Analyses were also carried out to examine if this relationship existed between individual cognitive tests and domain specific questions on the PDQ-E (i.e., subjective language and processing speed). A conservative threshold of $p \leq 0.01$ was used due to the multiple comparisons, and a one-tailed test. As demonstrated in Table 14, the executive functioning task (Stroop task) negatively correlated with both subjective language and processing speed, and the Working memory task (digit span) correlated with subjective processing speed.

Table 14: Correlations between cognitive domains and subjective questions on the PDQ-E

PDQ-E domains	Cognitive Domain (Neuropsychological Test)					
	Memory (CVLT)	**Processing Speed (SDMT)**	**Semantic Language (Word List)**	**Executive Functioning (Stroop)**	**Memory (Digit Span)**	**Visual Perception (Benton)**
Processing Speed	r= -0.12 p=0.17	r= -0.22 p=0.03	r= -0.21 p=0.03	r= -0.31* p=0.002	r= -0.26 p=0.009*	r= -0.14 p=0.1
Language	r= -0.10 p=0.19	r= -0.13 p=0.12	r= -0.08 p=0.24	r= -0.28* p=0.006	r= -0.20 p=0.04	r= -0.002 p=0.27

*p≤0 .01 (Figures rounded when >0.05)

5.3.3 PATIENTS' COGNITIVE REPORTS ON THE PDQ-E AND LEVELS OF DEPRESSION

Analyses were repeated with the PDQ-E to explore the relationship between patients' subjective reports and symptoms of depression. Due to the BDI-FS data violating the parametric assumptions of normality (Appendix 13), a Spearman's correlation was used to explore this relationship, and a one-tailed test.

A significant positive correlation was found between the PDQ-E and BDI-FS (r=0.42, p=0.0001), which suggests that as patients level of depression increased, so did the number of cognitive problems they reported. These findings are also consistent with findings from the PDQ (r=0.42, p=0.00001).

5.3.4 PATIENTS SUBJECTIVE COGNITIVE REPORTS (ON THE PDQ-E), THEIR NEUROPSYCHOLOGICAL TEST PERFORMANCE AND LEVELS OF DEPRESSION

An ANOVA was used to investigate the individual and interactional effects of neuropsychological test performance and symptoms of depression on patients' subjective cognitive reports. This analysis included patients' subjective cognitive reports on the PDQ-E as the dependent variable, and depression and neuropsychological test performance as the independent variables. Age was again entered as a covariate due to its effect on PDQ-E scores. The results of the ANOVA are presented in Table 15.

Table 15: ANOVA analyses using the PDQ-E

Source (Independent Variables & Covariate)	Sum of Squares	Degrees of freedom	Mean Square	F	Significance
Age (covariate)	1029.23	1	1579.94	4.43	0.03*
Cognitive impairment	518.61	1	518.61	2.46	0.12
Depression	3425.06	1	3425.06	15.28	0.0001**
Cognitive impairment*Depression	141.34	1	141.34	0.56	0.46

*p≤0 .01; **p≤0 .001 (Figures rounded when >0.05)

Findings were consistent with the analyses using the PDQ. There was no significant main effect of cognitive impairment on PDQ-E scores ($F(1,78)=2.46$, $p=0.12$), but there was a significant main effect of depression ($F(1,78)=15.28$, $p=0.0001$). The effect of patients' neuropsychological tests performance on their subjective cognitive reports was not significantly different for those who were depressed and not depressed ($F(1,78)=0.56$, $p=0.46$). Results from this analysis are also consistent with findings using the PDQ.

5.3.5 SUMMARY OF STUDY AIM TWO

The second aim of this study was to add questions about processing speed and language to the PDQ to provide a broader subjective measure for patients to report their cognition. Analyses identified that questions about processing speed seemed most relevant to patients' cognitive reports, as scores on this domain were higher than some of those included in the PDQ. Whilst these questions seemed relevant to patients concerns, results of the analyses using the PDQ-E are consistent with *all* findings using the PDQ.

5.4 OVERALL SUMMARY OF RESULTS

Descriptive analyses revealed that patients were aged between 31 and 75 and were near evenly split into males and females (40:60). The majority of patients were married (73%) and were either unemployed (26%) or retired (45%). Most patients stated that they were no longer able to work due to the symptoms of MS.

There were a significantly larger proportion of Relapse Remitting (n=35, 35%) and Secondary Progressive (n=37, 45%) type MS patients, and disease duration ranged from 3.07 years to 43.30 years (mean duration 18.33 years). Patients ranged from no symptoms of physical impairment to requiring a wheelchair for mobility, but on average showed moderate to severe impairment. 80% of patients reported that fatigue significantly impacted on their daily functioning, and 43% of patients were depressed.

54% of patients met the criteria for cognitive impairment on neuropsychological tests. Processing speed was the most commonly impaired cognitive domain, followed by memory and executive functioning. 43% of patients were subjectively 'impaired' on the PDQ. Mean scores demonstrated that subjective attention and retrospective memory were the domains patients subjectively reported the most problems on, followed by planning and prospective memory. A significant positive relationship was found between patients' age and their cognitive reports, and also between disease duration and cognitive reports. Both found that as length of time increased (i.e., patients became older or disease duration increased) patients reported less problems with their cognition.

The main aim of this study was to compare patients' reports of their cognitive functioning with their performance on neuropsychological tests and consider the role of depression. The first research hypothesis stated that patients who were impaired on neuropsychological tests would report more problems with their cognition. Analyses using an independent t-test revealed that there was a significant difference in PDQ scores between those who were cognitively impaired and unimpaired ($t(82)=-2.03$, $p=0.02$), with patients who were cognitively impaired reporting more problems with their cognition (higher PDQ score). This finding is consistent with research hypothesis one.

Further analyses using Pearson's product moment correlations identified a significant relationship between patients' reports and their performance on an executive functioning (Stroop) and working memory (Digit Span) task. This demonstrated that as patients' level of impairment increased on these tests they reported more problems with their cognition. Further analyses revealed that when

the PDQ was split into individual cognitive domains (i.e. subjective memory, attention and executive functioning) in addition to the executive functioning and working memory task, the processing speet task (SDMT) also negatively correlated with subjective retrospective memory on the PDQ. The results suggest that patients impaired on the executive functioning test report problems with their cognition across all subjective domains, patients impaired on the working memory test report more problems remembering future plans, keeping their attention and planning/problem solving, and those impaired on the processing speed test report difficulties remembering past events.

Consistent with findings from previous literature, a positive correlation between depression and patients' subjective reports was found. This demonstrated that as patients became more depressed, they reported more problems with their cognition. This is consistent with what was predicted in hypothesis two.

ANOVA analyses were then performed to identify the main and interactional effects of depression and neuropsychological test performance on patients' reports of their cognition. Inconsistent with the first research hypothesis, there was no significant effect of neuropsychological test performance on patients' cognitive reports, but as predicted in hypothesis two, a significant main effect of depression on patients' subjective cognitive reports was found. Because of the effect of depression on patients' reports of their cognition, the third research hypothesis predicted that the effect of neuropsychological test performance on patients' subjective cognitive reports would be different for those who are depressed and not depressed. However, analyses demonstrated that there was no interactional effect between depression and neuropsychological test performance, and hypothesis three was therefore rejected.

The second aim of this study was to expand the PDQ to include questions about language and processing speed, and provide patients with a broader subjective measure to report their cognition. Exploratory analyses identified that questions about these domains, in particular, questions about processing speed appeared to be most relevant to patients' cognitive reports, as mean scores for these questions were higher than some of those included in the PDQ. However, despite these questions being relevant to patients concerns, there were no differences in the analyses using the PDQ or PDQ-E.

CHAPTER SIX

DISCUSSION

6. OVERVIEW OF CHAPTER

This chapter begins with a summary of findings from the literature and rationale with regards to why further research into comparing patients' reports of their cognitive functioning with their performance on neuropsychological tests was needed. The current study's aims, hypotheses and findings are discussed. These are then reviewed in relation to the existing literature. The strengths and limitations of the current study are then considered. These are followed by a discussion regarding the clinical implications and directions for future research.

6.1 FOCUS OF RESEARCH

The main aim of this study was to compare patients' reports of their cognitive functioning with their performance on neuropsychological tests and consider the role of depression. Cognitive impairment is becoming increasingly identified as a common symptom of MS and is now recognised as one of the most common and profound consequences of the disease. Patients report that cognitive impairment negatively impacts on their QoL, affecting employment, social relationships and engagement in social activities, even when compared to MS patients with similar levels of physical disability (Benedict *et al*, 2005; Glanz *et al*, 2010; Rao *et al*, 1991b). Findings such as these reveal the importance of a valid and reliable assessment of patients' cognitive functioning, as failure to do so could be detrimental to patients' QoL, daily functioning and psychological well-being. However, the difficulty associated with assessing cognitive impairment on a routine clinical basis means there is often a reliance on patients' own reports of their cognitive functioning to determine whether further neuropsychological assessment is needed. If clinicians are going to rely on patients' reports to determine further intervention, it is important to distinguish if, in fact, these reports do indeed reflect their performance on neuropsychological tests. Further, it is also important to consider if other factors impact on this relationship, as these should also be considered when interpreting patients' subjective cognitive reports. The current study considered depression as a factor that may impact on patients' perceptions of their cognitive abilities and the relationship with neuropsychological test performance.

6.2 SUMMARY OF SYSTEMATIC REVIEW

A systematic review of the literature was carried prior to this research and identified 16 studies that had compared patients' subjective cognitive reports with their performance on neuropsychological tests. All of these studies included a measure of depression. Thirteen were cross sectional and three were longitudinal treatment trials. Patients included in these studies were mostly recruited from MS clinics, although some were referred into studies for reporting problems with their cognition (e.g. Marrie *et al*, 2005), or for displaying mild cognitive impairment (e.g. Carone *et al*, 2005). They were primarily female (up to 90% in some studies; Bruce *et al*, 2010) and mean age ranged from 37 to 50 years old. Mean disease duration ranged from 2-11 years and patients level of functional impairment mostly fell within the mild-moderate functional range (severe in two studies; Maor *et al,* 2001; Randolph Arnette & Freske, 2004). This level of functional impairment is consistent with the type of MS patients were presenting with; primarily Relapse Remitting, and the lower level of functional impairment associated with this sub-type.

Neuropsychological tests were used to measure cognitive functioning, but the number of tests, and cognitive domains assessed varied across the studies. Only three studies included a battery of neuropsychological tests that assessed all of the domains commonly impaired in MS (Benedict *et al*, 2003; Benedict *et al*, 2004; Carone *et al*, 2005). Cognitive impairment on tests ranged from 12-56% of the entire sample (Benedict *et al*, 2004; Crone *et al*, 2005; Deloir *et al*, 2006; Gold *et al*, 2003; Maor *et al*, 2001; Marrie *et al*, 2005; Randolph *et al*, 2004).

Patients' reports of their cognitive functioning were assessed using subjective cognitive measures. These included questions about cognitive domains found to be impaired in MS, but were often limited to only one cognitive domain e.g. Memory (Middleton *et al*, 2006) or by the number of questions they contained (e.g. Gold *et al* 2005). Subjective cognitive impairment ranged from 22% (Deloire *et al*, 2006) to 51% of the study's population (Maor *et al*, 2001).

Self report questionnaires were used to asses symptoms of depression, and only two studies included a measure that was sensitive to the somatic symptoms associated with MS i.e., not affected by symptoms such as fatigue or psychomotor problems (Benedict *et al*, 2004; Krch *et al*, 2010). Prevalence of depression to ranged from 27% -61% of patients affected (Benedict *et al*, 2004; Gold *et al*, 2003; Kinsinger *et al*, 2010; Krch *et al*, 2010; Lovera *et al*, 2006; Maor *et al*, 2001; Randolph *et al*, 2004), although these may be overestimates of depression given the measurement issues.

A number of findings were reported when comparing patients' subjective cognitive reports with their performance on neuropsychological tests. Studies who looked at significant differences in patients subjective cognitive reports reported a significant difference in neuropsychological test performance between patients who under, over, and accurately estimated their cognitive functioning (Carone *et al*, 2005), but Marrie *et al*, (2005) found no such difference. Marrie *et al* (2005) did however report a non-linear relationship, but this only existed between patients' subjective cognitive reports and a single processing speed task. This demonstrated that patients who were experiencing mild impaired processing speed (not enough to make criteria for impairment) reported the most problems with their cognition and those who were cognitively impaired, or in the upper extremity of functioning, reported very few problems with their cognition.
Studies exploring significant relationships reported that as patients became more impaired on neuropsychological tests they reported more problems with their cognition (Benedict *et al*, 2004; Deloire *et al*, 2006; Deloire *et al*, 2006; Goverover *et al*, 2005; Kinsinger *et al*, 2010; Krch *et al*, 2010; Krch *et al*, 2010; Randolph *et al*, 2004; Randolph *et al*, 2004), and patients' performance on neuropsychological tests significantly predicted their subjective cognitive functioning (Julian *et al*, 2007; Maor *et al*, 2001). Other studies however found no significant relationship between patients subjective cognitive reports and their performance on neuropsychological tests (Benedict *et al*, 2003; Benedict *et al*, 2004; Bruce *et al*, 2010; Christodoulou *et al*, 2005; Gold *et al*, 2003; Lovera *et al*, 2006).

Depression was found to significantly affect patients' subjective cognitive reports. Studies reported that as symptoms of depression increased patients' subjectively reported more problems with their cognition (e.g. Middleton *et al,* 2006) or that depression significantly predicted patients' reports of their cognitive functioning (14% to 17.7%) (Julian *et al*, 2007; Maor *et al*, 2001). Whilst depression significantly affected patients subjective cognitive reports, only one study reported a significant relationship between depression and patients' performance on neuropsychological tests; although this was relatively weak ($r= -0.19$, $p<0.05$; Maor *et al* 2001).

Five studies looked at the role of depression on the relationship between patients' subjective cognitive reports and their performance on neuropsychological tests (Carone *et al*; Julian *et al*, 2007; Kinsinger *et al*, 2010, 2005; Krch *et al*, 2010; Middleton *et al*, 2006). Two of these were longitudinal (Julian *et al*, 2007; Kinsinger *et al*, 2010). Julian *et al*, (2007) found that following a change in levels of depression (after psychological treatment), patients' subjective cognitive reports became more predictive of their neuropsychological test performance i.e. the size of the relationship significantly

improved, but Kinsinger *et al*, (2010) found no significant improvement in the relationship following treatment for depression. Other studies reported that depression significantly affected the relationship between patients' subjective cognitive reports and their performance on neuropsychological tests (Carone *et al*, 2005; Middleton *et al*, 2006) and Krch *et al* (2010) found that depression did not affect this relationship.

When reviewing these studies a number of limitations were identified. Firstly, although a number of significant findings were reported between patients' subjective reports and their neuropsychological test performance these were relatively weak e.g. Kinsinger, Lattie & Mohr (2010) $r=-0.23$, $p<0.001$ (Cohen, 1988). Some also existed between a *single* cognitive test (from a battery of neuropsychological tests) and *one* part (or question) from a subjective cognitive measure (e.g. Marrie *et al,* 2005) and should be considered when interpreting the findings.

Secondly, there was a large discrepancy in the sampling of patients between studies. Some studies only included patients with mild functional impairment in the early stages of the disease (e.g. Benedict *et al*, 2003), and is therefore unlikely to be representative of MS patients presenting to clinics; where typically patients present with more severe symptoms (Mariani *et al,* 1991). Patients were also referred into some studies from displaying cognitive impairment (Christodoulou *et al*, 2005) or reporting problems with their cognition (Lovera *et al*, 2006) which may have impacted on the findings.

Finally, a number of issues in the measurement of subjective cognitive reports, neuropsychological tests and depression were identified, and it is possible that this may account for some of the discrepancies in findings. Patients' subjective reports were often assessed using measures that were limited to one cognitive domain e.g. memory (Randolph *et al* (2004) or very few questions (e.g. Gold *et al* 2003) which may have limited patients opportunity to report cognitive difficulties they may have been experiencing. When implementing neuropsychological tests, only three studies assessed all of the cognitive domains impaired in MS (Benedict *et al* 2003; Benedict *et al,* 2004; Carone *et al,* 2005), and others failed to include the cognitive domain found to be most commonly impaired; processing speed (e.g. Krch *et al,* 2010).

The criterion for cognitive 'impairment' on tests also differed between studies which meant that patients who may have been defined as cognitively 'impaired' in some studies would have been defined as 'unimpaired' in others. Depression was assessed by patient self report questionnaires,

and only two studies included a measure that was sensitive to MS symptomatology i.e. omitted questions about fatigue, psychomotor problems (Benedict *et al*, 2004; Bruce *et al,* 2010). This should be considered particularly when interpreting findings from studies that explored the influence of depression on the relationship between patients' subjective reports and neuropsychological test performance, as none of these used a depression measure sensitive to MS symptomatology (Carone *et al,* 2005; Julian *et al,* 2007; Kinsinger *et al,* 2010; Krch *et al,* 2010; Middleton *et al,* 2006).

Given the limitations of these studies this study aimed to improve the knowledge about this literature by:

- Implementing a battery of neuropsychological tests that assessed *all* of the domains found to be impaired in MS;
- Applying a criterion of cognitive impairment that is consistent with neurological test criteria for impairment (i.e. a score less than the 5th percentile), so that cognitive impairment can be classified appropriately;
- Providing patients with a broader opportunity to subjectively report their level of cognitive functioning; and
- Using a measure of depression that was sensitive to the somatic symptoms associated with MS, so that the effect of depression on patients' reports was appropriately considered.

6.3. SUMMARY OF FINDINGS

6.3.1 DESCRIPTIVE FINDINGS

Descriptive findings from this study suggest that the sample was generally representative of patients presenting to MS clinics (who are usually more functionally impaired) and with studies included in the systematic review. The sample size of this study (n=82) was relatively large in comparison to some previous literature e.g. Goverover *et al*, 2005 (n=26) and was found to have adequate power. In contrast with studies in the systematic review, there was a near even split of male to female patients and the age range was also wider (31-75 years old in current study in comparison to 37-50 years old in the systematic review). The mean disease duration was also longer in the current study (possibly due to the broader age range of patients), due to the progressive nature of the disease and patients' level of functional impairment was more severe. This is consistent with only two studies indentified in the systematic review (Maor *et al*, 2001; Randolph *et al*, 2004), but is consistent with

the level of functional impairment patients present with to MS clinics (McIntosh-Michaelis *et al*, 1991; Rao *et al*, 1991).

Eighty percent of patients in the current study met the criteria for clinically significant levels of fatigue and 43% met the criteria for clinically significant levels of depression. Although patients were at the upper end of reported fatigue in comparison to other samples (i.e. 55-83% of patients; Bakshi *et al*, 2000), this is consistent with findings from studies in the systematic review (e.g. Lovera *et al*, 2006; Maor *et al*, 2001; Randolph, Arnette & Freske, 2004). Fifty four percent of patients were found to be cognitively impaired on neuropsychological tests, with processing speed, memory and executive functioning found to be the most commonly impaired domains. This is also consistent with previous research demonstrating that between 50-60% of MS patients are affected by cognitive impairment (e.g., Amato *et al*, 2005; Amato, Zipoli & Portaccio, 2006). At least some level of subjective impairment was reported by all patients (no-one scored zero on the subjective cognitive measure) and 43% met the studies criteria for subjective impairment. This falls between the 35-51% range reported by studies within the systematic review (Deloire *et al*, 2006; Maor *et al*, 2001).

The current study found a significant relationship between age and subjective cognitive reports, demonstrating that as participants became older, they reported fewer problems with their cognition. Only one study included in the systematic review found similar findings to this (Marrie *et al*, 2005). In an attempt to explain these findings, correlations between disease duration and subjective cognitive reports were performed and similar findings were observed i.e., as disease duration increased, patients reported less problems with their cognition. This finding was not reported by any of the studies in the systematic review. One possible reason for this finding is that there was a larger age range of patients in the current study, and subsequently, a larger range in disease duration. Studies in the systematic review reported patients' disease duration to range from as little as 3-15 years (Randolph *et al*, 2004) or from 5-23 years (Krch *et al,* 2010) which is much smaller in comparison to the current study (3-43 years). As a result of the larger disease duration, patients in the current study may have had more time to adapt to living with MS and put 'strategies' in place in order to compensate for their difficulties (Christodoulou *et al,* 2005). It is also possible that as a result of increased support, or indeed, cognitive impairment, patients may lack insight into their cognitive abilities (Carr *et al,* 2001). These possibilities are discussed in more detail in study aim one below (Section 6.3.2).

6.3.2 STUDY AIM ONE

The aim of the study was to compare patients' subjective cognitive reports with their performance on neuropsychological tests and consider the role of depression

6.3.2.1 HYPOTHESIS ONE

Following the review of the previous literature, the studies first hypothesis was:

1. Patients who are impaired on neuropsychological tests will report more problems with their cognition

The independent t-test demonstrated a significant difference in patients' cognitive reports on the PDQ between those who were cognitively impaired and unimpaired on neuropsychological tests. Although the effect size of this difference was found to be relatively small, it demonstrated that those who were impaired on neuropsychological tests reported more problems with their cognition than those who were unimpaired on tests. This finding was consistent with the research hypothesis.

Further analyses into specific relationships between neuropsychological tests and subjective cognitive reports revealed that there was a significant relationship between patients' PDQ score, the executive functioning task (Stroop task) and working memory task (digit span). This demonstrated that as patients' level of impairment increased on these tests, they subsequently reported more problems with their cognition. Further analyses into whether other relationships existed between neuropsychological tests and individual cognitive domains on the PDQ (i.e. subjective memory, attention and executive functioning) revealed that a significant correlation also existed between prospective memory on the PDQ and the SDMT (processing speed task). The analyses revealed that patients who were impaired on the Stroop task were more likely to subjectively report problems with all cognitive domains on the PDQ, patients impaired on the digit span task were more likely to report problems remembering future plans, keeping their attention, and planning/problem solving, and those impaired on the SDMT were more likely to report difficulties remembering past events.

Findings from this study are consistent with Carone *et al* (2005) who also found a significant difference between patients' reports of their cognitive functioning and their performance on neuropsychological tests, and with seven studies which reported a significant relationship between patients' subjective cognitive reports and their performance on at least one neuropsychological test (Benedict *et al*, 2004; Deloire *et al*, 2006; Goverover *et al*, 2005; Kinsinger *et al*, 2010; Krch *et al*,

2010; Middleton *et al*, 2006; Randolph *et al*, 2004). Correlations reported in the current study (r=-0.28, p=0.01) are also consistent with the lower range of those reported in the systematic review (r=-0.23, p<0.01; Kinsinger *et al*, 2010 to r=-0.63, p<0.01; Goverover *et al*, 2005). Whilst significant correlations were found in the current study, it must be considered that this was only found between two neuropsychological tests and patients' subjective cognitive reports and between one neuropsychological test and one part of the subjective measure. Furthermore, although significant results were found, the effect size from the t-test analyses was calculated to be -0.05, which is considered a *very* small effect size, and the size of the correlations were also relatively small (Cohen, 1988).

The small effect size and relationship found in the current study and previous literature suggests there are other factors that maybe affect patient' reports of their cognitive functioning and their neuropsychological test performance. One argument is that the discrepancy could be to do with life habits and daily demands of cognitive functioning and the adaption the patient makes to compensate these deficits (Rao, 1990). For example, patients may compensate for cognitive difficulties by withdrawing from demanding activities within their daily life or receiving increased support. Christodoulou *et al* (2005) termed this 'accommodation theory'. This theory speculates that a change in patients daily activities and responsibilities i.e., retirement and/or support from care givers, influences patients perceptions of their cognitive abilities, as they may no longer be involved in cognitively demanding activities and are less likely to be in situations where they 'test out' their cognitive abilities. This may account for patients who are cognitively unimpaired reporting more problems with their cognition than found on neuropsychological tests, and also, for patients who are cognitively impaired overestimating their cognitive abilities. For patients who are severely impaired or have long-standing cognitive impairment, they may also lack insight into their deficits, possibly because of their cognitive impairment and may not fully understand or notice the effect it has on their functioning (Carr *et al*, 2001).

Another possibility is that patients who are 'unimpaired' on neuropsychological tests but who report subjective cognitive problems are in fact noticing 'real' impairments and that the fault lies with the "ecological validity" of the tests. The validity of neurological testing has been widely discussed (Chaytor & Schmitter-Edgecombe, 2003) and it is questionable if tests are sensitive to detect subtle changes in cognition in MS patients (Marrie *et al*, 2005). Julian *et al* (2007) argued that subjective cognitive complaints may be related to very subtle cognitive deficits that are noticed by patients; particularly with respect to processing speed and working memory as these are the most commonly

impaired domains, but the magnitude of this impairment is not detectable by standard neuropsychological tests. Indeed, research into dementia has demonstrated that those who were cognitively 'unimpaired' but whom reported high levels of subjective complaints were more likely to develop dementia within 3 years and were more likely to have white matter lesions on an MRI scan (de Groot *et al*, 2001). Although this has not been researched within an MS population, it does highlight a possibility that 'unimpaired' MS patients reporting subjective cognitive reports are noticing 'real' declines which may result in increased reports of cognitive dysfunction.

Additionally, one of the difficulties of neuropsychological tests is that they have been 'normed' for the general population as opposed to an MS population and there is no specific guidance as to what should be classified as 'cognitive impairment' in MS. However, if the problem does lie with the ecological validity of neuropsychological tests, it is difficult to account for studies showing for example, strong correlations between caregivers' perceptions of patients' cognitive functioning and patients' performance on neurological tests (Benedict *et al*, 2003, Benedict *et al*, 2004). It seems likely therefore that factors, other than cognitive functioning may be impacting on patients' perceptions and reports of their cognitive functioning, which subsequently impacts on the relationship with neuropsychological test performance. The likelihood of this is supported by findings demonstrating that depressed patients report more problems with their cognition (e.g. Goverover *et al*, 2005) and that following treatment for depression, the relationship between patients cognitive reports and their performance on neuropsychological tests improves (Julian *et al*, 2007).

6.3.2.2 HYPOTHESIS TWO

The systematic review highlighted that **all** studies found a positive relationship between patients' reports of their cognition and symptoms of depression i.e. as patients become more depressed, they reported more problems with their cognition. In relation to these findings, the second research hypothesis stated that:

2. Patients who are depressed will subjectively report more problems with their cognition

The current study included a measure of depression that was sensitive to MS symptomatology and arguably provided a measure of depression that was not influenced by patients' symptoms of fatigue or psychomotor problems. Despite only two studies in the systematic review including a measure sensitive to MS symptomatology, findings from the current study ($r=0.42$, $p= 0.0001$) were

consistent with previous research (r=0.44, p<0.01; Gold *et al*, 2005 to r=0.59, p<0.001; Goverover *et al*, 2005) and demonstrated that as symptoms of depression increased, patients reported more problems with their cognition.

A number of hypotheses have been developed in an attempt to explain the mechanisms by which depression impacts on patients' subjective reports of their cognitive functioning. One suggestion is that mildly depressed patients may overestimate their memory impairment because of a depressed schema (Julian *et al*, 2007; Maor *et al*, 2001). It has been suggested that depressed patients have a negative feedback loop operating so that those that feel depressed focus more on their cognitive failures. As a result of this, it is possible that patients perceive their cognition as more severe, which in turn increases their depressive symptoms (Croyle & Uretsky, 1987; Maor *et al*, 2001). This suggestion is yet to be researched within an MS population, but is consistent with Beck's (1967) cognitive model of depression which is a well established model within the mental health field. This states that depressive symptoms are associated with a negative, pessimistic view of oneself, the environment and the future which subsequently effects behaviour, thoughts and feelings. MS patients with a negative bias may lead them to overestimate their cognitive problems, misinterpret everyday 'thinking errors' as cognitive impairment and subsequently distort the perception of their cognitive abilities.

Other suggestions have also been developed as it has been found that not all depressed patients overestimate their cognitive problems (Bruce & Arnett, 2004) and there is also evidence to suggest that other emotional difficulties i.e. anxiety, correlate significantly with patients subjective cognitive reports. Research by Bruce *et al* (2010) demonstrated a strong relationship between anxiety and self reported memory and argue that as anxiety does not typically create a globally negative world-view, that patients' perceptions of their cognitive functioning may also be influenced by changes in their behaviour; in addition to the presence of negative beliefs. As already discussed, changes in patients' everyday activities as a result of their impairments e.g. increased support, retirement, and difficulties engaging in the things they once enjoyed, result in them engaging in less social and meaningful activities, which is not only detrimental to patients QoL and psychological well-being, but leaves them with little opportunity to 'test out' their abilities.

The current study has supported findings from previous research demonstrating that depressed patients who are impaired on neuropsychological tests report the most problems with their cognition. In relation to these findings, it seems likely therefore that the relationship between

patients' cognitive reports and their functioning on neuropsychological tests are influenced by depression. Specifically, that the effect of neuropsychological test performance on patients' subjective cognitive reports will be less in depressed than non-depressed patients.

6.3.2.3 HYPOTHESIS THREE

In relation to the predicted effect of depression, hypotheses three stated that:

3. The effect of neuropsychological test performance on patients' subjective cognitive reports will be different for those who are depressed and not depressed

A two-way factorial analysis of variance (ANOVA) was used to test hypothesis three by measuring whether a combination of depression and performance on neuropsychological tests predicted reports of cognitive functioning on the PDQ. Age was entered as a covariate in the analyses after it was identified as an influential variable on patients' PDQ score. Results demonstrated a significant main effect of depression on patients' PDQ score, but no significant main effect of neuropsychological tests performance. This demonstrated that patients levels of depression was more predictive of their subjective cognitive functioning that their performance on neuropsychological tests. Analyses also revealed that there was no significant interactional between depression and neuropsychological test performance on patients' PDQ score. Hypotheses three was therefore rejected, as the effect of neuropsychological test performance on patients' subjective cognitive reports was not significantly different for those who were depressed and not depressed.

Findings from this study are consistent with Krch *et al* (2010), who found that although depression was related to patients' subjective cognitive reports it did not significantly affect the relationship between patients' cognitive reports and their performance on neuropsychological tests. However, the findings are inconsistent with research demonstrating that following treatment for depression patients' subjective cognitive reports were associated more with their performance on neuropsychological tests (Julian *et al*, 2007) and that depression was a significant predictor variable in the relationship between neuropsychological test performance and patients' reports (Carone *et al*, 2005; Middleton *et al*, 2006). The current study used a measure of depression that was sensitive to MS symptomatology; something previous research investigating the role of depression has largely failed to do. It is possible that this may be the reason for the discrepancy in the findings between this study and previous research.

These findings also suggest that there may be other factors that are influencing patients' subjective cognitive reports and their performance on neuropsychological tests. For example, Middleton *et al* (2006) found that in addition to symptoms of depression, patients reports of their cognition was affected by levels of anxiety and fatigue. MS patients are frequently found to experience excessive worry and anxiety as a result of an uncertain future (Bruce & Arnett, 2009) and fatigue is reported to be one of the most disabling symptoms associated with MS (Arnett *et al*, 2001). These factors were not considered in the current study, but future research may identify them as significant contributing factors to the relationship between patients' subjective cognitive reports and their performance on neuropsychological tests. This is discussed in more detail in the future research (section 6.6).

6.3.2.4 SUMMARY OF STUDY AIM ONE

Study aim one therefore demonstrated that patients impaired on neuropsychological tests were more likely to report problems with their cognition. Depression also significantly affected patients' subjective cognitive reports, as depressed patients were more likely to report problems with their cognition. Whilst depression was found to significantly affect patients' reports of their cognitive functioning, the effect of neuropsychological test performance on patients' cognitive reports was not significantly difference for those who were depressed and not depressed.

From the systematic review it was highlighted that subjective cognitive measures were sometimes limited to one cognitive domain, or included very few questions about cognition. It is possible that another reason for the discrepancy between patients' subjective cognitive reports and their neuropsychological test performance is that subjective cognitive measures are too narrow, and that this is limiting patients' opportunity to report their cognition. If patients were provided with a subjective measure that included questions about multiple cognitive domains, it is possible that their subjective cognitive reports would be more reflective of their neuropsychological test performance.

6.3.3 STUDY AIM TWO

In order to address the limitation of previous measured of subjective cognitive functioning; additional questions about subjective processing speed and language were added to the subjective measure, the PDQ, to form the PDQ-E. These cognitive domains are found to be commonly impaired in MS, but are not included in the PDQ. Study Aim Two therefore was to expand the PDQ and provide a broader subjective cognitive measure for patients to report their cognition. This was an

exploratory analysis into comparing patients' subjective reports on the PDQ-E with their neuropsychological test performance, whilst considering the role of depression.

6.3.3.1 SUBJECTIVE COGNITIVE IMPAIRMENT ON THE PDQ-E

Forty three percent of patients had significant levels of subjective cognitive impairment on the PDQ-E. This is consistent with findings from the PDQ where 43% of patients were also 'subjectively impaired'. Subjective attention and retrospective memory remained the domains patients were the most impaired, followed by planning, processing speed (added by the PDQ-E), prospective memory and language (added by the PDQ-E). The findings suggest that the subjective processing speed questions (added to the PDQ) were the most relevant to patients' subjective cognitive reports, as mean scores for these questions were higher than some of those included in the PDQ. Consistent with findings using the PDQ, analyses identified a significant relationship between disease duration and PDQ-E scores and age and PDQ-E scores, demonstrating that as time increased (i.e., patients became older & disease duration was longer) they reported less problems with their cognition.

6.3.3.2 COMPARE PATIENTS SUBJECTIVE COGNITIVE REPORTS (ON THE PDQ-E) WITH THEIR PERFORMANCE ON NEUROPSYCHOLOGICAL TESTS AND CONSIDER THE ROLE OF DEPRESSION

Analyses into comparing patients' reports of their cognitive functioning on the PDQ-E with their performance on neuropsychological tests demonstrated that patients who were cognitively 'impaired' on tests reported more problems with their cognition. Consistent with findings using the PDQ, further correlational analyses revealed that the executive functioning task (The Stroop) and the working memory task (digit span) negatively correlated with the PDQ-E, demonstrating that that as patients level of cognitive impairment increased, they reported more problems with their cognition. When the PDQ-E was broken down into individual domains and compared with neuropsychological tests, the executive functioning task (The Stroop) and working memory task (digit span) remained the only tests that correlated with subjective processing speed and language on the PDQ-E.

6.3.3.3 PATIENTS COGNITIVE REPORTS ON THE PDQ-E AND LEVELS OF DEPRESSION

A significant positive correlation was found between the PDQ-E and depression which suggested that as patients' level of depression increased, so did the number of cognitive problems they reported. These findings are also consistent with findings from the PDQ.

6.3.3.4 PATIENTS SUBJECTIVE REPORTS, THEIR NEUROPSYCHOLOGICAL TEST PERFORMANCE AND LEVELS OF DEPRESSION

A two-way ANOVA was used to investigate the individual and interactional effects of neuropsychological test performance and symptoms of depression on patients' reports of their cognitive functioning on the PDQ-E. Age was again entered as a covariate due to its effect on PDQ-E scores. There was no significant main effect of cognitive impairment on PDQ-E scores but there was for depression, which again demonstrated that levels of depression were more predictive of patients' neuropsychological test performance than their subjective cognitive reports. The effect of patients' neuropsychological tests performance on their subjective cognitive reports was also not significantly different for those who were depressed and not depressed and all findings were consistent with the analyses using the PDQ.

6.3.3.5 SUMMARY OF STUDY AIM TWO

Analyses identified that questions about processing speed seemed most relevant to patients' cognitive reports, as scores on this domain were higher than some of those included in the PDQ. Whilst these questions seemed relevant to patients' concerns, results of the analyses using the PDQ-E are consistent with *all* findings using the PDQ. Results from this study suggest that in order to assess patients' perceptions of their cognitive functioning, clinicians may not necessarily have to include a subjective measure that assesses all of the cognitive domains found to be impaired in MS. It also suggests that subjective measures may not be the most reliable way of assessing whether or not patients need further neuropsychological assessment, as even when patients are provided with a broader measure that assesses multiple subjective domains, the relationship with neuropsychological tests is still relatively small.

6.4 STRENGTHS OF THE STUDY

6.4.1 SAMPLE CHARACTERISTICS

As already discussed, a key strength of this study was the large sample size (n=82) and adequate power. Previous research has been limited by the small samples included in the study (e.g. Lovera *et al*, 2006) which has resulted in insufficient power and poor generalisability of findings. The age range of this sample was also much larger than reported by studies within the systematic review (e.g. Bruce *et al,* 2010; Krch *et al*, 2010; Marrie *et al* 2005). A further strength of the research was the near even split of male to female ratio. Previous research has been limited in that samples have included up to 80-90%female participants (Benedict *et al*, 2004; Bruce *et al,* 2005; Gold *et al*, 2005; Goverover *et al*, 2005), but this was not a limiting factor in this study.

Impairment on neuropsychological tests was also consistent with levels reported by studies in the systematic review, (e.g. Benedict *et al*, 2004), as was the type impairment i.e., memory, processing speed and executive functioning being the most impaired domains (Carone *et al*, 2005; Christodoulou *et al*, 2005; Middleton *et al*, 2006; Randolph *et al*, 2004). Patients subjective cognitive reports were also consistent with previous literature (e.g. Deloire *et al*, 2006; Maor *et al*, 2001), as was level of depression (Feinstein, 2006; Siegert & Abernethy, 2005) and fatigue (Bakshi *et al*, 2000; Krupp *et al*, 1988).

6.4.2 NEUROPSYCHOLOGICAL TESTS

The study implemented a battery of neuropsychological tests that objectively assessed all of the cognitive domains found to be impaired in MS. Only three of the 16 studies in the systematic review did this (Benedict *et al*, 2003; Benedict *et al,* 2004; Carone *et al,* 2005), two of which found similar results to the current study (Benedict *et al*, 2003; Carone *et al*, 2005). These tests are also commonly used tests within MS services and were utilised by studies within the systematic review (e.g. Benedict *et al*, 2004; Julian *et al*, 2007). Consistent with ten studies in the systematic review, this study also included two measures of memory (measured both verbal and working memory), which may have provided a more comprehensive assessment of the cognitive domain that is the most commonly impaired in MS (Benedict *et al*, 2004; Christodoulou *et al*, 2005; Christodoulou *et al*, 2005; Deloire *et al*, 2006; Goverover *et al*, 2005; ; Kinsinger *et al*, 2010; Krch *et al*, 2005; Marrie *et al*, 2005; Middleton *et al*, 2006; Randolph *et al*, 2004).

6.4.3 SUBJECTIVE COGNITIVE MEASURE

The study included a subjective measure than assessed multiple domains found to be impaired in MS. Previous research has included measures that were limited to questions about one cognitive domain (Bruce *et al*, 2010; Goverover *et al*, 2005; Krch *et al*, 2010; Randolph *et al,* 2004), or included a quality of life measure with limited questions about cognition (Gold *et al*, 2003; Julian *et al*, 2007; Maor *et al*, 2001). This study also expanded a widely used subjective cognitive measure to include questions about processing speed and language; domains found to be commonly impaired in MS (Arnett *et al*, 2001). Including these questions may have provided a more comprehensive assessment of patients' reports of their cognitive functioning.

6.4.4 DEPRESSION MEASURE

This study considered the difficulties of assessing depression in MS patients and a measure was selected that was sensitive to the somatic symptoms of MS i.e. questions about fatigue, psychomotor retardation, decreased concentration and insomnia/hypersomnia were omitted. This may have provided a more accurate assessment of depression and is therefore a key strength of this study.

6.5 LIMITATIONS

Despite the number of strengths identified about the current study there are a number of limitations which should be considered when interpreting the findings.

6.5.1 CONVENIENT SAMPLE

One possible limitation of this study is that patients were conveniently recruited from MS clinics. Although this is consistent with 14 of the 16 studies included in the systematic review and with prevalence of cognitive impairment found in community based studies (McIntosh-Michaelis *et al*, 1991), the severity of patients' symptoms of MS may be higher and prevalence rates of cognitive impairment may reflect this (McIntosh-Michaelis *et al*, 1991; Rao *et al*, 1991;).

6.5.2 STUDY DESIGN

The cross-sectional design of this study means it is not possible to explore if patients' cognitive reports and their performance on neuropsychological tests change over time. Further research using a longitudinal design could help draw conclusions about the direction of any possible relationship, and could explore whether patients' subjective cognitive reports predict future impairment.

6.5.3 SAMPLE BIAS

Another limitation is that the study may be subject to a sample bias. Patients who took part may have wanted too because they were concerned about, or had noticed a change in their cognition, which may have resulted in them being more likely to report cognitive problems. However, patients were attending routine clinic appointments and were not anticipating to be asked to take part in a research study. This is very different to some studies in the systematic review that required patients to be referred into them for reporting problems with their cognition or displaying mild cognitive impairment (Carone *et al*, 2005; Christodoulou *et al,* 2005; Chiaravalloti *et al,* 2005; Lovera *et al*, 2006; Marrie *et al,* 2005).

6.5.4 DISEASE DURATION

The mean disease duration was significantly higher (18.33 years) in the current study than those included in the systematic review where mean disease duration ranged from 2-11 years. Despite this however, this did not appear to impact on patients' functional abilities, level of fatigue, depression or cognitive impairment, as results from this study are consistent with those that included samples with shorter disease durations.

6.5.5 CRITERIA FOR CLINICALLY SIGNIFICANT LEVELS OF DEPRESSION

Another possible limitation of this study is that clinically significant levels of depression were defined by the scoring on the BDI-FS as opposed to a diagnostic interview. However, this is consistent with all of the studies included in the systematic review. This study also failed to assess other forms of psychopathology, for example anxiety, which has been associated with subjective memory impairment in non-MS samples (Jonker, Smits & Deeg, 1997; McDougall, 1995) and MS samples (Bruce *et al*, 2010). It is possible that patients' level of anxiety may have influenced their cognitive reports, but this was not assessed in the current study.

6.5.6 EFFECT OF FATIGUE ON PATIENTS REPORTS OF THEIR COGNITION

Previous research has demonstrated a significant relationship between fatigue and patients' reports of their cognitive functioning (Middleton *et al*, 2006), and patients have been found to report that fatigue significantly contributes to poor cognitive performance (Krupp & Elkins, 2000). A limitation of this study is that fatigue was not included in the analyses between patients' reports of their cognitive functioning and their performance on neuropsychological tests, as this was not the aim of the current study. Future research could consider both fatigue and depression as contributing factors to patients' subjective cognitive reports and their neuropsychological test performance, and may also help clarify why there are discrepancies in findings.

6.6 CLINICAL AND SERVICE IMPLICATIONS

This study demonstrated that cognitive impairment is a significant symptom associated with MS and adds to previous research highlighting the importance of routine cognitive assessment within MS services; particularly as cognitively impaired patients can become progressively worse over time (Piras *et al*, 2003). Findings from the current study also demonstrate that subjective cognitive measures may not be the most reliable assessment of patients cognitive functioning, as the relationship between patients' cognitive reports and their performance on neuropsychological tests was relatively small. This has implications for clinical practice and recommendations from the

current study suggest that services may benefit from using other forms of assessment to determine whether further cognitive assessment is needed. Memory and processing speed were found in the current study and systematic review to be the domains most commonly impaired in MS (e.g. Benedict *et al*, 2003) and it is possible that clinicians could administer a measure of one or both of these cognitive functions to determine whether further assessment is needed. The SDMT was used in the current study as a measure of processing speed and research has highlighted it as the best test to predict cognitive impairment, classifying up to 75% of patients correctly (Deloire *et al*, 2006). This timed task took patients 120 seconds to complete, was not overburdening and easily administered, and could possibly be used as a screening tool in MS services to determine if further assessment is needed.

Whilst not utilised in the current study, there is also the possibility that services could implement a brief computerised neuropsychological battery to screen for impairment. Computerised batteries have the advantage of being less costly and are shorter to administer, which saves service resources and are not too demanding on patients who are affected by symptoms such as fatigue. The precision of computer tests also allows for greater accuracy in processing speed and has the ability to provide patients with immediate performance on their performance (Gottschalk *et al*, 2000; Kane & Kay, 1992). They also have the advantage of coming in alternative forms, which is necessary for minimising practice effects when monitoring patients with progressive disorders over time.

A third option could also be to administer a subjective cognitive measure to both patients and their care givers. Two studies included in the systematic review administered subjective measures to patients and their care givers during routine clinical appointments to determine the 'accuracy' of patients' subjective cognitive reports. They found that caregivers' reports provided a more accurate account of patients cognitive functioning on neuropsychological tests (Benedict *et al*, 2003; Benedict *et al*, 2004). This may be an option which services could implement relatively easy in conjunction with patient reports (as it does not take a significant amount of time or cost) and may provide a better means of identifying patients needing further assessment.

In comparison with previous research, this study also demonstrated that depression was a significant symptom associated with MS and that depression has a negative effect on patients' perceptions of their cognitive abilities. This study used a measure of depression that was sensitive to the somatic symptoms associated with MS and recommendations from this research suggest that a similar measure should be implemented when determining levels of depression in MS patients. Although

the effect of neuropsychological test performance on patients' reports of their cognitive functioning was not significantly different for patients who were depressed and not depressed, depressed patients were found to report significantly more problems with their cognition. Services should consider this as a factor when patients are reporting problems with their cognition, as this may be because they are depressed, as opposed to cognitively impaired. Recommendations from this study are that services may benefit from administering a measure of depression; sensitive to the symptoms of MS when investigating patients' reports of their cognitive functioning and this may facilitate decisions as to whether or not further cognitive assessment is needed.

If health providers screen patients for depression when they report cognitive impairment, it is possible that depressed patients could then be successfully treated with behavioural, psychological and pharmacological interventions (Julian *et al*, 2007; Randolph *et al*, 2004). Longitudinal studies have evidenced the benefits of providing treatment for depressed MS patients, demonstrating that following treatment, patients' mood improves; as does their ability to accurately perceive their functioning (Chiaravalloti *et al*, 2005; Julian *et al*, 2007; Kinsinger, Lattie & Mohr, 2010). Interventions such as these could be facilitated by Clinical Psychologists within MS services and would potentially improve patients' quality of life, their emotional wellbeing and their perceptions of their cognitive abilities.

6.7 FUTURE RESEARCH

The findings from this study support some studies in the systematic review that reported that patients who were impaired on neuropsychological tests report more problems with their cognition (Carone *et al*, 2005) and that there are some small relationships between patients reports and their performance on neuropsychological tests (e.g. Krch *et al*, 2010). However, the difference in patients' subjective cognitive reports between those who were impaired and unimpaired on neuropsychological tests was relatively small. Furthermore, although significant relationships were found, these existed between two neuropsychological tests and patients' subjective cognitive reports, and the size of these relationships were relatively small. This suggests that there still needs to be a great deal more research into understanding patients reports of their cognitive functioning and their performance on neuropsychological tests, and the most effective manner in which to investigate this area.

In addition to the cost and time implications of routine cognitive testing, there appears to be insufficient guidance for clinicians to recognise cognitive deficits in MS (Achiron & Barak, 2006).

Research has established that there are a number of domains that are more likely to be impaired in MS, but there is no guidance as to how many, or what level of impairment patients need to be presenting with to define cognitive impairment. When diagnosing dementia or Learning Disabilities, clear guidance is available for clinicians to make a decision based on how patients are presenting and their level of intellectual functioning (i.e. below 70 for a learning disability) and this then informs appropriate interventions and service entitlement. Future research could help collaborate findings from previous studies and develop guidance for services to recognise and define impairment in MS, which may facilitate more routine assessment of cognition.

Consistent with previous literature, this study demonstrated the significant effect depression has on cognitive reports, but failed to provide information about the mechanisms by which depression influences patients' appraisals. Research has demonstrated that patients report less cognitive impairment following treatment for depression (Julian *et al*, 2007; Randolph *et al*, 2004), which suggests that the way patients perceive themselves can be modified. Cognitive-behavioural therapy has been found to be effective with MS patients (Foley *et al*, 1987; Julian *et al*, 2007; Mohr *et al*, 2000), but it is uncertain how this changes patients' perceptions of their abilities i.e. is it the behavioural aspect that encourages patients to do more and they see that they can, or is it a change in negative thinking? Future research could help distinguish what patients use to distinguish their level of functioning (i.e. is it that patients just need to encouraged to do more) and if there are differences in patients' subjective cognitive reports between those who are 'depressed' and 'not-depressed'. Understanding these mechanisms may help clinicians improve the ability to obtain accurate information from self reports and identify patients who may benefit from treatment for depression.

There is also evidence to suggest that cognitive-behavioural interventions may also improve mood and decrease subjective reports by 'skilling up' patients coping strategies. Rabinowitz & Arnett (2009) suggest that the relationship between cognitive functioning, subjective cognitive reports and depression varies according to the patient's coping style. This has been supported by Arnett *et al* (2002) who found that MS patients were more likely to experience depression when they used either low levels of adaptive coping or high levels of maladaptive avoidant coping. They argue that because coping involves cognitive processes, it may have a direct effect on the cognitive and behavioural strategies needed for enacting adaptive types of coping, thus making MS patients more susceptible to developing depression. Future research is needed to further explore the relationship between coping and depression in MS and how this impacts on subjective cognitive reports and

functioning on neuropsychological tests. Once this has been established, an intervention to help patients cope may be useful, as it may have a positive influence on levels of depression and patients subjective cognitive reports.

As discussed in service implications (section 6.7), on-line computerised measures of cognitive impairment have been developed and *could* be a more reliable tool for screening cognitive impairment. Computerised batteries have been found to be as effective as a several hour battery of neuropsychological tests in detecting cognitive impairment in MS (Wilken *et al*, 2003; Younes *et al*, 2007), demonstrating to be nearly three times more sensitive than the PASAT (commonly used processing speed task) and more sensitive in detecting visual memory impairment (Younes *et al*, 2007). More research is needed to validate the use of computerised cognitive assessment within an MS population and determine whether it will save patient and health care resources.

Further research could also investigate how emotional difficulties other than depression influence patients' perceptions of their functioning. Anxiety disorders have an estimated prevalence of 36% in MS (Korostil & Feinstein, 2007) and patients have been reported to frequently experience excess worry and anxiety (Bruce & Arnett, 2009). The relationship between cognition and anxiety has not been extensively researched within MS, although there is evidence to suggest that high baseline negative affects (including anxiety and depression) predicts a decline in memory (Christodoulou *et al*, 2009) in MS patients, and slowed information processing within the general population (Beck & Clark, 1997). Research is needed to further explore the effect of anxiety on cognition, and also, to investigate its effect on patient' perceptions of their cognitive abilities.

6.8 SUMMARY

Cognitive impairment is a symptom frequently associated with MS, occurring in approximately 40-70% of patients across the disease course (McIntosh-Michaelis *et al*, 1991; Rao *et al*, 2001). Patients with MS-related cognitive impairment are less likely to be employed, engage in fewer social activities and have difficulty developing relationships (Langdon & Thompson, 1999; Rao *et al*, 1991), all of which may have a detrimental effect on patients QOL and psychological wellbeing. The importance of detecting cognitive impairment in MS is therefore evident, but the difficulty assessing cognitive impairment on a routine basis (administration time of tests and the expertise required for their interpretation) means there is often a reliance on patients to report whether or not they are experiencing problems with their cognition. As further assessment and intervention may be based

on patients' reports, it is important to compare patients' cognitive reports with their performance on neuropsychological tests and identify significant factors that may impact on this.

A systematic review of the literature identified 16 studies that had compared patients' report of their cognition with their performance on neuropsychological tests. Findings from these studies were mixed, with some reporting significant differences in patients cognitive reports between those who are impaired and unimpaired on neuropsychological tests (e.g. Carone *et al*, 2005), others reporting that patients subjective cognitive reports were related to their performance on neuropsychological tests (e.g. Benedict *et al*, 2004) and others finding no such relationship (e.g. Gold *et al*, 2005). Whilst some studies found that patients' reports of their cognition were related to their performance on neuropsychological tests, most studies failed to find a substantial relationship (Christodoulou *et al*, 2005; Lovera *et al*, 2006; Middleton *et al*, 2006). Depression was found to be more highly correlated with patients' subjective cognitive reports than any neuropsychological test in *all* studies, and some studies identified it as a significant mediating factor in the relationship between patients' reports and their performance on neuropsychological tests.

A number of limitations were identified from the systematic review, including studies using a limited number of neuropsychological tests, subjective cognitive measures that were limiting to only one cognitive domain, measures of depression that were sensitive to MS symptomatology and no clear definition of cognitive impairment. These limitations were considered when developing the current study.

The main aim of this study was to compare patients' subjective cognitive reports with their performance on neuropsychological tests and consider the role of depression. Results from this study demonstrated that patients who were cognitively impaired on neuropsychological tests reported more problems with their cognition than those unimpaired and that there was a significant relationship between some neuropsychological tests and patients reports of their cognition. However, the magnitude of this difference was very small, as was the size of the correlations. Depression was found to correlate highly with patients' subjective cognitive reports and was larger than any correlation with neuropsychological tests. Despite the significance of depression, the effect of patients' performance on neuropsychological tests on their subjective cognitive reports was not significantly different for patients who were depressed and not depressed.

When reviewing previous research, subjective cognitive measures were identified as being limiting in the number of cognitive domains they assessed and it is possible that this restricted patients' ability to report their cognition. In order to address this, the second aim of the current study was to provide a broader subjective cognitive measure for patients to report their cognition. Additional questions about subjective processing speed and language were added to the subjective cognitive measure (the PDQ), as these domains are found to be commonly impaired in MS, and formed the PDQ-E. Analyses identified that questions about processing speed seemed most relevant to patients' cognitive reports, but while these questions seemed relevant, there were no differences in the analyses using the standard or expanded subjective cognitive measure.

Results from this study suggests that in order to assess patients' perceptions of their cognitive functioning, clinicians may not necessarily have to include a subjective measure that assesses all of the cognitive domains found to be impaired in MS and that subjective measures may not be the most reliable way of assessing whether or not patients need further neuropsychological assessment. The present study also demonstrates that non-cognitive factors play an important role in determining patients' subjective reports of their cognitive functioning, and complaints of cognitive problems should therefore be accompanied by a measure of depression before prompting a full neuropsychological assessment. Services may need to think about how interventions for depression can also be implemented effectively into routine care, as this is potentially a treatable symptom of MS, and is likely to have a positive effect on patient's perceptions of their cognitive abilities, their quality of life and psychological well-being.

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APPENDIX 1 – Studies included in systematic review

Study	Aims	Study type	Design	Sample	Sample characteristics	Control group	Type Of MS	Sample recruited: clinic/ community	Neuropsychological test	Subjective cognitive Measure	Depression measure	Results (*Exact p-value reported when possible)	Limitations
Goverover et al, 2005	Awareness of cognitive functioning& relationship with mood	Cross-Sectional	Correlation	26 Patients 26 Informants	Age: range= 27-56; mean-=46 Average years of education = 15.5yrs 80% female Most patients had mild physical impairment Mean disease duration : 11yrs (range: 1-26.6 years)	No	Not Reported	Clinic & Community	-COWAT - AF - BNT -Reading Subtest - WMS - PASAT -WCST	FrSBe (Executive functioning). Subjective cognitive impairment determined by comparing patient reports with informant reports	BDI-II	Correlations between increased self awareness of executive function & better cognitive ability (range from r= - 0.47, p<0.05 to r= -0.63, p<0.01). Correlation between decreased self awareness and BDI-II (r= 0.59, p<0.01). Neuropsychological test performance was predictive of self awareness after controlling for depression (r=0.56, p<0.01)	MS type not reported. Depression much lower compared to other studies. Small sample size Patients had mild cognitive impairment. Subjective cognitive impairment based on deviation from informant reports. BDI-II sensitive to MS symptomology
Carone et al, 2005	Assess meaning of informant/patient discrepancy scores on the MSNQ	Cross-sectional	Case-control	122 Patients 122 Informants	Age: no range; mean = 44 Average years of education = 14.5yrs 72% Women Most patients had mild physical impairment Mean disease duration: 12yrs	37	RR=88 SP=30 PP= 2	Clinic	COWAT JLO CVLT-II BVMT-R PASAT SDMT WCST	MSNQ. Subjective cognitive impairment determined by comparing patient reports with informant reports	BDI-II	Significant difference between patients who accurately estimated, overestimated and underestimated their cognitive ability on neuropsychological tests [F(2,95)= 4.0, p=0.02] to [F(2,95)= 5.3, p=0.007]. Student Newan-Keuls post hoc test showed accurate and underestimators were the least cognitively impaired. Patients who overestimated their cognitive abilities performed the worst on cognitive tests. Significant differences in levels of depression between over and underestimators of cognitive ability [F(2,48) = 3.7, p<0.05]	Patients were referred for study to investigate correlates of euphoria and cognition. Therefore may have been selected as experiencing increased difficulties with mood. BDI-II sensitive to MS symptomology

Study	Aims	Study type	Design	Sample	Sample characteristics	Control group	Type of MS	Sample recruited (clinic/ community)	Neuropsychological test	Subjective cognitive Measure	Depression measure	Results (*Exact p-value reported when possible)	Limitations
Krch et al, 2010	Relationship between subjective cognitive reports & 1-trial learning task	Cross-sectional	Correlation	64 Patients	Age: range =38-57 Average years of education = 15.7yrs 75% women Most patients had mild physical impairment Mean disease duration: 14yrs (range: 5-23 years)	No	RR=47 SP= 2 PP=1	clinic	CVLT-II OT-SRT Prose Memory	MFQ	CMDI	Significant positive correlation between MFQ & trial 1 of the OT-SRT (r=0.42; p=0.001) and trial 1 of the CVLT (r=0.39; p=0.002), but not between the delayed recall performance and the MFQ (r=0.23, p=0.08) Significant correlation between CMDI & MFQ (r= -0.29, p=0.02). When depression controlled for, relationship between MFQ & trial 1 OT-SRT remained significant (r=0.04, p=0.002)	Mostly RR. Younger sample No measure of processing speed CMDI sensitive to MS symptomology
Julian et al, 2007	Relationship between subjective cognitive reports & cognitive functioning pre & post treatment for depression	Longitudinal	Experimental	58 Patients	Age: No range; mean = 44 Average years of education = 15yrs 76% female Most patients had mild-moderate physical impairment Mean disease duration: 8yrs	No	Not available	Clinic	SDMT Stroop Digit Span RAVLT COWAT	MSQOL-54	BDI-II	No change in cognitive functioning following treatment. Cognitive functioning predicted 8% of variance (r^2 =0.08, p<0.05). Depression predicted 14% (r^2 =0.14, p<0.01). Patients who 'responded' to treatment, cognitive ability predicted 39% of variance (r^2 =0.39, p<0.01) and depression was no longer significant. Patients who didn't respond and remained 'depressed', cognitive ability did not predict subjective cognitive reports (r^2 =0.01, p=0.55)	Did not provide information on type of MS. QOL measure used to assess patients cognitive reports BDI-II sensitive to MS symptomology
Gold et al, 2003	Examine HAQUAMS & HADS in MS Ps with & without cognitive dysfunction	Cross-sectional	Between groups	196 Patients	Age: no range; Mean = 41 Education not provided 77% female Most patients had mild-moderate physical impairment Mean disease duration 9 yrs	No	RR= 75 SP= 55 PP= 29 unknown= 40	Clinic	SDMT	HAQUAMS	HADS	Higher reports of cognitive impairment and depression rating in cognitively impaired group (r=0.44, p<0.01) No significant correlation between SDMT and HAQUAMS in cognitively impaired patients (r=0.01, p>0.05) and unimpaired patients (r=-0.13, p>0.05).	HAQUAMS is a fatigue/thinking measure. Only used SDMT. Patients in early stages of disease

Study	Aims	Study type	Design	Sample	Sample characteristics	Control group	Type of MS	Sample recruited (clinic/ community)	Neuropsychological test	Subjective cognitive Measure	Depression measure	Results (*Exact p-value reported when possible)	Limitations
Benedict et al, 2004	Replicate use of MSNQ with controls & larger sample	Cross-Sectional	Case-control	85 Patients 53 Informants	Age: no range; mean = 42 Average years of education = 15 yrs 80% female Most patients had mild physical impairment Disease duration not provided	40	RR= 68 SP= 17	Clinic	COWAT JLO CVLT-II BVMT-R PASAT SDMT WCST	MSNQ	BDI-FS CES-D-10	MSNQ correlated with cognitive dysfunction (ranging from r= -0.37 to - 0.45, p<0.001) but correlated most with BDI-FS (r=0.61, p <0.001).	Impairment was classed as impairment across *all* measures. Patients mainly mild physical impairment Disease duration not provided therefore difficult to compare with other studies
Middleton et al, 2006	Relationship between perceived & objective cognitive functioning	Cross-sectional	Case-control	221 Patients	Age: range = 20-71; mean = 45 Average years of education = 15 years 74% female Most patients had mild-moderate physical impairment Mean disease duration – 6.5yrs	31	RR= 144 SP= 26 PP= 4	clinic	TOL CVLT-II PASAT SRT WLG	CFQ Performance Estimates Interview.	CES-D	Patients underestimated their cognitive functioning (t=7.93, p<0.001). No correlation between CFQ and neuropsychological test (r=-0.11, p =0 .10). Cognitive tests and performance estimates interview correlated significantly (r=0.55, p<0.001). CES-D significantly correlated with CFQ (r=0.52, p<0.001)	CFQ only asks Q's about attention and memory. CES-D sensitive to MS symptomology
Bruce et al, 2010	Association between emotional functioning, dissociation, cognitive functioning & self reported memory	Cross-sectional	Case-control	79 Patients	Age: range =36-58; mean = 47 Average years of education = 15yrs 90% female Most patients had mild physical impairment Mean disease duration - 10yrs (range 2-18 years)	20	RR=71 SP= 8	clinic	SDMT WCST Stroop AVLT LNS	PRMQ	BDI-FS	PRMQ did not correlate with any cognitive test (r=-0.10, p>0.05) PRMQ correlated with BDI-FS (r=0.32, P<0.01) Depression was a significant predictor in relationship between cognitive tests and CFQ (B=0.54, t=8.08; p<0.001) BDI-FS & cognitive tests (r=0.03 to r=0.13, p>0.05)	Not many patients in later stages or progressive disease forms. Patients mainly female (90%)

Study	Aim	Study type	Design	Sample	Sample characteristic	Control group	Type of MS	Sample recruited (clinic/ community)	Neuropsychological test	Subjective cognitive Measure	Depression measure	Results (*Exact p-value reported when possible)	Limitations
Benedict et al, 2003	Design a neuropsychological screening tool based on self or observer reports that could be administered by nonprofessional staff in clinical setting	Cross-sectional	correlation	102 Patients 102 Informants	Age: range =29-60; mean = 43 Average years of education = 15 yrs 66% female Most patients had mild physical impairment Mean disease duration – 10.5yrs (range 1-30 years)	No	RR= 82 PP= 20	Clinic	BNT JLO CVLT-II Trail making test WCST PASAT	MSNQ CFQ	BDI-II CES-D	MSNQ correlated with BDI-II (r= 0.53, p<0.01) but not with cognitive tests (r value not reported).	The MSNQ did highlight more false positives than false negatives. Patients were early MS patients, most of whom had normal or only mildly impaired cognitive functioning. Depression measures sensitive to MS symptomology
Christodoulou et al, 2005	Examine how changes in self-report may relate to changes in neuropsychological performance	Longitudinal	Experimental	53 Patients	Age: range =20-55; mean =44 Average years of education = 15yrs 68% female Most patients had mild physical impairment Mean disease duration not provided	No	Not available	Clinic	BRB: Spatial recall SRT SDMT PASAT COWA TOH	PDQ Two single questions asking about memory & attention/ concentration.	MADRS	No significant correlation between PDQ and overall cognitive functioning (r= -0.01, p>0.05). Relationship between a change in overall neurological performance (following treatment) and scores on the PDQ (r=-0.53, p≤ 0.01) MADRS correlated with PDQ (r= 0.32, p= 0.02). MADRS did not correlate with cognitive tests (r=-0.09 to r=-0.24, p>0.05)	Patients excluded with high depression All participants had to display a mild impairment to take part in the study. No information on MS type. MADRS sensitive to MS symptomology
Marrie et al, 2005	Examine relationship between subjective cognitive reports and objective cognitive performance	Cross Sectional	Correlation	136 Ps	Age: range =38-56; mean= 47 Average years of education = 15 yrs 69% female Physical ability and disease duration not provided	No	RR =97 SP= 39	Clinic	WAIS WMS	PDQ	MHI	MHI & PDQ (impaired and unimpaired) (t=not reported, p<0.0001) No difference on neuropsychological tests between patients subjectively impaired and unimpaired on PDQ (t=not reported, p=0.09 to 0.37). Non-linear relationship between PDQ &WAIS/WMS (Hosmer Lemeshow p value = 0.54) and excellent predictive power (c-index=0.91)	Patients took part as they already had subjective complaints. MHI sensitive to MS symptomology

Study	Aims	Study type	Design	Sample	Sample characteristics	Control group	Type of MS	Sample recruited (clinic/ community)	Neuropsychological measure	Subjective cognitive Measure	Depression measure	Results (*Exact p-value reported when possible)	Limitations
Deloire et al, 2006	Evaluation of 2 strategies for identifying Ps needing neuropsychological assessment during the early stages of MS	Cross-Sectional	Case-control	57 Patients	Age (mean 37) 75% female Average years of education = 12 yrs Most patients had mild physical impairment Average disease duration= 2 yrs	44	RR =57	Clinic	SRT SPART SDMT PASAT WLG Stroop Similarities (WAIS-R) BNT RFF	SEP-59	MADRS	SDMT correlated with one question about memory complaints on the MSQOL (r =0.31, p<0.02). No other correlations. MADRS correlated with SEP-59 (r= -0.43, p<0.01)	Newly diagnosed patients. Only looked at RR therefore unsure how can generalise to other types of MS. The SEP-59 does not cover all cognitive problems i.e., it only includes questions about memory and concentration/attention. MADRS is sensitive to MS symptomology
Maor et al, 2001	Relationship between patients reports and cognitive functioning	Cross-Sectional	Correlation	161 Patients	Age: no range; mean= 44 63% female Average education not provided Most patients mild-moderate physical impairment Av disease duration = 10yrs (range: 3-18 years)	No	Not provided	Clinic	NCSE	MSQOL-54	CES-D	NCSE explained 7.4% of variance in MSQOL-54 score (R^2=0.07, p=0.001) Weak correlation between NCSE & CES-D (r=-0.19, p<0.05)	No information processing measure. Type of MS not provided CES sensitive to MS symptomology
Kinsinger, Lattie & Mohr, 2010	Influence of depression and fatigue on patients reports and cognitive functioning	Longitudinal	RCT	127	Age (mean 48) Av education 15 yrs 77% female Moderate physical impairment Disease duration not provided	No	RR= 113 SP =13 PP= 1	Clinic and community	COWAT Digit Span & Letter-Number sequencing from WAIS-III CVLT-II	PDQ	BDI-II HDRS	PDQ correlated with neuropsychological tests pre and post treatment (r = -0.23, p<0.01; r = -0.37, p<0.01). PDQ significantly associated with depression (r=0.37, p<0.001) at time 1 and 2. Change in BDI-II following treatment related in better relationship between PDQ & cognitive tests (odds ration [OT] =0.77, p<0.001)	Excluded those with severe levels of cognitive impairment. Neuropsychological tests administered over telephone. No visual cognitive tasks. Depression measures sensitive to MS symptomology

Study	Aims	Study type	Design	Sample	Sample characteristics	Control group	Type of MS	Sample recruited (clinic/ community)	Neuropsychological test	Subjective cognitive Measure	Depression measure	Findings	Limitations
Lovera et al, 2006	Relationship between Cognitive reports and cognitive performance on tests	Cross Sectional	Correlation	49 Patients	Age: No range; mean= 49 Education not provided 76% female Physical ability and disease duration not provided	No	RR = 32 SP= 15 PP = 2	clinic	PASAT CVLT-II COWAT SDMT Stroop	PDQ	BDI-IA	BDI-IA did not correlate with any of the cognitive tests (r=0.19; 95% CI, -0.10 to 0.45; p=0.19) PDQ correlated with the BDI (r=0.42, p=0.003) PDQ did not correlate with cognitive tests (r=0.18; p=0.20)	Patients were volunteers who were taking part in a drug trial for cognitive impairment. Patients needed to be functioning at 0.5 SD below the norm to participate. No information provided re: disease duration, physical ability and education. No measure of executive functioning, visuospatial reasoning or non-verbal memory. BDI-IA sensitive to MS symptomology
Randolph, Arnett & Freske, 2004	Examine contribution of depression, depressive attitudes & executive functioning on metamemory reports	Cross-Sectional	Correlation	48	Age: no range; mean=50 Average years of education = 15 yrs 77% female Most patients had mild physical impairment Disease duration =10yrs (range: 3-15years)	No	RR= 28 SP= 13 PP= 6	Clinic	TOH LNS from (WAIS-III) SRT	MFQ	BDI-II CMDI	Negative correlation between forgetting when reading (on the MFQ) and the TOH (r=0.36, p<0.01) MFQ correlated with BDI-II (but not CMDI) (r=0.45, P<0.001). MFQ associated with CMDI (r=0.26, p=0.07)	Limited number of neuropsychological tests Depression measures sensitive to MS symptomology

Acronym key for systematic review table (Appendix 1)

AI- Ambulation Index

AVLT – Auditory Verbal Learning Test

BDI – Beck Depression Inventory

BDI-A – Beck Depression Inventory – Amended

BDI-FS - Beck Depression Inventory – Fast Screen

BNT – Boston Naming Test

BVMT-R – Brief Visuo-spatial Memory Test-Revised

CES-D-10 – 10 Item version of the Centre for Epidemiologic Studies Depression Scale

CFS - Cognitive Function Subscale

CFQ – Cognitive Failures Questionnaire

CMDI – Chicago Multiscale Depression Inventory

COWAT – Controlled Oral Word Association Test

CVLT – California Verbal Learning Test

DAS – Dysfunctional Attitude Scale

FrSBe - Frontal Systems Behaviour Scale

GNDS – Guy's Neurological Disability Scale

HADS – Hospital Anxiety and Depression Scale

HAQUAMS – Hamburg Quality of Life Questionnaire in Multiple Sclerosis

HVLT – Hopkins Verbal Learning Test

JLO – Judgement of Line Orientation

LNS – Letter Number Sequencing

MADRS – The Montgomery and Asberg Depression Rating Scale

MFIS – Modified Fatigue Impact Scale

MFQ – Memory Functioning Questionnaire

MHI – Mental Health Inventory

MSNQ – Multiple Sclerosis Neuropsychological Screening Questionnaire

MSQOL-54 – Multiple Sclerosis Quality of Life - 54

NCSE – Neurobehavioral Cognitive Status Examination

NPI – Neuropsychological Performance Index

OT-SRT – Open Trial-Selective Reminding Test

PASAT – Paced Auditory Serial Addition Test

PDQ – Perceived Deficits Questionnaire

PRMQ – Prospective and Retrospective Memory Questionnaire

RAVLT – Rey Auditory Verbal LearningTest

RFF – Ruff Figural Fluency Test

SEP-59 – Self administered health-related QOL questionnaire

SDMT – Symbol Digits Modalities Test

SRT – Selective Reminding Test

SRTest – Spatial Recall Test

SRT Trial – Selective Reminding Test 6 Trial Version

STAI – State-Trait Anxiety Inventory

TOH – Tower of Hanoi

TOL – Tower of London

UKNDS – UK Neurology Disability Scale

WAIS – Wechsler Adult Intelligence Scale

WCST –The Wisconsin Card Sorting Test

WLG – Word List Generation

WMS – Wechsler Memory Scale

Appendix 2: Perceived Deficits Questionnaire

INSTRUCTIONS
Everyone at some point experiences problems with memory, attention, or concentration, but these problems may occur more frequently for individuals with neurologic diseases like MS. The following questions describe several situations in which a person may encounter problems with memory, attention or concentration. Please circle the appropriate response (0, 1, 2...) based on your cognitive function during the past 4 weeks. Please answer every question. If you are not sure which answer to select, please choose the one answer that comes closest to describing you. The interviewer can explain any words or phrases that you do not understand.

During the past 4 weeks, how often did you....

	Never	Rarely	Some-Times	Often	Almost-always
1. Find your speed of thinking has slowed down?	0	1	2	3	4
2. Lose your train of thought when speaking?	0	1	2	3	4
3. Have difficulty remembering the names of people, even the ones you have met several times?	0	1	2	3	4
4. Forget what you came into the room for?	0	1	2	3	4
5. Find it harder to keep track of a conversation when several people were talking?	0	1	2	3	4
6. Have trouble getting things organised?	0	1	2	3	4
7. Have trouble concentrating on what people are saying during a conversation?	0	1	2	3	4
8. Forget if you have already done something?	0	1	2	3	4
9. Miss appointments and meetings you had scheduled?	0	1	2	3	4
10. Have difficulties recalling the names of familiar objects?	0	1	2	3	4

11. Have difficulties planning what to do in the day?	0	1	2	3	4
12. Have trouble concentrating on things like watching a television program or reading a book?	0	1	2	3	4
13. Forget what you did the night before?	0	1	2	3	4
14. Forget the date unless you looked it up?	0	1	2	3	4
15. Have trouble getting started, even if you had a lot of things to do?	0	1	2	3	4
16. Find your mind drifting?	0	1	2	3	4
17. Find it takes you longer to think of an answer when asked a question?	0	1	2	3	4
18. Forgot what you talked about after a telephone conversation?	0	1	2	3	4
19. Forgot to do things like turn off the stove or turn on your alarm clock?	0	1	2	3	4
20. Unintentionally use the wrong words during a conversation?	0	1	2	3	4
21. Feel like your mind went totally blank?	0	1	2	3	4
22. Have trouble holding phone numbers in your head, even for a few seconds?	0	1	2	3	4
23. Forget what you did last weekend?	0	1	2	3	4
24. Have difficulties recalling the names people you know well?	0	1	2	3	4
25. Forget to take your medication?	0	1	2	3	4
26. Have trouble making decisions?	0	1	2	3	4
27. Take you longer to think of a solution when solving a problem?	0	1	2	3	4
28. Experience difficulties finding the right word during a conversation?	0	1	2	3	4

APPENDIX 3: EDSS

SOUTH WALES DOCTORAL PROGRAMME IN CLINICAL PSYCHOLOGY
CWRS DOCTORIAETH DE CYMRU MEWN SEICOLEG CLINIGOL

Question 1: Are you able to walk independently-without the use of a walking stick or frame or person to hold or FES machine or other support? (please tick)

☐ Yes- **Please go to Question 2**

☐ No- **Please go to Question 3 on the next page**

Question 2: At your best, how far can you walk without a rest or help from a stick or frame or person or FES or other walking aid? (please tick)

☐ Unrestricted (I can walk for 2-3 hours with no problem)

☐ Clearly more than 500 metres/550 yards

☐ About 500 metres/550 yards

(about the length of Queens Street in Cardiff)

☐ About 300 metres/330 yards

(the length of 3 football pitches)

☐ About 200 metres/220 yards

(half of Queens Streets in Cardiff or 2 football pitches)

☐ About 100 metres/110 yards

(the length of one football pitch or the outpatients

Corridor in the UHW hospital)

☐ Less than 100 metres/110 yards

If you can walk without the aid of a walking aid such as a stick, you have finished the questionnaire.

If you need help to walk or use a wheelchair, please continue to Question 3

Question 3: Please tick the box below that best describes your walking ability.

☐ I can walk more than, or about, 100 metres/110 yards (the length of a Football pitch) with 1 stick or person or support

☐ I use an FES machine to walk (on **one** leg/on **both** legs-please ring)

☐ I need support on both sides to walk, such as 2 sticks or a walker/frame

☐ I can only walk about 10 metres (just about across a room)

☐ I can only walk a few steps even with help and normally use a wheelchair

☐ I use a wheelchair all of the time and can't take even a few steps

Question 4: If you are bed or chair bound, do you have trouble using your hands for writing and eating, etc.

Yes ☐

No ☐

Question 5: Are you totally confined to bed and need help with all daily tasks?

Yes ☐

No ☐

Appendix 4: Fatigue Severity Scale

INSTRUCTIONS

Read each statement and circle a number from 1 to 7, based on how accurately it reflects your condition during the past week and the extent to which you agree or disagree that the statement applies to you. It is important that you circle a number (1 to 7) for every question. A low value (e.g., 1) indicates strong disagreement with the statement, whereas a high value (e.g., 7) indicates strong agreement.

During the past week, I have found that:

	Disagree			<-------->			Agree
1.My motivation is lower when I am fatigued	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties & responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

APPENDIX 5: Letter's from Research & Development department

GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Caerdydd a'r Fro
Cardiff and Vale University Health Board

Ysbyty Athrofaol Cymru
University Hospital of Wales

Heath Park,
Cardiff, CF14 4XW
Phone 029 2074 7747
Fax 029 2074 3838
Minicom 029 2074 3632

Parc Y Mynydd Bychan,
Caerdydd, CF14 4XW
Ffôn 029 2074 7747
Ffacs 029 2074 3838
Minicom 029 2074 3632

Eich cyf/Your ref
Ein cyf/Our ref
Welsh Health Telephone Network 1872
Direct line/Llinell uniongyrchol

Tel: 029 20746986
Fax: 029 20745311
CAV_Research.Development@wales.nhs.uk

From: Professor JI Bisson
R&D Director
R&D Office, 2nd Floor TB2
University Hospital of Wales
Cardiff
CF14 4XW

13 July 2011

Miss Helen Jones
Trainee Clinical Psychologist
1st floor
Archway House
Ty Glas Avenue
Llanishen
Cardiff
CF14 5DX

Dear Miss Jones

Project ID : 11/MEH/5095 : Do Reports Of Cognitive Dysfunction Differ According To The Severity Of An Individual's MS

Further to recent correspondence regarding the above project, I am now happy to confirm receipt of:

- Evidence of favourable opinion from the relevant NHS Research Ethics Committee
- Revised documentation as required by the REC in order to obtain favourable opinion
- Evidence of appropriate informed consent training for the CI / PI / delegated researchers

The following amended documentation is approved for use with this study:

Documents	Version	Date
Favourable Ethical Opinion Letter from South East Wales REC		24 June 2011
Research Proposal	3.0	2 June 2011
Participant Information Sheet	3.0	2 June 2011
Tick box question to Consent	1.0	20 March 2011

Please accept this letter as confirmation of sponsorship by Cardiff and Vale UHB and permission for the project to begin.

May I take this opportunity to wish you success with the project, and to remind you that as Principal Investigator you are required to:

- Ensure that all members of the research team undertake the project in accordance with ICH-GCP and adhere to the protocol as approved by the Research Ethics Committee
- Inform the R&D Office if any external or additional funding is awarded for this project in the future
- Inform the R&D Office of any amendments relating to the protocol, including personnel changes and amendments to the actual or anticipated start and end dates
- Complete any documentation sent to you by the R&D Office or University Research and Commercial Division regarding this project
- Ensure that adverse event reporting is in accordance with the UHB adopted Cardiff and Vale NHS Trust Policy and Procedure for Reporting Research-Related Adverse Events (refs 164 & 174) and Incident Reporting and Investigation (ref 108)
- Ensure that the research complies with the Data Protection Act 1998
- Ensure that arrangements for continued storage or use of human tissue samples at the end of the approved research project comply with the Human Tissue Act, 2004 (for further information please contact Sharon Orton, HTA Coordinator OrtonS@cf.ac.uk).

If you require any further information or assistance, please do not hesitate to contact staff in the R&D Office.

Yours sincerely,

Professor Jonathan I Bisson
Cardiff and Vale University Local Health Board R&D Director

CC R&D Lead Prof Nick Craddock

GIG CYMRU NHS WALES
Bwrdd Iechyd
Aneurin Bevan
Health Board

Research & Development
Research Scrutiny Committee
Tel: 01633 234768

Miss Helen Rhianne Jones
Pantybedw
10 Golwg Y Mynydd
Craig Cefn Parc
Swansea
SA6 5RF

Ref: RSC.48.10
11th July 2011

Dear Miss Jones,

Reports of subjective cognitive dysfunction in MS
Researcher: Miss Helen Rhianne Jones
Reg: RD/975/11

The Research Scrutiny Committee reviewed your project at their meeting held on 6th July 2011.

It was agreed your project be approved.

The Committee felt that maybe the project was a little too ambitious. It was agreed that Dr Charlie Jones, Clinical Psychologist would email yourself to go through some possible amendments to your study that could make it a little more attainable.

These amendments are merely suggestions but the Committee would recommend that you give them some serious consideration.

I wish you every success with this project.

Please note that no substantial changes or amendments can be made to the protocol without notifying the Trust Research & Development Office.

Kind Regards

Professor Sue Bale
Chairman
Research Scrutiny Committee

Y Friars
Ffordd Friars
Casnewydd
De Cymru
NP20 4EZ
Ffôn: 01633 234234

The Friars
Friars Road
Newport
South Wales
NP20 4EZ
Tel: 01633 234234

APPENDIX 6: Letter from South East Wales Research Ethics Committee

han o seilwaith ymchwil Cymru a ariannir gan y Sefydliad Cenedlaethol ar gyfer Ymchwil Gofal Cymdeithasol ac Iechyd, Llywodraeth Cynulliad Cymru

art of the research infrastructure for Wales funded by the National Institute for Social Care and Health Research, Welsh Assembly Government

NISCHR

Uned Cydlynu Caniatâd PCU Permissions Co-ordinating Unit

South East Wales Research Ethics Committee
Sixth Floor, Churchill House
17 Churchill Way
Cardiff CF10 2TW

Telephone : 029 2037 6823

Miss Helen Jones
Trainee Clinical Psychologist
Cardiff and Vale NHS
1st Floor, Archway House,
77 Ty Glas Avenue, Llanishen
Cardiff, **CF14 5DX**

24 June 2011

Dear Miss Jones

Study title: **Do reports of cognitive dysfunction differ according to the severity of an individual's MS?**

REC reference: **11/WA/0134**

Thank you for your letter of the 15 June 2011, responding to the Committee's request for further information on the above research and for submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation [as revised], subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

- Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

- Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

- Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

- Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

- For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

- Sponsors are not required to notify the Committee of approvals from host organisations

- It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

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

Document	Version	Date
Investigator CV	A Vidgen	25 February 2011
Investigator CV	P Moore - Undated	
Investigator CV	H R Jones	04 May 2011
Letter of invitation to participant	2	20 March 2011
Other: Letter from CaRRS		26 April 2011
Participant Consent Form	No Version/No date	
Participant Information Sheet	3	02 June 2011
Protocol	3	02 June 2011
Questionnaire: BDI - FastScreen		
Questionnaire	1	01 April 2011
Questionnaire	1	01 April 2011
Questionnaire	1	01 April 2011
REC application	3.1	03 May 2011
Response to Request for Further Information		15 June 2011

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

Notifying substantial amendments
Adding new sites and investigators
Progress and safety reports
Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures. We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

11/WA/0134	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Mrs J Jenkins
Chair, Panel C
South East Wales Research Ethics Committee
Email: Carl.phillips@wales.nhs.uk

Enclosures: "After ethical review – guidance for researchers" SL-AR2

Copy to: R&D office for Cardiff & Vale University Health Board

APPENDIX 7: Patient Information Sheet

Patient Information Sheet

Title: Do reports of cognitive dysfunction differ according to the severity of an individual's Multiple Sclerosis?

You are being invited to take part in a research study. Before you decide it is important that you understand why the research is being done and what it will involve. Take the time to read the following information carefully and discuss it with others if you wish. Part 1 tells you the purpose of the study and what will happen if you take part. Part 2 gives you more detailed information about the conduct of the study.

Part 1

What is the purpose of the study?

We are looking at some of the cognitive and psychological difficulties individuals who have Multiple Sclerosis (MS) sometimes experience. In particular we are looking at difficulties people sometimes experience in memory, concentration and language, and also emotional difficulties. The study aims to involve **both** individuals who are experiencing difficulties and those who are not, so that we can develop a better understanding of the types of difficulties that different people experience.

Why is this research useful?

There is currently little research that helps to inform our understanding of the thinking processes, and emotional and social wellbeing of individuals with MS. Understanding more about this can then help in the management of these conditions.

Why have I been asked to take part?

The study aims to involve as many people as possible who have been diagnosed with MS, and who have and haven't experienced any significant or noticeable cognitive, social or emotional difficulties.

Do I have to take part?

No. You do not have to take part in this research if you do not want to, and you do not have to give a reason why you do not want to take part. This decision will not affect the service you receive in any way. If you agree to take part then we will ask you to sign a consent form.

What will taking part in the study involve?

The study will take place either at a suitable NHS hospital or in your own home. The first component will require you to complete a short questionnaire. The questionnaire will take between 20 - 30 min to complete. Following this, you will be asked to complete some 'paper and pencil' type tests of memory and concentration that are similar to information gathered in standard clinical practice. Again, this will take no longer than 20 - 30 min to complete. If you usually wear glasses for reading please bring them with you.

What are the possible disadvantages of taking part?
Participating in this study only requires you to complete one questionnaire and some pen and paper type tests. It is highly unlikely that anything will go wrong. Should you wish to talk about any issues raised during the study, a contact name and details are provided at the end of this information.

What are the possible benefits of taking part?
There will be no direct clinical benefit to you from taking part in this study. Your experiences are important to us and may enable us to develop ways of helping people manage cognitive or emotional difficulties.

What will happen if I don't want to carry on or if there is a problem?
You are free to withdraw at any time from the study without it affecting your future care.

This completes Part 1 of the information sheet. If the information in Par 1 has interested you and you are considering taking part, please continue to read the following information in Part 2 before making any decision.

Part 2
Will my taking part be kept confidential?
All information you provide will remain strictly confidential. Only relevant information will be collected during the study, and this may be accessed by responsible individuals from the NHS only when it is relevant to my taking part in the research. The consent form containing personal information will be locked in a secure place, and only the research team will have access to it. Any data and written results will be anonymised in accordance with the Data Protection Act 1998.

What will happen to the results of the study?
All data collected as part of this study will be added to the data gathered for the South Wales epidemiological study for neuroinflammatory diseases. The results of the study will be used to inform future studies and in the management of MS and the types of services that would best support people's needs.
Data gathered will also be used to supplement the research database gathered as part of the multiple sclerosis epidemiological study that you have previously consented to participate in.

Finding out more before deciding
If you would like to discuss this study further or if there are any questions you would like to ask, please contact the lead Consultant Clinical Psychologist Dr Phil Moore, or myself, Helen Jones, by e-mail, letter or telephone.

Helen Jones
Trainee Clinical Psychologist
Helen Durham Centre for Neuroinflammatory diseases
University hospital of Wales
Cardiff
CF14 4XW

Telephone: 02920 748161
E-mail: phil.moore@wales.nhs.uk

Dr Phil Moore
Helen Durham Centre for Neuroinflammatory diseases
University hospital of Wales
Cardiff
CF14 4XW

Telephone: 02920 748161
E-mail: phil.moore@wales.nhs.uk

APPENDIX 8: Letter of invitation to study

Letter of invitation inside study pack

Cardiff and Vale LHB headed paper

Study title: Do reports of cognitive dysfunction differ according to the severity of an individual's MS?

Thank you for taking the time to read more about this study.

Please read the Participant Information Sheet carefully. This sheet should tell you all you need to know about the study. If you have any questions, please contact Helen Jones on 02920 748161

If you decide to take part in the study after reading the Patient Information Sheet, please complete the tick box question stating whether you would like to participate. When completed, please return this to a member of your clinical team, or place it in the post using the pre-paid addressed envelope enclosed.

Finally, please remember that taking part in this study is voluntary. Whether or not you decide to take part will not change any care you receive now or in the future.

Yours sincerely

Helen Jones

Trainee Clinical Psychologist

APPENDIX 9: Tick box consent question

Title of Project: Do reports of cognitive dysfunction differ according to the severity of an individual's MS?

Please complete to inform us of your interest in taking part in the above study.

After reading the Patient Information Sheet I would (please tick):

Like to take part in the above study ☐

Would not like to take part in the above study ☐

For those that would like to take part, please could you complete the information below so that you can be contacted to arrange a suitable day for you to participate.

Name:_____

Address:_____

_____

Telephone Number:_____

Please could you return this to a member of the clinical team at a clinical appointment, or return by post to:

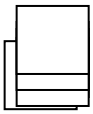
Helen Jones
Helen Durham Centre for Neuroinflammatory diseases
University hospital of Wales
Cardiff
CF14 4XW

APPENDIX 10: Consent form

CONSENT FORM

Title of Project: Do reports of cognitive dysfunction differ according to the severity of an individual's MS?

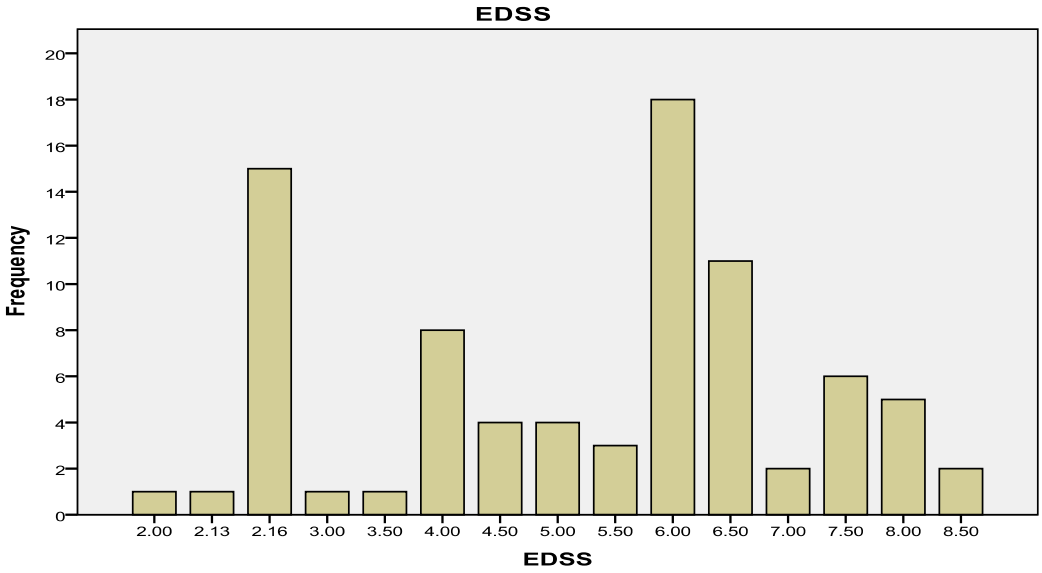
Name of Researcher: Ms Helen Jones

1. I confirm that I have read and understand the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I understand that only relevant information will be collected during the study, and this may be accessed by responsible individuals from the NHS only when it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4. I agree that the data collected as part of this study will be added to data gathered for the South Wales epidemiological study in neuroinflammatory diseases and may be utilised as part of that research study.	
5. I agree to take part in the above study.	

Name of Participant	Signature	Date
_____	_____	_____
Researcher	Signature	Date
_____	_____	_____

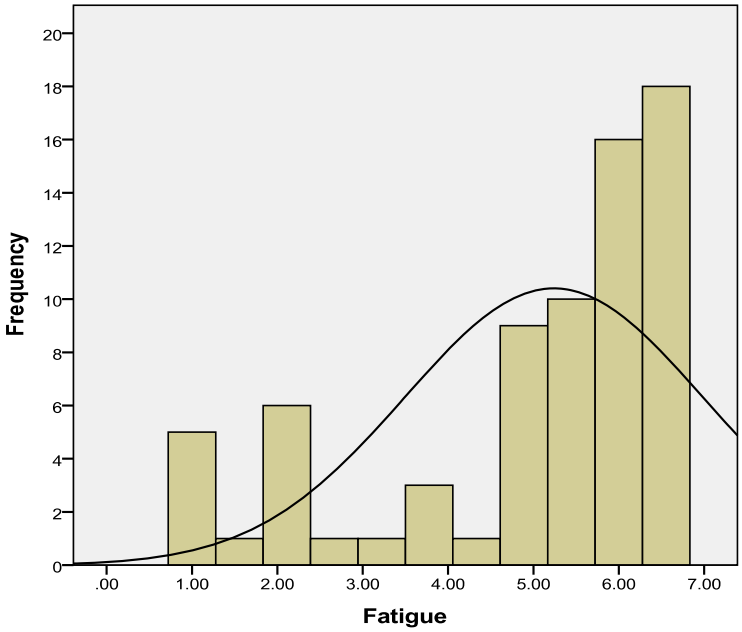
APPENDIX 11: EDSS Scores

Figure 2: EDSS scores



APPENDIX 12: Distribution of fatigue

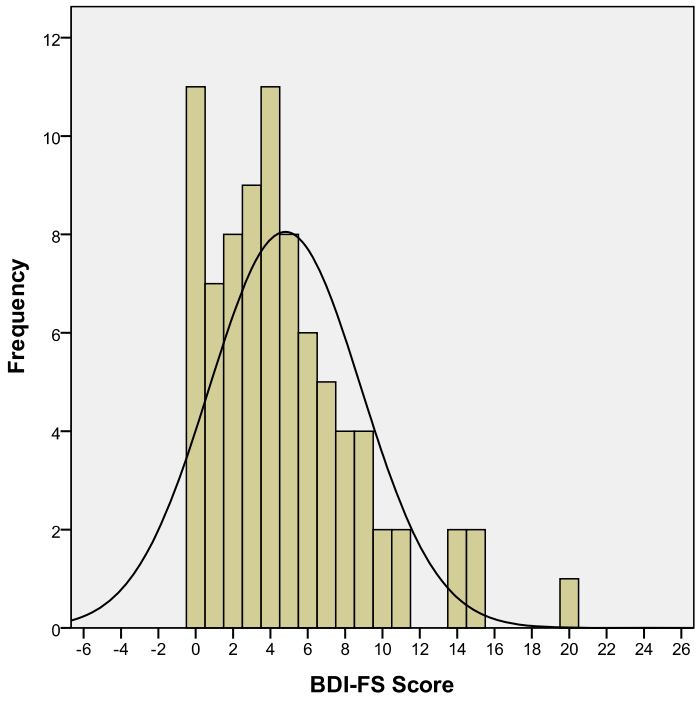
Figure 3: Distribution of level of fatigue



APPENDIX 13: Analysis of Beck Depression Inventory – Fast Screen

Figure 1 below demonstrates that the BDI-FS scores were not normally distributed. Analysis using the Kolmogorov-Smirnov (K-S) test was used to decide whether the sample was significantly different from a normal distribution. Analysis identified that the K-S test was highly significant ($D(82)= 0.14$, $p=0.0003$), indicating that the distribution was significantly different to a normal distribution.

Figure 6: Histogram of scores on the BDI-FS



The distribution of scores on the histogram also highlighted that there were a number of data points that could be potential outliers. The data was checked, and three outliers were identified. In order to determine how much the outliers affected the mean, the 5% Trimmed mean was compared with the new mean value (excluding outliers). Descriptive analysis calculated the 5% Trimmed mean to be 4.44, and the original mean to be 4.79. As these two means are relatively similar, the outliers were retained in the data file.