Cognitive functioning in chronic fatigue syndrome

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Abstract

Chronic fatigue syndrome (CFS) involves long-standing and disabling fatigue of unknown aetiology that has a profound effect on a persons' ability to function in daily life. However, little is understood of the condition and many of the research findings are conflicting, making the treatment and identification of causes problematic. Aside from fatigue, problems with memory and concentration are reported to be amongst the most disabling symptoms; however cognitive testing has revealed ambiguous results, with numerous studies finding deficits and others not. Few studies have investigated how these problems impact on daily functioning. In the absence of a recognised cause for CFS, cognitive problems have been attributed to a range of factors - including psychiatric problems, reduced effort, fatigue and poor sleep - but the contribution of each of these variables to cognitive impairment is unknown.

This thesis was designed to clarify the type and magnitude of cognitive problems in CFS by undertaking a meta-analysis to examine the literature on cognitive testing (Chapter 3), which has previously only been summarised in narrative reviews. This was used to select the cognitive tests for a subsequent empirical study that investigated cognitive functioning in CFS, and explored factors that may influence impaired cognitive performance, specifically test effort (Chapter 4); motor slowing, psychological problems, fatigue and poor sleep, and also investigated factors that may be impacted by cognitive dysfunction, including everyday functioning, employment and mental fatigue (Chapter 5). Self-reported memory and attention problems form part of the CFS diagnostic criteria, consequently their relationship with memory and attention test results were also studied (Chapter 6). The results of these investigations have been published in four journal articles (Cockshell & Mathias, 2010, 2012, 2013, 2014).

The meta-analysis analysed data from fifty studies that had assessed cognitive performance in adults who had been diagnosed with CFS (using published criteria) and in healthy controls (Chapter 3; Cockshell & Mathias, 2010). Compared to their healthy peers, persons with CFS showed large deficits on tests of reaction time and moderate deficits on tests of attention, memory and motor functioning. Smaller deficits were found on tests of visuospatial ability, cognitive reasoning and flexibility, indicating subtle problems in these areas. Global functioning and verbal abilities were unaffected. These findings indicated that people with CFS have moderate to large impairments in simple and complex information processing speed, and on tasks that required the sustained use of working memory. Tests that assessed these impairments were then selected for use in an empirical study, as were tests on which the CFS group was not impaired, to enable the differentiation of specific impairments from global deficits due to fatigue and/or lack of effort.

The empirical study assessed 54 people with CFS and 54 age-, gender- and education- matched healthy controls on tests of reaction time, attention, memory, motor functioning, verbal and visuospatial abilities. All participants were additionally assessed for factors that may be related to cognitive impairment, which included a test of effort, a psychiatric interview (to screen for drug and alcohol abuse, and diagnose depressive and anxiety disorders), and questionnaire measures of psychological status (levels of depression and anxiety), CFS symptom severity, fatigue (prior, during and after the testing session), sleep quality, everyday functioning and self-reported problems with attention and memory.

The initial analysis focussed on test effort which was assessed using the Validity Indicator Profile (VIP), to determine the extent to which people with CFS were performing to the best of their ability to ensure that their cognitive test results could

be validly interpreted (Chapter 4; Cockshell & Mathias, 2012). The VIP identifies effort (high or low) and intention to perform well (or not) by analysing the pattern of responses, providing potential causes of poor performance. Four people in each group demonstrated an intention to perform well, but with reduced effort, possibly due to fatigue. Fifty people in each group demonstrated good effort, and only the results of this group were further analysed.

The cognitive performance of the CFS and controls was then examined, and those measures on which the CFS group performed poorly were correlated with psychological status, CFS symptomatology and everyday functioning (Chapter 5; Cockshell & Mathias, 2013). People with CFS were found to be impaired on tests of simple and choice reaction time. Further analyses revealed that slowed choice reaction time was primarily the consequence of slower simple reaction times, and that neither were the consequence of impaired motor speed. The deficits in reaction time were not related to psychiatric status or severity of CFS symptoms. Similarly, the cognitive deficits were not related to everyday functioning, indicating that level of impairment could not be used to directly predict functional ability.

Lastly, self-reported attention and memory problems were compared to attention and memory test results, and the impact of the testing session on fatigue was examined (Chapter 6; Cockshell & Mathias, 2014). Subjective and objective measures of attention and memory were not related in people with CFS or healthy controls, suggesting they may be measuring different constructs. However, people with CFS reported greater fatigue following cognitive testing and took several days longer than their peers to return to pre-testing fatigue levels.

Overall, the findings from this thesis suggest that people with CFS are impaired in a number of cognitive domains, including memory and attention; consistent with the

problems they frequently report. Many deficits are only minor and very specific, such as sustained working memory. The greatest impairment for people with CFS, however, was information processing speed; which was not explained by poor test effort, psychological problems or the severity of CFS symptoms (fatigue or poor sleep). People with CFS report experiencing cognitive problems and, although they are not directly related to their performance on cognitive tests, this research suggests that cognitive exertion can cause disabling fatigue for many days afterwards.

Declaration

I certify that this work contains no material that has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide.

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List of Publications

Publications are listed in order of appearance in this dissertation. All publications are presented in the body of the thesis in a common format (double spaced), with the published version appearing in the appendices when permitted.

Cockshell, S. J., & Mathias, J. L. (2010). Cognitive functioning in chronic fatigue syndrome: a meta-analysis. *Psychological Medicine, 40*(8), 1253-1267.

Cockshell, S. J., & Mathias, J. L. (2012). Test effort in persons with Chronic Fatigue Syndrome when assessed using the Validity Indicator Profile. *Journal of Clinical and Experimental Neuropsychology, 34*(7), 679-687.

Cockshell, S. J., & Mathias, J. L. (2013). Cognitive deficits in Chronic Fatigue Syndrome and their relationship to psychological status, symptomatology and everyday functioning. *Neuropsychology, 27*(2), 230-242.

Cockshell, S. J., & Mathias, J. L. (2014). Cognitive functioning in people with Chronic Fatigue Syndrome: A comparison between subjective and objective measures. *Neuropsychology, 28*(3), 394-405.

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Author Contributions

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Name of Principal Author (Candidate)	Susan J. Cockshell
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Name of Co-Author	Jane L. Mathias
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Lastly, and very importantly, I would like to thank the participants involved in the empirical study. I am aware that for many it was a considerable effort to travel and undertake the cognitive testing, with consequences unbeknownst to me at the commencement of the study that would impact your health for many days afterwards. Your involvement in this research was of great importance, and I hope that the sharing of these findings via publications and presentations has helped improve understanding of this condition and made it worthy of your contribution.

Chapter 1: An Overview of Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS) is characterised by severe and unexplained fatigue that is present for at least 6 months, does not reduce with rest, and results in a substantial reduction in occupational, educational, social or personal activities (Fukuda et al., 1994). The most commonly used definition of CFS additionally requires at least four of the eight following symptoms to be present: muscle myalgia, post-exertional malaise, sleep disturbance, sore throat, painful lymph nodes, headaches, arthralgia (joint pain), and memory and concentration problems (Fukuda et al., 1994). Moreover, medical and psychiatric explanations for these symptoms (e.g., narcolepsy, psychotic disorders) must be excluded before a diagnosis of CFS can be made (Fukuda et al., 1994). In the absence of a defined cause of CFS, there has been an ongoing debate regarding the physical and psychological cause of CFS (David & Wessely, 1993; Sykes, 2002; Wessely, Hotopf, & Sharpe, 1998; Wojcik, Armstrong, & Kanaan, 2011), particularly as it applies to cognitive symptoms (Moss-Morris, Petrie, Large, & Kydd, 1996; van der Werf, Prins, Jongen, van der Meer, & Bleijenberg, 2000).

Problems with memory and concentration are reported by up to 89% of people with CFS (Jason, Richman, et al., 1999) and, other than fatigue, these symptoms are reported to have the greatest impact on their ability to work and function (Abbey & Garfinkel, 1991). Objective evaluations of cognition have been inconclusive, with deficits reported by some studies (e.g., Claypoole et al., 2007; DeLuca, Christodoulou, Diamond, Rosenstein, Kramer, & Natelson, 2004; Thomas & Smith, 2009), but not by others (e.g., Krupp, Sliwinski, Masur, Friedberg, & Coyle, 1994; Short, McCabe, & Tooley, 2002). Methodological differences – such as the use of

different diagnostic criteria - are likely to have contributed to some of this variability (Tiersky, Johnson, Lange, Natelson, & DeLuca, 1997). This thesis will therefore examine cognitive deficits in people with CFS and explore some of the potential causes.

Before examining the research on cognitive functioning, it is necessary to situate this literature within the context of how CFS has been defined and identify who is affected by it and how. With no theories of CFS and few models of causality, most research has focussed on single medical or psychological factors that may contribute to CFS. An overview of these factors provides a context for the potential causes of the cognitive deficits that have been investigated. The course of the condition, expected prognosis, and the limited efficacy of current treatments, highlights our limited knowledge of this condition and the potential benefits that may come from further research into the symptoms of CFS, particularly those that are claimed to have the greatest functional impact, such as memory and attention problems.

Definitions of CFS

Fatigue is frequently experienced in the general population, but in the majority of cases it resolves either with rest or resolution of the primary cause (van't Leven, Zielhuis, van der Meer, Verbeek, & Bleijenberg, 2010). For a small minority, however, fatigue may persist for months or years in the absence of an identifiable cause. Over the past century, people presenting with long-term, unexplained fatigue have been labelled with neuroasthenia, Myalgic Encephalomyelitis (ME), post-viral fatigue syndrome, Royal Free disease, and Iceland disease (Wessely, 1990) - the latter two names reflecting the location of an outbreak or cluster of presenting cases. The term ‘Chronic Fatigue Syndrome’ was first introduced in 1988 by the US Centers for

Disease Control and Prevention (CDC) to describe a condition presenting with unexplained fatigue of new onset, which is present for at least 6 months and does not resolve with rest (Holmes et al., 1988). This description has formed the basis for subsequent definitions of CFS for research with adults (e.g., Fukuda et al., 1994; Schluederberg et al., 1992; Sharpe et al., 1991).

Definitions of CFS have also been developed for clinical use (e.g., Carruthers et al., 2003; Institute of Medicine, 2015). These contrast with research definitions because they are designed to detect all *possible* cases of CFS, instead of the more restrictive research definitions, which require a higher degree of specificity in order to ensure that all participants *definitely* have CFS (Holmes, 1991). Clinical case definitions are rarely used for research purposes and will not be considered further. Adult definitions of CFS have also been modified for use with children (Joint Working Group of the Royal Colleges of Physicians, 1996), but as the definition and children's cognitive capabilities differ from adults, they are not examined here.

There are five published research definitions of CFS, which are summarised in Table 1. The first definition of CFS by the CDC (Holmes et al., 1988) was refined by groups in the UK (Sharpe et al., 1991), Australia (Lloyd, Hickie, Boughton, Spencer, & Wakefield, 1990), and the US National Institute of Health (Schluederberg et al., 1992). This led to the CDC publishing a revised definition in 1994 (Fukuda et al., 1994), which is currently the most widely used basis for identifying cases of CFS for research purposes (Prins, van der Meer, & Bleijenberg, 2006). Researchers also continue to use the other definitions (e.g., Hickie et al., 2009; Wessely et al., 1998; White et al., 2011), hence it is important to identify the similarities and differences between these criteria.

The major criteria for all of the research definitions require a severe and persistent fatigue of at least six months duration, which is not explained by an existing medical condition or ongoing exertion and results in a major reduction in work or social functioning (see Table 1). The Australian criteria, however, deviates from the other definitions by including two additional major criteria – exacerbation of the fatigue by minor exercise, and concentration and short-term memory problems (Lloyd et al., 1990). This makes the criteria similar to the definition of ME, which requires the presence of unknown fatigue, post-exertional malaise and cognitive problems (Hyde, Goldstein, & Levine, 1992). Differences in symptom type and severity have been identified between people diagnosed with ME and people diagnosed with CFS according to the 1994 CDC criteria (Jason, Helgerson, Torres-Harding, Carrico, & Taylor, 2003; Jason, Sunnquist, Brown, Evans, & Newton, 2014; Maes, Twisk, & Johnson, 2012). Given the similarities in the criteria for diagnosing ME and CFS using the Australian criteria, the Australian definition may capture a different group of people than the other CFS definitions. Consequently, to facilitate homogeneity of the population under investigation, this thesis will focus on the four research definitions of CFS, from the US CDC (Fukuda et al., 1994; Holmes et al., 1988), the UK (Sharpe et al., 1991) and the US NIH (Schluederberg et al., 1992).

Table 1. A comparison of major and minor criteria for published research definitions of Chronic Fatigue Syndrome.

Criteria		**US 1988 CDC Definition** (Holmes et al. 1988)	**Australian Definition** (Lloyd et al. 1988; 1990)	**UK Definition** (Sharpe et al. 1991)	**US NIH Definition** (Schluederberg et al. 1992)	**US 1994 CDC Definition** (Fukuda et al. 1994)
Major Criteria	Unexplained fatigue	New onset (no history) Not resolved with rest	Exacerbated by minor exercise	New onset (no history) Disproportionate to exertion		New onset Not resolved with rest Not the result of ongoing exertion
	Fatigue present for a at least 6 months	✓	✓	✓	✓	✓
	Description of impact on functioning	Daily activity below 50% of premorbid activity level	Significant disruption of usual daily activities	Severe and disabling		Substantial reduction in previous levels of occupational, educational, social or personal activities.
	Other		Concentration and short-term memory problems			
Minor Criteria	Started during or after the onset of fatigue	8 of 11 symptoms or 6 of 11 symptoms and 2 of 3 physical signs	1988 definition included option of reduction in absolute count of T8 and/or T4 lymphocyte subsets and/or cutaneous anergy	Not required but may be present	Need to reconsider minimum number of symptoms and signs	Concurrent occurrence of 4 of 8 symptoms
	Symptoms	Muscle myalgia Post-exertional malaise Sleep disturbance Sore throat Painful lymph nodes (sign) Headaches Arthralgia Neuropsychologic complaints Generalized muscle weakness Mild fever (sign) Rapid onset	Muscle myalgia Post-exertional malaise Sleep disturbance Headaches Arthralgia Depression	Myalgia Sleep disturbance Mood		Muscle myalgia Post-exertional malaise Sleep disturbance Sore throat Painful lymph nodes Headaches Arthralgia Memory & concentration problems
	Signs	Pharyngitis	Pharyngitis Tinnitus Paraesthesiae			

* Note. CDC = Centers for Disease Control and Prevention; NIH = National Institute of Health

Greater differences are evident between the minor criteria of the CFS definitions, as seen in Table 1. The number and type of symptoms differ between the definitions and, although some early definitions also included signs, such as pharyngitis and low grade fever (37.6°C – 38.6°C oral), they were subsequently found to have limited specificity and were only rarely confirmed in people with CFS (Holmes, 1991; Schluederberg et al., 1992). Signs were not included in subsequent definitions, hence the more objective criteria were removed (Fukuda et al., 1994; Sharpe et al., 1991).

The first definition of CFS originally excluded co-existing psychiatric disorders (Holmes et al., 1988), with the aim of reducing heterogeneity. However, subsequent research found that a large number of people with CFS become depressed or anxious after the illness commenced, hence it was suggested that psychiatric disorders may be an important part of the condition and that patients should not be excluded on this basis (Komaroff & Buchwald, 1991). Other research found that CFS patients who had a non-psychotic psychiatric history did not differ from CFS patients without a psychiatric history on physical measures or laboratory tests, indicating that they may not be distinct groups (Schluederberg et al., 1992). Paradoxically, the large number of symptoms (8 out of 11) required to meet the 1988 CFS case definition was found to create a bias toward individuals with a psychiatric disorder, thereby increasing the likelihood of selecting the people they were aiming to exclude (Katon & Russo, 1992). Subsequently, the revised CDC definition did not exclude non-psychotic psychiatric disorders and reduced the number of symptoms required for diagnosis from eight to four (Fukuda et al., 1994). However, it recommended that people with psychiatric co-morbidity be treated as a separate subgroup in order to understand the role of psychiatric disorders in CFS (Fukuda et al., 1994).

Exclusion criteria and co-existing conditions.

A diagnosis of CFS cannot be given if a person has a medical condition that has fatigue as a major component (e.g., multiple sclerosis, sleep apnoea, untreated hypothyroidism), is taking medication with fatigue as a known side-effect, has a previously diagnosed condition that has been treated but is likely to re-occur (e.g., malignancies), is severely obese, or is abusing substances (Fukuda et al., 1994; Holmes et al., 1988; Reeves et al., 2003; Schluederberg et al., 1992; Sharpe et al., 1991). Psychological conditions that preclude a diagnosis of CFS are any current or previous psychotic disorder, which includes psychotic or melancholic major depressive disorder, bipolar affective disorder, schizophrenia, delusional disorder, dementia, anorexia and bulimia nervosa (Fukuda et al., 1994; Holmes et al., 1988; Reeves et al., 2003; Schluederberg et al., 1992; Sharpe et al., 1991).

Conditions that do not explain the chronic fatigue and may, therefore, coexist with CFS are those that do not have an identifiable cause; such as nonpsychotic or reactive depression, anxiety disorders, fibromyalgia, somatoform disorders, neuroasthenia (profound fatiguability), and multiple chemical sensitivity disorder (Fukuda et al., 1994). Fatigue is a common symptom of these conditions, along with pain, sleep disturbance and headaches; which are also commonly experienced by people with CFS (Wolfe et al., 1990; World Health Organization, 2010; Zigmond & Snaith, 1983). CFS may also be diagnosed in any person who has an excluded medical condition if that condition has been successfully treated (e.g. normal hormone levels in a patient previously diagnosed with hypothyroidism).

Diagnostic reliability and specificity.

Standardised scales and questionnaires have been developed for the assessment of CFS to improve diagnostic reliability (Jason, King, Taylor, & Kennedy, 2000; King &

Jason, 2005; Reeves et al., 2005). At the present time, however, there are problems with relying on these scales to diagnose people with CFS and a physician interview is still required to apply the exclusion criteria (Jason, Ropacki, et al., 1997; King & Jason, 2005; Prins, Elving, Koning, Bleijenberg, & van der Meer, 2003) and to ensure that a more appropriate diagnosis is not applicable, such as major depressive disorder (Jason, Evans, Brown, et al., 2010; Jason, Najar, Porter, & Reh, 2009).

Research has also been conducted into refining the diagnostic criteria to improve specificity (Jason, Torres-Harding, Carrico, & Taylor, 2002; Komaroff, Fagioli, Geiger, et al., 1996), however different studies have recommended different symptoms for inclusion and exclusion; so there is no consensus on how to improve the list of CFS symptoms for diagnosis. It has also been found that the 1994 CDC definition is currently the most effective for discriminating between people with CFS and other fatiguing conditions, such as major depression and multiple sclerosis (King & Jason, 2005; Komaroff, Fagioli, Geiger, et al., 1996); justifying its continued use.

Epidemiology

Prevalence.

Fatigue is commonly reported in the general community, but its prevalence decreases with the duration of the fatigue. For example, the point prevalence rate for fatigue is 36% (van't Leven et al., 2010), with 6% to 18% of people reporting prolonged fatigue that lasts longer than one month (Reeves et al., 2007; Reyes et al., 2003), and 4% to 12% reporting having experienced fatigue on a more chronic basis for greater than 6 months (Bierl et al., 2004; Jason, Richman, et al., 1999; Reyes et al., 2003; Wessely, Chalder, Hirsch, Wallace, & Wright, 1997). Moreover, it is estimated that the cause of the fatigue is only known in half of these cases (van't Leven et al.,

2010). CFS, as defined by the 1994 CDC criteria (Fukuda et al., 1994), however, has a much lower prevalence rate, with estimates ranging from 0.19% to 2.6% (Bierl et al., 2004; Hamaguchi, Kawahito, Takeda, Kato, & Kojima, 2011; Jason, Richman, et al., 1999; Nacul, Lacerda, Pheby, et al., 2011; Reeves et al., 2007; Reyes et al., 2003; Solomon, Nisenbaum, Reyes, Papanicolaou, & Reeves, 2003; van't Leven et al., 2010; Wessely et al., 1997).

The only prevalence estimate of CFS in Australia is 0.037% (Lloyd et al., 1990), but this was based on the Australian definition of CFS (Lloyd et al., 1990; Lloyd, Wakefield, Boughton, & Dwyer, 1988) which, as previously discussed, requires post-exertional malaise, and memory and concentration problems (optional symptoms for the other criteria); potentially resulting in a more limited subgroup of people with CFS (Jason et al., 2003) and, consequently, a lower prevalence estimate. Application of the overseas prevalence estimates to the Australian population of 23.4 million (Australian Bureau of Statistics, 2014), suggests that between 45,000 and 600,000 people in Australia may have CFS.

Risk factors.

CFS is more prevalent in women than men, with similar percentages of women found in the community (72%-83%, Jason, Richman, et al., 1999; Reyes et al., 2003) and primary and tertiary clinics (68%-82%, Euba, Chalder, Deale, & Wessely, 1996; Wilson et al., 2001). Prevalence estimates are highest for those aged in their 40s (Jason, Richman, et al., 1999; Reyes et al., 2003) and the average age of onset is mid- to late-30s (36-37 years old, Jason, Richman, et al., 1999; Nisenbaum, Jones, Unger, Reyes, & Reeves, 2003).

The popular media dubbed CFS the 'yuppie flu' in the early 1990s, associating it with middle to high socioeconomic status, as described in early research published on the topic (e.g., Komaroff & Buchwald, 1991). However, subsequent community surveys have found that CFS occurs in all age, educational, socioeconomic, ethnic and community (i.e., urban and rural) groups (Jason, Richman, et al., 1999; Reeves et al., 2007). This suggests that the over-representation of this condition among higher socioeconomic groups may have resulted from greater access to health care and, hence, a selection bias when studying patients in primary and secondary care (Jason, Richman, et al., 1999; Wessely et al., 1997).

Functional impairment and the economic impact of CFS.

The 1994 CDC definition for CFS requires fatigue to cause a substantial reduction in work, educational, social and/or personal activities (Fukuda et al., 1994). While many people with CFS are able to maintain employment on a full-time or part-time basis (53%-63%, Jason, Richman, et al., 1999; Nisenbaum et al., 2003), up to one third are unable to work (17%-36%, Nisenbaum et al., 2003). Community surveys have found that people with CFS are as functionally impaired as those who have fatigue caused by a known medical or psychiatric condition (Solomon et al., 2003) and may even be more physically impaired than other chronically-ill medical patients (Komaroff, Fagioli, Doolittle, et al., 1996; Nacul, Lacerda, Campion, et al., 2011).

The economic implications of CFS in the US has been estimated at between two to seven billion dollars in direct medical expenses (Jason, Benton, Valentine, Johnson, & Torres-Harding, 2008), and 17 to 24 four billion dollars when also including indirect costs, such as lost income (Reynolds, Vernon, Bouchery, & Reeves, 2004). These estimates were based on the lower prevalence rate of 0.42% (Jason, Richman,

et al., 1999) and may underestimate the real cost of CFS if higher prevalence estimates prove correct (e.g. 2.5%, Lin et al., 2011; Reeves et al., 2007). Research into understanding and improving the symptoms of CFS therefore has the potential to provide considerable benefit, both to the individual and the community.

Aetiology

A single cause of CFS has yet to be identified. As indicated, this has led to debate about whether CFS is primarily physical or psychological in origin (e.g., David & Wessely, 1993; Sykes, 2002; Wessely et al., 1998; Wojcik et al., 2011). Many of the symptoms of CFS are a manifestation of both medical and psychological conditions, hence similar symptom complexes (e.g. post-viral fatigue syndrome, neurasthenia) have been differentially classified as neurological or psychiatric, depending on their assumed origin (American Psychiatric Association, 2013; Fulford, 2002; World Health Organization, 2010). It is also possible that CFS is not the result of a single causal agent; instead multiple causes may contribute to its onset (Perry & Santhouse, 2012) or it may have different causes in some subgroups of people with CFS (Hickie et al., 2006).

Causal Models.

There are currently no theories to explain how CFS develops or what may cause its range of symptoms, however a number of models have been proposed that provide a structure to investigate and analyse different causes. The models differ in their focus and emphasis on medical and psychological causes. One model that is frequently used to explain CFS is the biopsychosocial model (David, Wessely, & Pelosi, 1988; Sharpe, 1996; Yeomans & Conway, 1991), which categorises biological, psychological and social factors according to their role in predisposing a person to

CFS, precipitating the condition, or perpetuating the symptoms (Perry & Santhouse, 2012; Sharpe, 1996; Surawy, Hackmann, Hawton, & Sharpe, 1995). According to this model CFS develops as a consequence of one or more factors in each category (Prins et al., 2006). The biopsychosocial model has been used to explain and treat a range of conditions, including cardiovascular disease, type 2 diabetes and schizophrenia (Engel, 1981; Kotsiubinskii, 2002; Peyrot, McMurry, & Kruger, 1999).

Factors that may *predispose* an individual to CFS include genetic vulnerability (Norheim, Jonsson, & Omdal, 2011; Prins et al., 2006), neuroendocrinal abnormalities (Perry & Santhouse, 2012), previous psychiatric problems (Clark, Goodwin, Stansfeld, Hotopf, & White, 2011; Kendell, 1991), and personality traits, such as neuroticism, introversion and perfectionism (Perry & Santhouse, 2012; Prins et al., 2006). *Precipitating* factors that may trigger CFS are viral illnesses (Perry & Santhouse, 2012) and acute psychological stress (e.g., loss of loved one or job, Perry & Santhouse, 2012; Prins et al., 2006; Surawy et al., 1995). Finally, those factors that may *perpetuate* the condition are infectious agents (Mihrshahi & Beirman, 2005); poor sleep (Perry & Santhouse, 2012); co-morbid mental illness (e.g., depression, Perry & Santhouse, 2012); lack of social support (Prins et al., 2006); avoidance of physical activity leading to physical deconditioning (Perry & Santhouse, 2012; Vercoulen, Swanink, et al., 1998); a boom and bust cycle, wherein a lot of activity is undertaken when feeling well, resulting in an exacerbation of symptoms and need to rest (Perry & Santhouse, 2012); and the perceived benefits of the sick role, such as care, attention, and financial benefits (Prins et al., 2006).

The biopsychosocial model is useful for clinicians who need to take a wholistic approach to evaluating and treating people with CFS (DeLuca & Tiersky, 2003),

however its use in guiding researchers is less clear. Research has supported some elements of the model, such as the identification of cognitive and behavioural factors that contribute to the persistence of fatigue (Vercoulen, Swanink, et al., 1998), but other elements have not been supported, such as the finding that CFS is not perpetuated by depression (Song & Jason, 2005; Vercoulen, Swanink, et al., 1998). Overall, the model does not appear to have been tested empirically for CFS, but some researchers have identified a subset of factors that may fit the model. For example, Mihrshahi et al. (2005) proposes that stress and psychiatric status may predispose an individual to CFS by weakening their immune system. CFS may then be triggered by an infection, which may cause changes to the immune and neuroendocrine systems due to the infection becoming chronic or the person becoming focussed on the illness. Proposals such as this need to be evaluated empirically to understand the relative contribution of each factor in the development of CFS. Furthermore, despite the potential of the model to move the focus of causal factors away from dichotomous medical or psychiatric origins (Sharpe, 1996), its use has been criticised for emphasising the psychological and social contributors to the condition, to the neglect of biological factors (Song & Jason, 2005; Twisk & Maes, 2009).

Another model of the aetiology of CFS proposes that it is similar to other fatiguing illnesses for which there are no medical explanations (Wessely, Nimnuan, & Sharpe, 1999). Although claimed to be independent of causation, this model presents a primarily psychological cause for these conditions (Song & Jason, 2005). These conditions are labelled Functional Somatic Syndromes and include irritable bowel syndrome, fibromyalgia, multiple chemical sensitivity, chronic pelvic pain, temporomandibular joint dysfunction, and Gulf War illness (Wessely et al., 1999). This model proposes that because people with these conditions all present with fatigue

and pain, they may have similar causes and respond to the same treatments (Cho, Skowera, Cleare, & Wessely, 2006; Wessely et al., 1999). Differences in diagnosis are attributed to the speciality of the physician, rather than any unique pattern of symptoms (Kanaan, Lepine, & Wessely, 2007). Research comparing these conditions has found evidence of co-morbidity (e.g. Dansie et al., 2012), however differences in the symptoms used to diagnose each condition (Taylor, Jason, & Schoeny, 2001), precipitating factors (Moss-Morris & Spence, 2006) and illness outcomes (Ciccone, Chandler, & Natelson, 2010), suggests that they may not be the same condition.

Another model for studying the aetiology of CFS conceptualises CFS as the end-point on a continuum of fatiguing illnesses (Swartz, 1988), rather than a distinct clinical entity (Jason, Richman, et al., 1997). There is some support for this proposal (Bleijenberg, 2003), with differences between short- and long-duration fatigue, and chronic fatigue and CFS, appearing to be primarily in terms of severity of symptoms (van't Leven et al., 2010). Comparisons between people with CFS and fatigue of lesser durations may provide insights into the symptom of fatigue. However, to understand the broader symptoms associated with CFS, it is also necessary to study people with CFS as a distinct group.

A number of models have also been developed that are based predominately on the biological causes of CFS. For example, a model of hypersensitivity or sustained activation of the stress response (limbic-hypothalamic-pituitary axis) has been proposed (Jason, Sorenson, Porter, & Belkairous, 2011), as has a neuroimmunological model of CFS, positing chronic inflammation in the brain (Arnett, Alleva, Korossy-Horwood, & Clark, 2011), for which there is some support (Maes et al., 2013). It has also been postulated that some people with CFS may have a prolonged or abnormal

response to infection, which persists after the infectious agent has gone (e.g., Gupta & Vayuvegula, 1991; Landay, Lennette, Jessop, & Levy, 1991), or that CFS results from a complex interaction between the immune, central nervous and neuroendocrine (hormonal regulation) systems (Prins et al., 2006). Others have not necessarily proposed models, but suggested approaches to investigate the cause of CFS that target the molecular level (Klimas, Broderick, & Fletcher, 2012), the central nervous system (Chen et al., 2008), or the large-scale analysis of epidemiologic, clinical and laboratory data (Vernon & Reeves, 2006).

In summary, it is generally considered that the cause of CFS is multifactorial, rather than due to a single disease or cause (Afari & Buchwald, 2003; Perry & Santhouse, 2012). Medical and psychological factors are likely to contribute to the development of CFS, although the extent to which they contribute is unclear. Research into single medical and psychological causes of CFS provides an important basis for studying how they may interact.

Medical Causes.

Throughout the 1900s there were a number of outbreaks of debilitating fatigue around the world, with the condition named after its place of origin. For example, Royal Free disease was named after an outbreak at the Royal Free Hospital in England, and Iceland disease after an outbreak in that country (Wessely, 1990). Many individuals presenting with debilitating fatigue also had accompanying flu-like symptoms with a sudden onset, suggesting a physical cause for the condition that was subsequently named CFS (Lloyd, 1990). The similarity between the outbreaks and individual presentations of fatigue led researchers to search for a viral or bacterial causal agent (e.g. Daugherty et al., 1991). While a number of viral agents were

initially identified in people with CFS, such as Epstein-Barr virus (glandular fever) and Ross-River virus (epidemic polyarthritis), subsequent studies also found these viral agents in healthy groups (e.g. Matthews, Lane, & Manu, 1991), hence it appeared unlikely that they were the cause of CFS. More recently, however, an Australian longitudinal study of people presenting with an infection at medical clinics found that, of the people who initially presented with Epstein-Barr virus, *Coxiella burnetii* (Q fever) or Ross River virus, 11% met the 1994 CDC diagnostic criteria for CFS six months later (Hickie et al., 2006). This rate is considerably higher than the prevalence rate for CFS in similar settings (0.2%-2.6%, Nacul, Lacerda, Pheby, et al., 2011; Wessely et al., 1997), which suggests that infection may be the cause of CFS in at least some individuals. The severity of the initial infection was the best predictor of prolonged fatigue, which was not influenced by mood or psychiatric status (Hickie et al., 2006). Further research has identified other viruses that may either trigger or perpetuate CFS in some subgroups (Rosenblum, Shoenfeld, & Amital, 2011).

People with CFS may also have subtle immunological abnormalities, such as increased immune activity (Bradley, Ford, & Bansal, 2013; Curriu et al., 2013; Gupta & Vayuvegula, 1991; Landay et al., 1991; Maes et al., 2013) and increased sensitivity to the activation of the immune response (Jason et al., 2011). An increase in an inflammatory agent (i.e. cytokine) has also been related to increases in fatigue severity in some individuals with CFS over time (Stringer et al., 2013), and in those people with CFS who reported greater worsening of symptoms after exercise compared to those who did not (White et al., 2010). Immunological abnormalities are claimed to be one of the most consistent findings in people with CFS (Klimas et al., 2012).

The higher incidence of CFS in women than men has led to the study of genes and hormones in CFS as possible causal agents (Buchwald et al., 2001). Genetic subtypes or markers have been identified in people with CFS (e.g. Buchwald et al., 2001), some of which have been found to be related to symptoms, such as cognitive difficulties or post-exertional malaise (Kerr et al., 2008). The specific genes identified vary between studies, however one reviewer has identified some candidate genes and suggested that genetic inheritance may contribute to the development of CFS (Norheim et al., 2011). Disruption in hormonal regulation, which is controlled by the neuroendocrine system, has also been found in people with CFS. Specifically changes in the stress response and regulation of physiological process, as controlled by the Hypothalamic-Pituitary-Adrenal (HPA) axis, have been identified in people with CFS (for a review see Chen et al., 2008). However, it is unclear whether changes to the HPA axis are a cause, consequence or perpetuating factor of CFS (Cleare, 2004; Perry & Santhouse, 2012).

Physical deconditioning has additionally been proposed as a potential cause or perpetuating factor of CFS. Muscle strength has been examined in order to determine whether the fatigue has peripheral or central nervous system origins. While a number of studies have found that CFS is not due to physical deconditioning (Bazelmans, Bleijenberg, Van Der Meer, & Folgering, 2001; Gibson, Carroll, Clague, & Edwards, 1993; Schmaling, Fiedelak, Bader, & Buchwald, 2005) or an aversion to exercise (Gallagher, Coldrick, Hedge, Weir, & White, 2005), other studies have found evidence to the contrary (Riley, O'Brien, McCluskey, Bell, & Nicholls, 1990; Silver et al., 2002; Sisto et al., 1996). The role of physical deconditioning is therefore unclear. What is known, however, is that physical exertion has a negative effect on people with CFS, resulting in post-exertional malaise. Following an exercise test, people with CFS commonly report experiencing a worsening of CFS symptoms (Yoshiuchi et

al., 2007), including debilitating physical and cognitive fatigue (VanNess, Stevens, Bateman, Stiles, & Snell, 2010), increased cognitive symptoms (Blackwood, MacHale, Power, Goodwin, & Lawrie, 1998; LaManca et al., 1998), and reduced peripheral muscle capacity (Paul, Wood, Behan, & Maclaren, 1999). Thus, it does not appear that the fatigue experienced by people with CFS is primarily peripheral, hence central nervous system origins have also been examined.

Several studies of brain functioning in persons with CFS support a central nervous system pathophysiology (Chen et al., 2008; Cho et al., 2006). Specifically, magnetic resonance imaging studies have identified some structural abnormalities in the brains of people with CFS, such as white matter hyperintensities (indicating possible lesions or demyelination) (Lange et al., 1999; Natelson, Cohen, Brassloff, & Lee, 1993) and reduced white and grey matter volume (de Lange et al., 2005; Puri et al., 2012; Zeineh et al., 2015); although these abnormalities may not be unique to CFS (Greco, Tannock, Brostoff, & Costa, 1997; Perrin, Embleton, Pentreath, & Jackson, 2010). One study found that reduced white matter was related to longer fatigue duration in CFS (Barnden et al., 2011), suggesting that imaging abnormalities may have a direct relationship with the condition. These abnormalities may also be greater in people with CFS who do not have co-morbid psychiatric disorders (Lange et al., 1999; Yoshiuchi, Farkas, & Natelson, 2006), again highlighting the importance of studying particular subgroups.

It would be expected that a reduction in white and grey matter in CFS would result in increased ventricular size, however, several studies have found that ventricular size and cerebrospinal fluid (CSF) volume is not increased in CFS (Mathew et al., 2009; Perrin et al., 2010), although their CSF may contain higher concentrations of lactate

(Mathew et al., 2009). The findings on blood flow in CFS appear to differ, depending on how it has been measured. Reduced absolute cortical blood flow has been found in CFS using computed tomography (Yoshiuchi et al., 2006), with another study that used a near infrared spectrophotometer finding reduced blood volume and oxygenation in CFS, which was also related to a reduced capacity for exercise (Patrick Neary et al., 2008). Two other studies using magnetic resonance imaging did not find reduced blood flow in CFS (Perrin et al., 2010; Zeineh et al., 2015). Hence, structural brain abnormalities appear to be present in at least some subgroups of CFS, but there is uncertainty regarding functional abnormalities, and no causal relationship has yet been established.

Lastly, the contribution of poor sleep to fatigue and other symptoms of CFS has been studied due to the large number of people with CFS reporting problems with sleep (82% - 88%, Jason, Richman, et al., 1999; Unger et al., 2004). Accurate community-based prevalence rates for objectively measured sleep disorders in CFS (e.g. using polysomnography) are lacking, however studies conducted in specialist clinics have found that between 5% and 58% of CFS patients may have a primary sleep disorder (Ball et al., 2004; Fossey et al., 2004; Le Bon et al., 2000). The most common sleep disorders are sleep apnoea (frequent pauses in breathing) and hypopnoea (very shallow breathing), although movement disorders (periodic leg movement disorder, restless legs syndrome) are also experienced by a minority of people with CFS (Fossey et al., 2004; Le Bon et al., 2000). Narcolepsy, a neurological disorder that causes excessive daytime sleepiness, is not generally associated with CFS (Le Bon et al., 2000). While the presence of a sleep disorder automatically excludes a diagnosis of CFS, sleep disorders are not always assessed. Indeed, it is estimated that 18% of people with CFS may have an undiagnosed and

treatable sleep disorder, which may account for their symptoms (Reeves et al., 2006). Sleep problems may contribute to the disability experienced by people with CFS, however they do not generally explain the severity or range of symptoms that are associated with this condition (Fischler, 1999).

Psychological Causes.

Psychiatric diagnoses are common in people with CFS, with estimates ranging from 55% to 57% in community-based samples (Jason, Richman, et al., 1999; Nater et al., 2009) and 75% in primary care settings (Wessely, Chalder, Hirsch, Wallace, & Wright, 1996). These rates are higher than those seen in the general population, which range from 19% to 23% (Jason, Richman, et al., 1999; Wessely et al., 1997). Lifetime rates of psychiatric disorders in people with CFS range from 81% to 89% (Jason, Richman, et al., 1999), compared to 45% in healthy samples (Jason, Richman, et al., 1999; Nisenbaum et al., 2003). For the majority of people with CFS, the psychiatric disorder developed after the onset of fatigue (59%, Jason, Richman, et al., 1999).

The most common co-morbid psychiatric conditions identified in people with CFS attending primary and tertiary clinics are major depression, which occurs in 20% to 47% of cases (DeLuca, Johnson, & Natelson, 1994; Pepper, Krupp, Friedberg, Doscher, & Coyle, 1993; Wessely et al., 1996), and anxiety, which occurs in 44% of cases (Wessely et al., 1996). These rates may be partially inflated because fatigue is also a key symptom of major depression, which if removed as a diagnostic symptom reduces the prevalence of depression in people with CFS from 47% to 28% (Wessely et al., 1996). However, in the absence of a defined cause of fatigue in CFS, psychiatric rates should be reported both with and without fatigue as a symptom. The

high prevalence of depression in people with CFS has raised questions about whether CFS is a manifestation of depression, whether depression is a consequence of CFS, or whether they are co-existing conditions for some people with CFS (Abbey & Garfinkel, 1991; Ray, 1991; Sharpe, 1996).

The depression experienced by people with CFS has been found to differ in a number of important ways from that of people diagnosed with major depressive disorder (MDD, Komaroff, Fagioli, Doolittle, et al., 1996). Although their symptoms overlap, there are differences in the primary complaint for each condition - fatigue for CFS and depressed mood for MDD - and the type of symptoms that are reported. People with CFS report low levels of positive affect (e.g. joy, interest, alertness) but normal levels of negative affect (e.g. loss of pleasure, self-esteem, guilt), however people with MDD report low levels of both positive and negative affect (DeLuca, Tiersky, & Natelson, 2004; Johnson, DeLuca, & Natelson, 1996; Marshall et al., 1996; Moss-Morris & Petrie, 2001; Wood, Magnello, & Sharpe, 1992). People with CFS also experience greater post-exertional malaise, unrefreshing sleep, and problems with memory and concentration than people with MDD (Hawk, Jason, & Torres-Harding, 2006) and are more impaired in health, work and social functioning. People with MDD score lower on scales of mental health and emotional roles than people with CFS (Komaroff, Fagioli, Doolittle, et al., 1996) and both groups have different causal attributions, which are predominately physical for CFS and psychological for MDD (Powell, Dolan, & Wessely, 1990). These differences in the pattern and severity of symptoms indicate that CFS may not be just an atypical manifestation of depression (Jason, Richman, et al., 1997).

People with CFS have also been compared to people experiencing chronic fatigue due to a known medical cause (i.e. multiple sclerosis, MS) in order to determine the extent to which a psychiatric disorder may be the consequence of living with a chronic condition. Most studies have found that, compared to people with MS, those with CFS have higher levels of depression and anxiety (e.g. Daly, Komaroff, Bloomingdale, Wilson, & Albert, 2001; DeLuca, Johnson, Beldowicz, & Natelson, 1995; Johnson et al., 1996; Krupp et al., 1994), but similar rates of personality disorders (Pepper et al., 1993). Therefore, it is unlikely that the high prevalence of psychiatric disorders in CFS can be solely attributed to living with a chronically fatiguing condition.

The presence of a co-morbid psychiatric disorder may also identify a distinct subgroup of people with CFS. Differences have been found in cognitive performance, such that the absence of a psychiatric disorder has been associated with greater cognitive deficits in people with CFS (DeLuca, Johnson, Ellis, & Natelson, 1997a). Additionally, there is evidence that CFS and psychiatric conditions can resolve independent of each other (Matsuda et al., 2009), suggesting they are distinct conditions. Collectively, these findings suggest that the presence of a psychiatric disorder does not fully explain the condition of CFS. However, the high rates of psychiatric co-morbidity in CFS make it an essential element to study for its role in CFS and how it interacts with or influences other symptoms.

Course, prognosis and treatment

Course.

Early studies of CFS in primary and tertiary clinics found that the majority of people presented with a sudden onset to their condition and viral/flu-like symptoms

(e.g. 75% had an acute viral illness preceding the onset of CFS, Lloyd et al., 1990). Subsequent community surveys, however, found that the majority of people with CFS (77%-83%) developed symptoms gradually over the course of weeks or months (Nisenbaum et al., 2003; Reeves et al., 2007; Reyes et al., 2003). A longitudinal study found that people with CFS experience a clinical course of intermittent relapse and remission of symptoms (Nisenbaum et al., 2003). For example, over a 3 year period, half of the participants experienced a minimum of 6 remission periods that ranged from 8 to 30 days (Nisenbaum et al., 2003).

Prognosis.

Full spontaneous recovery from CFS is rare and only reported by approximately 5% of people (Cairns & Hotopf, 2005). A systematic review found that a median of 40% (range 8% - 63%) of people with CFS experience some improvement in symptoms over periods ranging from 1 year to 10 years, but few of them return to work (8%-30%, Cairns & Hotopf, 2005). Thus, for the majority of people with CFS symptoms do not change and may even worsen (Joyce, Hotopf, & Wessely, 1997; Reyes et al., 1999).

Improvement is associated with shorter illness duration at the initial assessment (i.e. < 15-24 months, Nisenbaum et al., 2003; van der Werf, de Vree, Alberts, van der Meer, & Bleijenberg, 2002; Vercoulen, Swanink, Fennis, et al., 1996). With 84% to 93% of people in the community meeting the criteria for CFS, but remaining undiagnosed (Hamaguchi et al., 2011; Reyes et al., 2003; van't Leven et al., 2010), detection of CFS is essential to improve outcomes. Other predictors of improvement in the absence of any intervention include less fatigue at the time of the initial evaluation, a sense of control over symptoms, and not attributing the illness to a

physical cause (e.g. recognising the influence of stress on exacerbating symptoms) (Cairns & Hotopf, 2005; Joyce et al., 1997; Vercoulen, Swanink, Fennis, et al., 1996; Wilson et al., 1994). Several studies have also found that more symptoms at baseline, or a co-morbid diagnosis of fibromyalgia, reduced the likelihood of experiencing remission (Ciccone et al., 2010; Nisenbaum et al., 2003; Ray, Jefferies, & Weir, 1997). Similarly, most studies have found that a psychiatric diagnosis was related to poorer outcomes (Bombardier & Buchwald, 1995; Clark et al., 2011; Wilson et al., 1994), although one study found it predicted improvement (Tiersky et al., 2001). The severity of depression does not appear to be related to outcome (Vercoulen, Swanink, Fennis, et al., 1996).

Treatment.

There is presently no cure for CFS, with treatments primarily focussing on the management of symptoms. There are two main treatments — Cognitive Behaviour Therapy (CBT) and Graded Exercise Therapy (GET) — that consistently lead to moderate improvements (40%-41%) in symptoms and levels of functioning (Castell, Kazantzis, & Moss-Morris, 2011; Edmonds, McGuire, & Price, 2013; Price, Mitchell, Tidy, & Hunot, 2008). However, these improvements are only 14%-15% above the standard care provided by a general practitioner (Malouff, Thorsteinsson, Rooke, Bhullar, & Schutte, 2008; Price et al., 2008; White et al., 2011) and may be most effective for groups with depression or anxiety (Castell et al., 2011). CBT and GET aim to improve symptoms by modifying cognitive and behavioural factors that may perpetuate fatigue and disability (Cella, White, Sharpe, & Chalder, 2013). For CBT, this involves encouraging people to accept their functional limitations, manage energy levels, reduce stress, and reduce bursts of activity. GET involves gradual, but systematic, increases in physical activity (Pardaens, Haagdorens, Van Wambeke, Van

den Broeck, & Van Houdenhove, 2006). For CBT and GET to be effective, they need to be conducted by specialists with appropriate training and experience in treating CFS (Cella et al., 2013; Cho et al., 2006; Perry & Santhouse, 2012).

There is a relatively high drop-out rate for CFS patients who are involved in CBT (M (15 studies) = 16%, range 0%-40%, Price et al., 2008) and GET (17%, Bentall, Powell, Nye, & Edwards, 2002), which may be due to the adverse effects experienced by some patients, such as increased pain and poorer physical functioning (Nunez et al., 2011; Twisk & Maes, 2009). Additionally, nearly one third of people with CFS show no improvement after CBT or GET (Deale, Chalder, Marks, & Wessely, 1997; Powell, Bentall, Nye, & Edwards, 2001) and, even when the severity of fatigue is reduced, the level to which it is reduced may still be abnormally high (Friedberg & Krupp, 1994). A poor response to GET treatment has been linked to mild depression (dysphoria), as well as the receipt of sickness benefits and membership of a self-help group (Bentall et al., 2002). In contrast, CBT has been shown to be effective whether or not psychiatric disorders are present (Prins, Bleijenberg, Rouweler, & van der Meer, 2005), suggesting that effectiveness is not solely the consequence of improving psychiatric symptomatology. However, the long-term effectiveness of CBT is unclear, with a systematic review finding that the benefits were not consistently maintained over time (Price et al., 2008). Lastly, CBT and GET have not been assessed for their applicability to people with CFS who are severely disabled or housebound, as most treatments require people to attend clinics (Price et al., 2008).

The reason for the limited success of CBT and GET is still largely unclear (Friedberg & Sohl, 2009), with some studies indicating that it may be the result of changes to illness beliefs (Wiborg, Knoop, Frank, & Bleijenberg, 2012) or a

decreased focus on fatigue (Wiborg, Knoop, Prins, & Bleijenberg, 2011) rather than an increase in physical activity (Wiborg, Knoop, Stulemeijer, Prins, & Bleijenberg, 2010). The Energy Envelope Theory provides one possible explanation as to why these treatments are effective. It suggests that people with CFS have limited energy that fluctuates over time and, therefore, potential energy expenditure should be assessed on a daily basis and then maintained within those limits (Jason, Muldowney, & Torres-Harding, 2008). This enables a gradual improvement in functioning, rather than consistent increases in activity or 'boom and bust' activity, both of which have the potential to exacerbate symptoms, cause a relapse, and prolong recovery (Jason, Melrose, et al., 1999). Specifically, the Energy Envelope Theory recognises that some people with CFS may function at their maximum energy limit, whereas others may not; making it important to understand an individual's unique condition in order to determine their appropriate level of activity and rest (Jason, Muldowney, et al., 2008). This theory has received some support based on research using CBT and GET, and also other non-pharmacological treatments, such as training in coping skills and relaxation (Brown, Khorana, & Jason, 2011; Jason, Benton, Torres-Harding, & Muldowney, 2009).

Pharmacological treatments have shown limited success in improving CFS symptoms. The short-term use of anti-depressants (between 6 weeks and 6 months) has not been found to improve CFS symptoms (Natelson et al., 1996; Wearden et al., 1998) or depression (Vercoulen, Swanink, Zitman, et al., 1996). Longer-term use of antidepressants, over a three-year period, found some reduction in fatigue (Thomas & Smith, 2006), although patients were not randomised to treatment. Research into the use of other pharmacological treatments (e.g. corticosteroids) or immunological treatments (e.g. immunoglobulin) for CFS has generally been inconclusive

(Chambers, Bagnall, Hempel, & Forbes, 2006), with some treatments potentially worsening symptoms (Reid, Chalder, Cleare, Hotopf, & Wessely, 2008). New medications continue to be investigated, some of which have shown the potential to improve CFS symptoms, such as specific immunological antibody treatments (Fluge et al., 2011). Potential treatments need to be researched in randomised controlled trials; ensuring adverse effects are also monitored.

The overall effectiveness of CFS treatments are limited to short-term improvements in symptoms, for only a subset of those treated. CBT and GET are currently the best treatments available, however many people may receive no benefit, and there is a risk that symptoms will worsen for some individuals.

Summary

CFS is a disabling condition for which no cure has been established, and treatments provide only a limited improvement in symptoms. Different criteria have been used in the study of CFS, however, similarities exist between the most widely used CFS criteria (Fukuda et al., 1994) and a number of variants (Holmes et al., 1988; Schluederberg et al., 1992; Sharpe et al., 1991). These research criteria are likely to identify a more homogeneous group of people with CFS, compared to people identified by other definitions (Jason et al., 2014; Maes et al., 2012). The review of the CFS literature in this chapter has primarily selected studies that have used these definitions, in an attempt to clarify the conflicting findings that are frequently associated with this condition. This approach will also continue in Chapter 2, when the literature on cognitive deficits in CFS is reviewed.

As the literature in this chapter shows, the cause of CFS is unknown. This means that a cohesive theory has yet to be developed that would structure the diverse findings. Medical and psychological factors that may contribute to the condition include viral infections, immunological abnormalities, genetics, hormonal abnormalities, physical deconditioning, brain abnormalities, poor sleep, depression and anxiety. Specific subgroups have also been identified as relevant to the study of CFS, including the type of illness onset, such that people presenting with a sudden illness onset may have an infectious cause and those with a co-morbid psychiatric diagnosis may be differentially impaired from those without. The diversity of medical and psychological causes of CFS that have been examined has influenced the factors that have been evaluated as likely or possible causes of cognitive deficits. These factors will be discussed in Chapter 2, together with factors that are specific to cognitive functioning, such as test effort.

Chapter 2: Cognitive functioning in CFS: An overview

Problems with short-term memory and concentration that interfere with normal work and leisure activities are amongst the symptoms that may contribute to a diagnosis of CFS (Fukuda et al., 1994). They are also some of the most commonly reported symptoms, with up to 89% of people with CFS experiencing problems in this area (Jason, Richman, et al., 1999), and are very disabling, due to their impact on daily activities (Abbey & Garfinkel, 1991; Moss-Morris et al., 1996). Other specific cognitive problems reported by people with CFS include confusion, being easily distracted when reading, word finding problems, and difficulty following instructions and directions (Friedberg, Dechene, McKenzie II, & Fontanetta, 2000).

Cognitive testing has been employed to objectively assess the nature of the problems that are reported by people with CFS (e.g., Michiels & Cluydts, 2001; Tiersky et al., 1997; Togo, Lange, Natelson, & Quigley, 2013; Van Den Eede et al., 2011). This chapter reviews the literature on cognitive testing in people with CFS and discusses some of the methodological limitations of this research and how it has been integrated, factors that may influence test results, the impact of cognitive impairments on everyday functioning, and the extent to which these deficits are related to the self-reported problems that are used to diagnose CFS.

Cognitive testing in CFS

Cognitive testing has revealed deficits in the general areas that people with CFS have reported problems; namely attention and memory (Constant et al., 2011; Dickson, Toft, & O'Carroll, 2009; Fuentes, Hunter, Strauss, & Hultsch, 2001; Krupp

et al., 1994; Michiels, Cluydts, & Fischler, 1998; Thomas & Smith, 2009; Tiersky, Cicerone, Natelson, & DeLuca, 1998), as well as in other domains, including learning (Claypoole et al., 2001; Marcel, Komaroff, Fagioli, Kornish II, & Albert, 1996), motor functioning (Busichio, Tiersky, DeLuca, & Natelson, 2004; Lawrie, MacHale, Cavanagh, O'Carroll, & Goodwin, 2000; Majer et al., 2008; Van Den Eede et al., 2011), reaction time (Constant et al., 2011; Fuentes et al., 2001; Thomas & Smith, 2009; Vercoulen, Bazelmans, et al., 1998) and verbal fluency (Claypoole et al., 2001; Joyce, 1996). However, there are also many studies that have found that persons with CFS perform comparably to healthy groups on tests of these functions (e.g., Beaumont et al., 2012; Capuron et al., 2006; Claypoole et al., 2007; DeLuca, Christodoulou, Diamond, Rosenstein, Kramer, & Natelson, 2004; Dickson et al., 2009; Dobbs, Dobbs, & Kiss, 2001; Grafman et al., 1993; Mahurin et al., 2004; Majer et al., 2008; Ross, Fantie, Straus, & Grafman, 2001; Schmaling, Lewis, Fiedelak, Mahurin, & Buchwald, 2003; Schrijvers et al., 2009; Short et al., 2002; Tiersky, Matheis, DeLuca, Lange, & Natelson, 2003; Vercoulen, Bazelmans, et al., 1998).

A number of narrative reviews have attempted to clarify the functions that are impaired in persons with CFS by comparing the number of studies that have found deficits with the number that have not (Moss-Morris et al., 1996; Tiersky et al., 1997; Wessely et al., 1998). The only consistent conclusion between these reviews is that there is a deficit in information processing speed, particularly for complex tasks, and that only applies to reviews of greater than 20 studies (DeLuca & Tiersky, 2003; Moss-Morris et al., 1996; Tiersky et al., 1997; Wessely et al., 1998). Conclusions regarding impairment in other domains are more mixed. For example, in the domain of attention, some reviewers have concluded that simple tests of attention (such as digit span) are preserved (DeLuca & Tiersky, 2003; Tiersky et al., 1997), whereas

another concluded that the findings for attention span and working memory were inconsistent (Michiels & Cluydts, 2001). Even when reviewing performance on the same test - such as the Stroop Colour Word Task (Stroop, 1935) - some reviewers have concluded performance was impaired (DeLuca & Tiersky, 2003; Tiersky et al., 1997) and others that it was not (Michiels & Cluydts, 2001), which may in part reflect the use of different scores/measures. For the domain of memory, one reviewer concluded that there were no consistent or severe memory impairments (Moss-Morris et al., 1996), whereas others found the results to be inconsistent (DeLuca & Tiersky, 2003; Michiels & Cluydts, 2001; Tiersky et al., 1997). There is also some evidence for a slowed acquisition of new information (DeLuca & Tiersky, 2003; Michiels & Cluydts, 2001), but is not consistent (Moss-Morris et al., 1996). One reviewer found little evidence for motor deficits (Moss-Morris et al., 1996), but others were unable to draw conclusions regarding motor speed (DeLuca & Tiersky, 2003; Michiels & Cluydts, 2001). Reaction time was also considered to be consistently impaired by one reviewer (Moss-Morris et al., 1996). Notably, these conclusions were often drawn from the findings of only a few studies, hence differences between the studies that were reviewed are likely to have impacted on the conclusions that were drawn.

The conclusions from narrative reviews of fewer than 10 studies appear to be less reliable, introducing further uncertainty as to which domains are impaired by CFS. Some conclusions are tentatively offered based on the findings of a single study, and a number of claims are contrary to those outlined above, such as evidence of deficits in story learning (DiPino & Kane, 1996) and visual information processing (Grafman, 1996), and but no impairment in word list learning (DiPino & Kane, 1996). Thus in the domains of memory, motor functioning and, to a lesser extent, attention, there are

conflicting findings that narrative reviews have been unable to resolve. This suggests that a quantitative review of the literature is needed.

There is greater consensus regarding higher-order cognitive functioning in people with CFS. All reviewers have concluded that it is preserved (DeLuca & Tiersky, 2003; Moss-Morris et al., 1996; Tiersky et al., 1997) based on studies that have found CFS functioning is comparable to healthy peers in the areas of abstract reasoning (DeLuca, Johnson, & Natelson, 1993; Krupp et al., 1994), planning and problem solving (Capuron et al., 2006; Grafman et al., 1993; Majer et al., 2008), and intelligence (Capuron et al., 2006; Grafman et al., 1993; Majer et al., 2008). However, it should also be noted that fewer studies have investigated these functions.

Limitations with previous research and in the integration of findings

Some of the aforementioned conflicting findings may be the consequence of the methodological limitations of many of the early studies (Michiels & Cluydts, 2001; Moss-Morris et al., 1996; Tiersky et al., 1997). For example, some researchers used small samples (i.e., < 15) (Sargent, Anderson, & Budek, 1997; Scheffers, Johnson, Grafman, Dale, & Straus, 1992), lowering power and reducing the chance of significant findings. In addition, normative test data was frequently used for comparative purposes instead of a control group (Altay et al., 1990; McDonald, Cope, & David, 1993; Sandman, Barron, Nackoul, Goldstein, & Fidler, 1993). However, the use of normative data has been criticised for not being matched to the CFS groups on variables known to influence cognitive performance, such as age, education and IQ (Tiersky et al., 1997). Similarly, some studies failed to use published criteria to diagnose CFS or to describe the diagnostic criteria that were used (Beh, Connelly, & Charles, 1997; Prasher, Smith, & Findley, 1990; Riccio, Thompson, Wilson, Morgan,

& Lant, 1992; Smith, 1991), potentially resulting in different groups being studied (Solomon et al., 2003). These limitations are present in a third to a half of the studies that have been reviewed (Michiels & Cluydts, 2001; Moss-Morris et al., 1996; Tiersky et al., 1997) and are likely to have had a considerable influence on the conclusions that were drawn. The exclusion of studies without control groups or that have used unpublished CFS criteria, as well as the calculation of effect sizes to provide a measure of the magnitude of group differences independent of sample size, may help clarify which functions are impaired by CFS and which are not.

The diversity of tests that have been used to assess each domain, also makes it difficult to directly compare research findings and to draw conclusions regarding the different cognitive domains. Therefore, in addition to reviewing study findings at the domain level, it is also necessary to consider the specific tests that have been used. This becomes particularly important when very different tests are used to assess the same cognitive domain or when the same test is described as assessing different cognitive domains. For example, motor functioning has been assessed with tests of motor speed and reaction time (Busichio et al., 2004; Claypoole et al., 2007); and speed of information processing has been assessed with tests of reaction time and more complex tests that require working memory, such as the Paced Auditory Serial Addition Test (Claypoole et al., 2007; DeLuca, Christodoulou, Diamond, Rosenstein, Kramer, & Natelson, 2004). Hence, while one study may conclude there is a deficit in motor functioning (e.g., Majer et al., 2008) and another no impairment (e.g., Marcel et al., 1996), this may be the consequence of using different tests to assess motor speed. Additionally, slowed reaction times may be variously attributed to motor or information processing impairments. Studies that only report test results aggregated

by cognitive domain (e.g., Claypoole et al., 2007; Vercoulen, Bazelmans, et al., 1998) further add to the challenges of integrating the research findings.

The focus on the statistical significance of findings has also been demonstrated to inhibit the integration of research results (Lipsey & Wilson, 2001; Rosenthal, 1991). Statistical significance provides a dichotomous categorisation of the results, which is influenced by sample size and the size of the underlying effect (Cohen, 1988). Hence, a non-significant finding may be due to multiple causes, only one of which may be because a deficit does not exist (Cohen, 1994). Categorising a finding as either significant or not may also generate perceived differences where there are none. For example, if a conventional p-value of 0.05 is adopted, a finding with a 4% chance of occurring will be treated differently (a significant finding) from a finding with a 6% chance of occurring (a non-significant finding), although these two findings may be more similar than different (Cumming, 2012). These difficulties can be reduced by employing meta-analytic techniques, which can be used to review the literature by statistically summarising the research findings (Cohen, 1988; Loftus, 1996; Zakzanis, Leach, & Kaplan, 1999), providing greater certainty in the conclusions that are drawn (Cooper & Rosenthal, 1980). Together with addressing the methodological limitations identified in this section, meta-analysis may be able to clarify the nature of impairment in people with CFS.

Potential causes, correlates and consequences of cognitive impairments

As is the case for the overall condition of CFS, the medical and psychological causes of the cognitive deficits seen in persons with CFS have been investigated for many years, with no single cause having yet been identified (Shanks, Jason, Evans, & Brown, 2013). The exploration of medical causes has primarily focussed on the

relationship between brain functioning and cognitive performance (e.g., Caseras et al., 2006; Schmaling et al., 2003), and while briefly reviewed here will not be a topic of study in this thesis. Cognitive performance may also be influenced by other physical and psychological factors, independent of the existence of brain abnormalities. Specifically, cognitive performance may be influenced by factors associated with taking the tests, such as motivation and effort; or factors specific to CFS, such as co-morbid psychological impairment, particularly depression; other CFS symptoms, including fatigue and poor sleep; or the type of onset of CFS (sudden versus gradual), which may reflect a different underlying cause of CFS. The main consequence of cognitive impairment in CFS is its impact on everyday functioning, which will also be reviewed.

As discussed in Chapter 1, there is evidence for structural and functional brain abnormalities in people with CFS, so how they relate to cognitive performance will be briefly reviewed here because of their possible influence on cognitive functioning. While performing complex cognitive tasks (e.g. 2-back, 3-back, PASAT) using functional magnetic resonance imaging (fMRI), reduced blood flow has been found in the brain regions of people with CFS associated with working memory (cerebellar, temporal, cingulate and frontal cortices), short-term storage of information (posterior parietal cortex) and executive functioning (dorsolateral prefrontal cortex) (Caseras et al., 2006; Cook, O'Connor, Lange, & Steffener, 2007). However, when performing simple cognitive tasks (e.g. 1-back, motor speed, complex RT), there was either no reduction in blood flow (Cook et al., 2007) or only some activation of medial pre-frontal regions (Caseras et al., 2006). This suggests that brain blood flow may be different in people with CFS compared to their healthy counterparts, but only for more complex tasks.

In contrast to those findings of reduced blood flow in persons with CFS, evidence of increased blood flow has also been found in specific regions of the brain during cognitive exertion, possibly as a consequence of people with CFS needing to employ more resources to undertake complex cognitive activities (Caseras et al., 2006; Lange et al., 2005; Schmaling et al., 2003). Specifically, several studies have identified activation in more regions in the brains of people with CFS when performing complex cognitive tasks (e.g. 2-back, 3-back, PASAT) compared to their healthy peers, even when their performance is comparable (Caseras et al., 2006; Lange et al., 2005; Schmaling et al., 2003). However, people with CFS reported greater mental exertion during these tasks (Lange et al., 2005; Schmaling et al., 2003). Other studies have found that impaired cognitive performance related to increased blood flow (Fischler et al., 1996) and that brain activity is related to mental fatigue in people with CFS (Cook et al., 2007; Tanaka et al., 2006). Using EEG, it was found that differences in spatial patterns effectively separated people with CFS from their healthy counterparts, both at rest and during a verbal cognitive task (Flor-Henry, Lind, & Koles, 2010). Therefore, people with CFS have brain abnormalities or differences compared to their healthy peers, which may be related to the complexity of task, performance and levels of fatigue. However, the instances in which blood flow increases or decreases is not well defined, and no causal relationship between brain functioning and cognitive performance has been established.

Cognitive deficits have also recently been related to some physiological measures. For example, increasing orthostatic stress (moving from the lying to upright position) resulted in impaired neurocognitive functioning in people with CFS who also had postural tachycardia syndrome (a condition in which orthostatic stress results in an abnormal increase in heart rate and other symptoms) (Ocon, Messer, Medow, &

Stewart, 2012); and an association has been found between reduced cardiac vagal tone (heart rate variability) and cognitive impairment (Beaumont et al., 2012). These results need to be replicated to determine the reliability of the findings, but are beyond the scope of this thesis.

Test effort.

The interpretation of the results of cognitive tests relies on the assumption that the individual taking the test has delivered their best performance; that is, their test performance is a valid reflection of their true ability (Bush et al., 2005; Rogers, 1997). One possible explanation for poor cognitive performance in people with CFS is that they do not perform to the best of their ability either because they are unable to expend sufficient effort to do so (e.g., due to poor attention, fatigue, psychological disturbance or discomfort with the testing situation) (Frederick, 2003) or because they are deliberately performing below their ability (e.g. exaggeration or production of false symptoms, suppression of true abilities) for financial or legal gain (Rogers, 1997). Reports of a large number of physical complaints by people with CFS in the absence of an identifiable medical cause, has led some researchers and clinicians to suggest that the symptoms of CFS and other medically unexplained conditions may be exaggerated or fabricated (Binder & Campbell, 2004; Heilbronner et al., 2009). These researchers have recommended the use of tests to assess the validity of cognitive performance when evaluating people with CFS for cognitive deficits, particularly when there is the potential to gain from disability through financial payments or the avoidance of work (Heilbronner et al., 2009).

One argument against the proposal that people with CFS are not performing to the best of their ability is that performance is not universally impaired across all cognitive

domains (DeLuca et al., 1997a). For example, while memory and attention may be impaired, planning, abstract reasoning and intelligence do not appear to be (Capuron et al., 2006; Claypoole et al., 2007; DeLuca et al., 1997a; Majer et al., 2008). Although this is a valid argument, tests that are specifically designed to assess effort may provide a more direct indication of the effort that has been employed during a testing session.

Studies that have used cognitive tests specifically designed to evaluate the validity of performance, however, have reported conflicting findings when assessing people with CFS. Numerous studies have found little or no evidence of reduced effort in people with CFS (Binder, Storzbach, Campbell, Rohlman, & Anger, 2001; Busichio et al., 2004; Fuentes et al., 2001; Schmaling, DiClementi, Cullum, & Jones, 1994). However, two studies found evidence of reduced effort in 23% to 30% of people with CFS (van der Werf, de Vree, van der Meer, & Bleijenberg, 2002; van der Werf et al., 2000). The latter two studies used the same test - one that required participants to learn a list of words – but remembering lists of words has been found to be impaired in people with CFS (Crowe & Casey, 1999; DeLuca, Christodoulou, Diamond, Rosenstein, Kramer, Ricker, et al., 2004; Michiels et al., 1998; Michiels, 1999; Tiersky et al., 1998; Vercoulen, Bazelmans, et al., 1998). Hence, poor performance on the test may reflect genuine cognitive deficits, rather than reduced effort. There is some support for this explanation, as one of the studies also found that 13% of people with Multiple Sclerosis were classified as demonstrating reduced effort, despite having a confirmed neurological impairment (van der Werf et al., 2000). This suggests that the cut-off scores for determining reduced effort may be too high. Another study, which used a shortened version of the effort test used by van der Werf et al. (2002; 2000) and cut-off scores that were determined on the basis of an earlier

unpublished study, found that only 4% of their CFS sample demonstrated reduced effort (Constant et al., 2011). Hence, a change to the cut-off value may considerably change the findings, making it difficult to interpret existing findings in the absence of an agreed or validated cut-off value. Furthermore, low scores do not provide information about the motivation of the individual and, consequently, it cannot be assumed that poor performance is deliberate (van der Werf et al., 2000).

Therefore, limitations with the tests used to assess effort in people with CFS may result in inaccurate estimates of people performing sub-optimally, and for those who do so, the test is unable to identify a likely cause for their poor performance. In addition, the role of secondary gain in influencing effort does not appear to have been previously studied in people with CFS in order to determine the potential influence of this factor on performance.

Psychological status.

Impaired cognitive performance may also be the result of, or related to, psychological problems. As discussed in Chapter 1, co-morbid psychiatric diagnoses are common in people with CFS (Jason, Richman, et al., 1999), and many people experience elevated levels of depression and anxiety (Nater et al., 2009). Clinical levels of depression and anxiety are independently associated with deficits in attention, learning, memory and executive functioning (Porter, Bourke, & Gallagher, 2007; Zakzanis, 1998); hence psychological status may directly influence cognitive functioning in CFS. Psychological status may be assessed via a clinical diagnosis of a psychiatric disorder (meeting certain criteria to achieve a diagnosis or not) or the levels of depression and anxiety, which may also be clinically significant if over a certain threshold.

Firstly, considering psychiatric disorders, a current or lifetime psychiatric diagnosis was not related to cognitive performance in CFS in one study (Claypoole et al., 2007). However, a number of studies by the same group of researchers have found that persons with CFS who did not have psychiatric co-morbidities had greater cognitive impairments, compared to those who did (DeLuca, Christodoulou, Diamond, Rosenstein, Kramer, Ricker, et al., 2004; DeLuca et al., 1997a). In contrast, people who had a psychiatric disorder prior to the onset of CFS were more cognitively impaired, compared to those who developed psychiatric problems after the onset of CFS or had never had a psychiatric disorder (Tiersky et al., 2003). These authors concluded that there are deficits in cognitive functioning independent of psychiatric status and, therefore, that this cannot be the sole cause of the cognitive dysfunction (DeLuca et al., 1997a). It is not clear from these studies, however, whether the presence of a psychiatric disorder is related to greater or lesser cognitive impairment in people with CFS.

Secondly, the symptoms of depression or anxiety in CFS show a more consistent relationship with cognitive functioning than psychiatric status. Most studies have found that the level of depression or anxiety in people with CFS is not related to their cognitive performance (Busichio et al., 2004; DeLuca et al., 1995; Johnson, Lange, DeLuca, Korn, & Natelson, 1997; Schmaling et al., 1994; Short et al., 2002; Thomas & Smith, 2009; Vercoulen, Bazelmans, et al., 1998), although this finding is not universal (Krupp et al., 1994; Marshall, Forstot, Callies, Peterson, & Schenck, 1997). Furthermore, cognitive deficits are evident, even after controlling for the effects of depression (e.g., Crowe & Casey, 1999; Daly et al., 2001; Vercoulen, Bazelmans, et al., 1998), suggesting that these cognitive problems are independent of depression. Hence, in contrast to the influence of psychiatric status, the level of depression or

anxiety does not appear to be related to cognitive dysfunction. Nevertheless, it is important to assess and control for the effects of both.

CFS onset.

The onset of CFS symptoms - either sudden or gradual - has also been studied for its potential influence on cognitive performance (Claypoole et al., 2007; DeLuca, Johnson, Ellis, & Natelson, 1997b). It has been identified by the CDC that the type of illness onset may identify important subgroups (Fukuda et al., 1994), with one study suggesting that people with a sudden onset to their symptoms may be more likely to have a defined medical cause for their condition, compared to those whose symptoms develop more gradually over weeks or months (Hickie et al., 2006).

The two studies that have examined the relationship between illness onset and cognitive functioning in people with CFS both found that people who had a sudden onset of symptoms were more cognitively impaired than those whose symptoms developed gradually (Claypoole et al., 2007; DeLuca et al., 1997b). However, the CFS group who developed their symptoms gradually had higher rates of psychiatric disorders (DeLuca et al., 1997b), indicating that the nature of onset may be confounded with psychiatric co-morbidity which, as previously discussed, may also influence cognitive functioning (DeLuca, Christodoulou, Diamond, Rosenstein, Kramer, Ricker, et al., 2004; DeLuca et al., 1997a; Tiersky et al., 2003). Hence, illness onset appears to be an important variable to study in cognitive research of CFS, but should not be investigated independent of psychiatric status.

CFS symptoms.

The presence and/or severity of CFS symptoms may also impact on cognitive functioning. More severe symptoms have been found to be associated with greater

impairments on simple reaction time tasks and the Stroop task (Stroop, 1935), but not the Repeated Digits Vigilance Task (Thomas & Smith, 2009) or the recall of a list of words (Thomas & Smith, 2009). It has also been proposed that the fluctuation in an individual's symptoms over time may impact on cognitive performance, such that performance is only impaired when symptoms are present (Fuentes et al., 2001). These authors found significant variability in cognitive performance over repeated sessions (Fuentes et al., 2001), suggesting that inconsistent findings in the literature may be the consequence of variation in an individual's performance. The assessment of symptom severity over a range of different time frames - such as over the past month, on the day of testing, and after testing - may provide some insight into the extent to which cognitive performance may be related to the timing and duration of symptoms. While overall symptom severity may influence cognitive functioning, there are some individual symptoms that are likely to have less impact (e.g., sore throat, muscle myalgia), than others (e.g., fatigue, poor sleep).

When fatigue has been assessed, the majority of studies have found that fatigue is not related to cognitive performance in people with CFS (Beaumont et al., 2012; Grafman et al., 1993; Johnson et al., 1997; Short et al., 2002; Vercoulen, Swanink, et al., 1998). However, a large study by Thomas and Smith (2009) found that higher levels of fatigue were related to greater cognitive impairments. A study of a non-CFS group also recently found that impaired cognitive performance may influence fatigue (Mizuno et al., 2011), with the implication that improvements in cognitive functioning may improve symptoms. These recent findings suggest there may be a relationship between fatigue and cognitive functioning that could benefit from further investigation in people with CFS.

Another symptom that may directly impact on cognitive performance in people with CFS is poor sleep. As discussed, sleep disturbances have been reported by up to 88% of people with CFS (Jason, Richman, et al., 1999; Unger et al., 2004). Despite the high prevalence of sleep problems, only one research group has examined the relationship between sleep and cognitive functioning in people with CFS (Smith, Pollock, Thomas, Llewelyn, & Borysiewicz, 1996; Thomas & Smith, 2009). Their first study found greater cognitive deficits in people with CFS who had abnormal sleep (e.g., abnormal duration, problems going to sleep and/or waking up early), compared to a CFS group with no sleep difficulties and healthy controls (Smith et al., 1996). Their second study found that poor sleep quality was associated with poorer performance on only one of the four tasks on which the CFS groups was impaired, a vigilance task (Thomas & Smith, 2009). When the authors statistically controlled for sleep quality, group differences in vigilance remained. Therefore, poor sleep does not fully explain cognitive deficits in people with CFS, but it may be related to them and should be assessed to identify any possible influence on cognitive functioning.

Everyday functioning.

The factors previously discussed – test effort, psychological status, CFS onset and symptoms – are all potential causes or correlates of impaired cognitive performance in people with CFS. However, the criteria for CFS require that cognitive problems are of sufficient severity to impair daily functioning (Fukuda et al., 1994). Many people with CFS report high levels of functional impairment (Solomon et al., 2003) and are unable to work (Nisenbaum et al., 2003); and that, apart from fatigue, cognitive problems have the greatest impact on their ability to work and perform daily activities (Abbey & Garfinkel, 1991; Moss-Morris et al., 1996).

Therefore, it is somewhat surprising that few studies have investigated the relationship between cognitive performance and everyday functioning in people with CFS (Christodoulou et al., 1998; Tiersky et al., 2001; Vercoulen, Bazelmans, et al., 1998). These studies have found that people with impaired cognitive performance were less active (Christodoulou et al., 1998; Vercoulen, Bazelmans, et al., 1998). A longitudinal study also found that both cognitive functioning and level of disability improved over time, but that there was no change in employment status (Tiersky et al., 2001). Further clarification of the relationship between cognitive impairment and everyday functioning in CFS is required to understand the extent to which cognitive deficits may affect – and potentially predict – the level of functioning in daily activities.

Relationship between self-reported cognitive problems and test performance

The use of cognitive tests to quantify and objectively assess the cognitive problems that are reported by people with CFS, has also led to comparisons between test performance and self-reported problems. Many studies and reviews have concluded that the cognitive problems reported by people with CFS do not relate to their test performance (e.g., Cope, Pernet, Kendall, & David, 1995; DeLuca et al., 1995; Short et al., 2002; Tiersky et al., 1997; Vercoulen, Bazelmans, et al., 1998; Wearden & Appleby, 1996). The majority of studies, however, did not directly compare self-reported cognitive problems and test performance. These studies have found a large number of reported problems, but minimal or no deficits on cognitive tests (e.g. DeLuca et al., 1995; Short et al., 2002; Tiersky et al., 1997; Vercoulen et al., 1994; Wearden & Appleby, 1997). Several of the reviews also included studies that did not use published CFS criteria (e.g., Cope et al., 1995; McDonald et al., 1993;

Smith, Behan, Bell, Millar, & Bakheit, 1993) and, consequently, may have been examining research that has been conducted with different groups of CFS.

The relationship between self-reported problems and performance has only been examined directly by a few studies and, although none have found them to be related (Ray, Phillips, & Weir, 1993; Short et al., 2002; Vercoulen, Bazelmans, et al., 1998; Wearden & Appleby, 1997), this may in part be explained by methodological limitations in some of the studies. One study compared a score that was an aggregate of self-ratings across a range of cognitive symptoms, with scores from specific tests of memory and attention (Ray et al., 1993), and hence may not have been comparing equivalent measures. Another study devised their own scale to assess the cognitive abilities measured by the tests, but found they were not related in either the CFS or healthy group (Short et al., 2002). The authors suggest this may in part be the consequence of problems with the design of the questionnaire, because it is difficult to rate how you might perform without exposure to the task (Short et al., 2002), or it may be that the measures were not related. Studies examining the relationship between subjective and objective measures in other populations suggests that this discrepancy is not unique to CFS, with self-reported problems being a poor predictor of cognitive performance in older adults (Rabbitt & Abson, 1990), people infected with the human immunodeficiency virus (Millikin, Rourke, Halman, & Power, 2003), those with acquired immune deficiency syndrome (Millikin et al., 2003), mild traumatic brain injury (Stulemeijer, Vos, Bleijenberg, & van der Werf, 2007) and bipolar disorder (Svendsen, Kessing, Munkholm, Vinberg, & Miskowiak, 2012). These findings indicate that further study, using more comparable measures of objective and subjective measures of cognitive functioning in people with CFS and healthy controls is required to determine whether or not a relationship exists.

Self-reported problems may also be influenced by factors other than cognitive deficits. For example, the number of self-reported symptoms has been found to be related to affective disturbances, such as depression (DeLuca & Tiersky, 2003; Ray et al., 1993; Tiersky et al., 1997), as well as fatigue and physical malaise (Ray et al., 1993); hence it is also important to study the relative influence of these variables on self-reports of cognitive problems.

Summary of cognitive functioning in CFS

Cognitive testing has been used to objectively assess the problems with memory and attention that are reported by people with CFS, however a clear understanding of the deficits associated with the condition is yet to emerge (Michiels & Cluydts, 2001; Wearden & Appleby, 1996; Wessely et al., 1998). There is evidence that deficits exist in the areas of attention, memory, motor functioning, reaction time and verbal abilities (e.g., Claypoole et al., 2001; Constant et al., 2011; Dickson et al., 2009; Fuentes et al., 2001; Van Den Eede et al., 2011), however there are also many studies that have not found impairment in these domains (e.g., Beaumont et al., 2012; Capuron et al., 2006; Grafman et al., 1993; Schrijvers et al., 2009). These conflicting findings may be the consequence of methodological limitations, such as differences in the samples under investigation due to differences in the diagnostic criteria, the use of normative data instead of matched controls, and small sample sizes (Michiels & Cluydts, 2001; Moss-Morris et al., 1996; Tiersky et al., 1997). The impact of these limitations on cognitive functioning in people with CFS has not been systematically investigated. Previous reviews have consistently claimed deficits in information processing speed, but have identified inconsistences in the literature on memory and motor functioning, and some aspects of attention (Moss-Morris et al., 1996; Tiersky et

al., 1997). There are also limitations with using statistical significance to evaluate the research findings. Therefore, there is still uncertainty about the type and magnitude of cognitive deficits in CFS, making it difficult for researchers and clinicians to know what aspects of cognition they should assess.

In the absence of an established cause of cognitive problems in CFS, several factors have been investigated for their potential contribution to cognitive dysfunction, including reduced effort or deliberate poor performance (van der Werf et al., 2000); psychological status, such as depression and anxiety (DeLuca et al., 1997a; Tiersky et al., 2003); and the severity of other CFS symptoms, particularly fatigue and sleep (Thomas & Smith, 2009). Subtypes of CFS that may indicate a different cause of the condition, such as a sudden or gradual onset of symptoms, may also differentially impact on cognitive functioning (Claypoole et al., 2007; DeLuca et al., 1997a). Many of these causes have been studied separately, hence in addition to some uncertainty associated with their contribution to cognitive impairment, their relative influence is poorly understood.

Most of the CFS definitions require that reported cognitive problems are of sufficient severity to reduce work or leisure activities (Fukuda et al., 1994; Holmes et al., 1988; Sharpe et al., 1991), however few studies have directly investigated the relationship between objectively assessed cognitive problems and everyday functioning. Test performance has been shown to be related to some aspects of daily functioning – such as level of activity (Christodoulou et al., 1998; Vercoulen, Bazelmans, et al., 1998) – but the relationship with employment status is less clear (Tiersky et al., 2001). Further research is required to understand how cognitive deficits are related to measures of everyday functioning.

Finally, although cognitive deficits have been identified, existing research shows that the problems reported by people with CFS do not appear to be directly related to their test performance (Moss-Morris et al., 1996). However, this may be because the studies did not find cognitive deficits (e.g. DeLuca et al., 1995; Wearden & Appleby, 1997) or, it may reflect a more general finding that self-reported problems are not related to test performance (Short et al., 2002; Svendsen et al., 2012).

Aims of the current research

As highlighted, there is some support for the existence of cognitive deficits in people with CFS, but the specific nature of these deficits remain unclear. Factors that may contribute to impaired cognitive performance include inadequate test effort, psychological impairment, or CFS symptom severity. Furthermore, the consequences of impairment are not well-understood, and possible explanations for test performance not being related to self-reported problems have not been adequately examined. The studies that follow were designed to systematically examine cognitive functioning and its possible correlates in people with CFS, while addressing limitations with previous studies and reviews. The broad aim of this research was to identify the type and severity of cognitive deficits in people with CFS (Study 1), and to examine how deficits may be related to test effort, psychological status, everyday functioning and self-reported problems (Study 2).

The specific objectives of this research were to:

1. Conduct a meta-analysis to identify the type and magnitude of cognitive deficits in people with CFS (Study 1, Chapter 3). This study was designed to 1) compare deficits in CFS performance relative to healthy controls across different cognitive

domains and tests; and 2) identify tests that appear to be most sensitive to cognitive impairment and may, therefore, be suited to detecting deficits for clinical or research purposes.

2. Evaluate the physical and psychological factors that may be related to cognitive deficits. This study involved an empirical investigation of cognitive functioning in people with CFS, which examined performance in relation to a number of possible causes, correlates or consequences of CFS, including test effort, psychological status and everyday functioning (Study 2, Chapters 4 and 5). In addition, the relationship between self-reported problems of memory and attention and test performance were investigated (Study 2, Chapter 6). More specifically this study was designed as follows:

    a. The first goal was to determine if there was evidence of reduced effort in people with CFS, and if found, to identify possible causes (Study 2, Chapter 4). A test of effort was chosen that 1) assess cognitive abilities that are not affected by CFS; and 2) separates effort and intention to perform well or not to determine whether impaired performance was deliberate or unintentional. Participants with invalid performance were excluded from all remaining analyses.

    b. The second goal was to examine the relationship between impaired performance on the cognitive tests and psychological status, CFS symptoms and everyday functioning in a single group of people with CFS, in order to identify the relative contribution of these factors to cognitive functioning (Study 2, Chapter 5). Cognitive performance was assessed using tests identified in the meta-analysis (Study 1) to be sensitive to

deficits in people with CFS, as well as tests not showing impairment, in order to discriminate between global and specific cognitive deficits. Test scores were correlated with measures of psychological status (depression and anxiety), CFS symptoms (overall severity, fatigue and sleep), type of CFS onset (sudden, gradual) and measures of everyday functioning (functional and employment status) to determine the relative contribution of these factors to impaired cognitive performance.

c. The third goal was to investigate the relationship between self-reported memory and attention problems and test performance, and to systematically assess some of the factors that may influence this relationship (Study 2, Chapter 6). Subjective problems in memory and concentration were assessed across different timeframes (day of testing, past week, past month) and compared with performance on tests of memory and attention. Factors previously demonstrated to be related to self-report problems, such as depression and anxiety, were also correlated with problems to determine their relative influence.

Chapter 3: Study 1

Cognitive functioning in chronic fatigue syndrome: a meta-analysis

This chapter consists of a published paper, reprinted with permission. The paper is presented in a format common with the body of the thesis in this chapter, and in the format of the journal in Appendix A.

Cockshell, S. J., & Mathias, J. L. (2010). Cognitive functioning in chronic fatigue syndrome: a meta-analysis. *Psychological Medicine, 40*(8), 1253-1267.

Preamble

The literature review in Chapter 2 identified conflicts in the existing research findings on cognitive functioning in people with CFS, with some studies finding deficits and others not. This first study was therefore designed to evaluate the pattern and magnitude of cognitive deficits in CFS through a meta-analysis of the research literature. Meta-analytic procedures were used to standardise the results from individual studies, enabling them to be compared and aggregated, while also providing a measure of the magnitude of differences between CFS and healthy control groups. This study also addressed a number of limitations identified with previous literature reviews by excluding studies that did not use published CFS diagnostic criteria and had not assessed a healthy control group.

Cognitive functioning in chronic fatigue syndrome: a meta-analysis

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Abstract

Background. Cognitive problems are commonly reported in persons with Chronic Fatigue Syndrome (CFS) and are one of the most disabling symptoms of this condition. A number of cognitive deficits have been identified, although the findings are inconsistent and hindered by methodological differences. The current study therefore conducted a meta-analysis of research examining cognitive functioning in persons with CFS in order to identify the pattern and magnitude of any deficits that are associated with this condition.

Method. A comprehensive search of the PubMed and PsycINFO databases for studies that examined cognitive functioning in CFS between 1988 and 2008 identified 52 eligible studies. Weighted Cohen's *d* effect sizes, 95% confidence intervals, and fail-safe *N*s were calculated for each cognitive score.

Results. Evidence of cognitive deficits in persons with CFS was found primarily in the domains of attention, memory, and reaction time. Deficits were not apparent on tests of fine motor speed, vocabulary, reasoning and global functioning.

Conclusions. Persons with CFS demonstrate moderate to large impairments in simple and complex information processing speed, and in tasks requiring working memory over a sustained period of time.

Key words: Chronic fatigue syndrome, cognitive, meta-analysis, review.

Chronic Fatigue Syndrome (CFS) is defined by a severe and unexplained fatigue of at least six months duration, resulting in a substantial reduction in occupational or leisure activities (Fukuda *et al.*, 1994, US Centre for Disease Control, CDC). Secondary symptoms include self-reported memory and concentration problems, tender lymph nodes, muscle pain, multi-joint pain, sore throat, headaches, unrefreshing sleep, and post-exertional malaise; four or more of which must be present for a diagnosis of CFS. Interestingly, cognitive problems are one of the most frequent and disabling symptoms associated with this disorder (Abbey & Garfinkel, 1991), with 89% of people with CFS reportedly experiencing memory and concentration problems (Jason *et al.*, 1999). This raises the question of whether these problems translate to measurable deficits on objective cognitive tests.

Research conducted over the past 20 years has provided some evidence of cognitive deficits in people with CFS (e.g. DeLuca *et al.*, 2004a, Grafman *et al.*, 1993, Smith *et al.*, 1996), although the results are inconsistent (e.g. Krupp *et al.*, 1994, Short *et al.*, 2002). For example, while some studies have reported deficits in complex information processing speed (e.g. DeLuca *et al.*, 1995, Johnson *et al.*, 1997, Marshall *et al.*, 1997), other studies have not (e.g. Kane *et al.*, 1997, Short *et al.*, 2002). Contradictory findings have also been noted for tests of verbal memory, with some (e.g. Michiels *et al.*, 1998, Tiersky *et al.*, 1998, Vercoulen *et al.*, 1998), but not all (e.g. Fiedler *et al.*, 1996, Lawrie *et al.*, 2000), studies finding that CFS is associated with poorer performance. Similar inconsistencies are apparent for other cognitive domains.

Methodological limitations are likely to contribute to some of the variation in findings, along with the suggestion that any deficits are likely to be relatively subtle (Moss-Morris *et al.*, 1996, Tiersky *et al.*, 1997). One limitation of some early studies

is that they failed to use control groups (e.g. Altay *et al.*, 1990, McDonald *et al.*, 1993, Schmaling *et al.*, 1994) and, instead, used normative data that was not well-matched for age, education or IQ (see Tiersky *et al.*, 1997). Other studies did not use published CFS criteria, which may impact on sample selection (e.g. Krupp *et al.*, 1994, Prasher *et al.*, 1990, Smith *et al.*, 1993), or used small samples (N < 15, e.g. Sargent *et al.*, 1997, Scheffers *et al.*, 1992). None of this research reported effect sizes to assess the magnitude of group differences independently of sample size and statistical significance, making it difficult to determine whether non-significant findings were due to poor statistical power. In addition, a wide variety of tests have been used to measure cognitive performance which, in the absence of effect sizes to standardise test scores, cannot be directly compared. The present study therefore undertook a meta-analysis of research examining the cognitive performance of people with CFS, when compared to healthy controls, in order to determine whether CFS is associated with measurable deficits in cognitive functioning and the nature and magnitude of these deficits.

Method

Identification of studies

The PubMed and PsycINFO databases were searched for 'chronic fatigue syndrome' and alternate terms (chronic fatigue and immune dysfunction syndrome, chronic fatigue disorder, chronic fatigue-fibromyalgia syndrome, chronic infectious mononucleosis-like syndrome, myalgic encephalomyelitis, postviral fatigue syndrome and royal free disease) from January 1988 (when the first operational definition of CFS was published, Holmes *et al.*, 1988) to November 2008.

All studies had to meet the following inclusion criteria: (a) CFS was diagnosed using CDC criteria (Fukuda *et al.*, 1994) or earlier variants (Holmes *et al.*, 1988, Schluederberg *et al.*, 1992, Sharpe *et al.*, 1991); (b) a healthy control group was assessed; (c) participants were adults (> 16 yr); (d) objective cognitive tests were administered (self-report measures were excluded); (e) if treatment was provided, cognition must have been assessed prior to treatment; (f) the provision of statistics that could be converted into a Cohen's *d* effect size (means and standard deviations; univariate F scores; t scores); (g) the study had been published in a journal; and (h) it was written in English.

This search identified 4,086 articles. The titles and abstracts of these articles were examined against the inclusion criteria. Full-text versions of 158 articles were obtained to establish study eligibility, with the reference lists of these papers yielding a further 6 articles. Of the 164 full-text articles, 27 were literature reviews or editorials and 137 were research studies; 56 of which met all of the inclusion criteria. Of the 81 research studies that were excluded, the primary reason for this was: 3 did not assess a CFS group, 11 did not use the specified diagnostic criteria for CFS, 31 did not include a healthy control group, 22 did not administer cognitive tests, three only evaluated cognitive functioning after treatment, four used the cognitive test as an independent rather than dependent variable, and seven did not provide statistics that would enable the calculation of effect sizes. The latter seven studies reported both significant and non-significant findings (three significant, two non-significant, and two both significant and non-significant results), reducing the likelihood of any systematic bias resulting from the exclusion of studies with non-significant findings.

Data from different studies must be independent to ensure that any given sample of participants is not over-represented in the calculation of an effect size (Matt &

Cook, 1994). Seven studies with the same or overlapping participants were identified (and confirmed by the authors: DeLuca *et al.*, 2004a & DeLuca *et al.*, 2004b; DeLuca *et al.*, 1997a & DeLuca *et al.*, 1997b; and Johnson *et al.*, 1996, Johnson *et al.*, 1998 & Johnson *et al.*, 1997). These seven studies were therefore treated as three separate studies, reducing to 52 the number of independent studies that were eligible for analysis.

Data preparation

Each test was categorised into one of eight cognitive domains, based on information provided in test compendiums (Lezak *et al.*, 2004, Strauss *et al.*, 2006) and descriptions provided by the test developer and/or the study authors. The cognitive domains were: attention (including working memory, attention span), memory, reaction time, motor functioning, visuospatial ability, verbal abilities and language, cognitive reasoning and flexibility, and global functioning.

Some of the 52 eligible studies did not report the data necessary to calculate effect sizes for *all* of the tests that they administered ($N_{studies}$ = 19). For example, 13 studies did not provide standard deviations or exact p-values for some of the tests, five did not provide data for non-significant findings, and one failed to provide data for a single test. All authors were contacted in order to request the missing data, with only four authors providing the necessary data (Claypoole *et al.*, 2001, Moss-Morris & Petrie, 2003, Schmaling *et al.*, 2003, Smith *et al.*, 1996).

Composite test scores were sometimes calculated to provide comparable scores across studies (e.g. total score for the Paced Auditory Serial Addition Test). A small number of studies provided data for specific CFS sub-groups: with and without coexisting psychiatric disorders (DeLuca *et al.*, 2004a, DeLuca *et al.*, 2004b, DeLuca

et al., 1997a, Tiersky *et al.*, 2003); premorbid and no premorbid psychiatric history (Gaudino *et al.*, 1997, Tiersky *et al.*, 2003); depressed and non-depressed (Wearden & Appleby, 1997); gradual versus sudden onset of CFS (DeLuca *et al.*, 1997b); medicated versus medication free (Michiels *et al.*, 1998, Sargent *et al.*, 1997) and morning versus afternoon test administration (Lawrie *et al.*, 2000). Unfortunately, there were too few studies to examine the data for these subgroups. The means for these sub-groups were therefore averaged (weighting by sample size) and the standard deviations combined (Higgins *et al.*, 2008) to provide a single score for the CFS group.

Effect size calculations and analyses

Cohen's *d* effect sizes were used in this study to determine whether persons with CFS demonstrated cognitive deficits relative to their healthy peers. This statistic measures the difference between the mean scores of two groups, divided by a pooled standard deviation (Cohen, 1988). If means and standard deviations were not available, standard errors were converted into standard deviations, and *t* values and one-way *F* statistics were converted to *d* using the formulas provided by Zakzanis (2001). Effect sizes were calculated in several stages. Firstly, effect sizes were calculated for each test score that was used by an individual study. Next, if a study had more than one score for a test variable (e.g. per minute scores for a reaction time task), the effect sizes for these scores were averaged so that the study contributed only one effect size for each test variable. Effect sizes were then combined across studies. As small samples are associated with greater variability, which affects the reliability of the effect size (Lipsey & Wilson, 2001), it is recommended that an effect size be weighted by the inverse of its variance (i.e. the inverse of the squared standard error,

Hedges, 1982). Thus, a mean weighted effect size d_w was calculated for each test variable by summing the effect size for each study (weighted by its inverse variance), and dividing by the sum of the weights (Lipsey & Wilson, 2001). Additionally, effect sizes were calculated for each cognitive domain (i.e., attention, memory) by averaging the weighted effect sizes (weighted by sample size) of each study for that domain. If a single study provided multiple measures for a domain, a mean weighted effect size for that study was calculated before combining it with the effect sizes from other studies. According to Cohen (1988), a small effect is defined as $d = 0.2$, a moderate effect as $d = 0.5$, and a large effect as $d = 0.8$. A medium effect size of 0.5 indicates that the mean test performance of the two groups differs by half a standard deviation. All effect sizes were calculated in such a way that a positive effect size represented poorer performance by CFS participants.

For the weighted effect sizes 95% confidence intervals (CIs) were additionally calculated (Lipsey & Wilson, 2001), which if they do not span zero indicates a significant difference between the performance of the CFS and healthy control groups. As there is a tendency for journals to publish studies with significant findings (Easterbrook *et al.*, 1991), fail safe N (N_{fs}) statistics were also calculated (Cooper, 1979). This statistic provides a measure of the number of *unpublished* studies with small effects ($d = 0.2$) that would need to be in existence in order to reduce the mean weighted effect size d_w to a small effect (Wolf, 1986). The larger the N_{fs}, the more confidence can be placed in that finding.

Only those effect sizes for tests that were used by two or more studies are reported here because effect sizes that are based on a single study do not provide a reliable measure of group differences (Rosenthal, 1995). This removed the findings of two studies, resulting in a total of 50 studies that underwent analysis.

Data interpretation

Researchers and clinicians would be more confident that CFS has impacted on cognitive functioning if there were moderate to large group differences in the performance of people with CFS compared to healthy controls ($d_w \geq 0.5$), the performance of the two groups differed significantly (i.e. 95% CIs do not span zero), and that it was unlikely that unpublished findings would draw the current findings into question (i.e., the number of unpublished studies with non-significant findings is greater than the number of studies already published: $N_{fs} > N_{studies}$). For the purposes of the current meta-analysis, an effect size had to meet all three criteria in order to conclude that cognitive performance is compromised by CFS.

Results

Study and participant characteristics

The 50 studies included in the meta-analysis provided data for 1,544 CFS participants and 1,487 healthy controls (see Table 1). The majority of participants were female and approaching middle age, with participants ranging from 17 to 79 years of age. There were small and non-significant differences between the CFS and control groups in terms of their age (t (93) = -0.70, p = 0.49; d = -0.17) and educational level (t (64) = 1.72, p = 0.09; d = 0.42).

Table 1. *Descriptive statistics for the study participants*

	CFS				Healthy Controls			
	$N_{studies}$	**$N_{participants}$**	**M**	**SD**	**$N_{studies}$**	**$N_{participants}$**	**M**	**SD**
Sample Size	50	1,544	**30.9**	24.0	50	1,487	**29.7**	26.2
Gender - female (%)	44	1,090	**76.7**	12.7	41	989	**75.9**	13.8
- male (%)	44	454	**23.3**	12.7	41	498	**24.1**	13.8
Age (years)	48	1,509	**39.7**	5.2	47	1,431	**38.9**	4.8
Education (years)	33	997	**14.7**	1.0	33	806	**15.1**	1.0
CFS Duration (years)	22	687	**5.7**	2.2				
Beck Depression Inventory	13	334	**13.8**	2.1	9	285	**3.5**	2.7
HADS - depression	8	172	**7.1**	1.3	8	144	**2.1**	0.7
- anxiety	8	172	**7.8**	2.5	8	144	**5.5**	1.0

HADS = Hospital Anxiety and Depression Scale

The average duration of CFS was almost 6 years, however participants in some studies had experienced CFS for up to 48 years. People with CFS experienced significantly greater levels of depression than healthy controls on the Beck Depression Inventory (BDI; t (20) = -9.95, $p < 0.01$, d = 4.32) and the depression subscale of the Hospital Anxiety and Depression Scale (HADS; t (14) = -9.83, $p < 0.01$, d = 6.05). While the average BDI scores indicate clinical levels of depression, the use of this measure with CFS patients has been questioned (Farmer *et al.*, 1996). In contrast, the mean HADS depression score, which has been validated for use with CFS patients (Henderson & Tannock, 2005, Morriss & Wearden, 1998), was within the normal to borderline range. For the 8 studies that reported HADS anxiety scores, the average for the CFS group was also in the normal to borderline range, with moderate and significant differences to that of the healthy controls (t (14) = -2.43, p = 0.03, d = 0.51). Psychiatric examinations were only undertaken by half of the studies ($N_{studies}$ = 29), with 10 studies using them to exclude participants with a co-existing psychiatric disorder. Of the remaining studies that reported their results ($N_{studies}$ = 10),

approximately one third of their CFS sample had a co-existing psychiatric condition (35%, range: 16% - 50%), which was primarily Major Depressive Disorder or Dysthymia (80%), and to a lesser extent Panic Disorder (18%), Phobias (14%), Anxiety (12%), Post-Traumatic Stress Disorder (1%) and Obsessive Compulsive Disorder (1%).

The current CDC diagnostic criteria (Fukuda *et al.*, 1994) was most frequently used to diagnose CFS ($N_{studies}$ = 27), followed by the first published criteria (Holmes *et al.*, 1988, $N_{studies}$ = 15), and its various revisions (Sharpe *et al.*, 1991, $N_{studies}$ = 13; Schluederberg *et al.*, 1992, $N_{studies}$ = 8). A total of 11 studies used more than one set of diagnostic criteria. Of those studies that reported the methods used to diagnose CFS ($N_{studies}$ = 33), only five used the comprehensive approach that is advocated by the CDC, which requires a full patient history, physical examination, laboratory tests to exclude other conditions and a psychiatric examination. Other methods of diagnosis included self-ratings and diagnosis by the participant's doctor.

Medication usage was not commonly reported ($N_{studies}$ = 14) and, while CFS participants were not on any medication in six studies, the other eight studies reported that between 10% and 71% of the CFS participants were on some form of medication. Low doses of anti-depressants were the most commonly used medication, followed by benzodiazepines, endocrine replacements, hypnotics/anxiolytics, anti-inflammatories and gamma-globulin for the immune system.

Cognitive domains

When effect sizes were calculated for each of the eight cognitive domains (see Figure 1), it was found that reaction time and attention were the only two domains to show moderate and significant group differences ($d \geq 0.5$, 95% CI $\neq 0$). However, the

effect sizes contributing to these, and two other domains, were not homogenous, hence these scores should be interpreted with caution: reaction time ($Q(20) = 58.86$, $p < 0.05$), attention ($Q(44) = 84.15$, $p < 0.05$), motor functioning ($Q(12) = 29.50$, $p < 0.05$) and visuospatial ability ($Q(11) = 26.53$, $p < 0.05$). For the visuospatial domain, the removal of one outlier created a homogenous grouping ($Q(10) = 7.71$, $p = 0.66$). This was not the case for the other three domains. Moreover, an examination of some of the variables that may have influenced these scores found that there were no significant correlations between age and RT ($r = 0.12$, $N = 19$, $p = 0.63$), attention ($r = 0.10$, $N = 45$, $p = 0.52$) or motor functioning ($r = -0.43$, $N = 12$, $p = 0.17$), or between education and reaction time ($r = 0.15$, $N = 11$, $p = 0.65$), attention ($r = -0.13$, $N = 32$, $p = 0.49$) or motor functioning ($r = -0.27$, $N = 7$, $p = 0.56$). There was insufficient data to examine any other relationships.

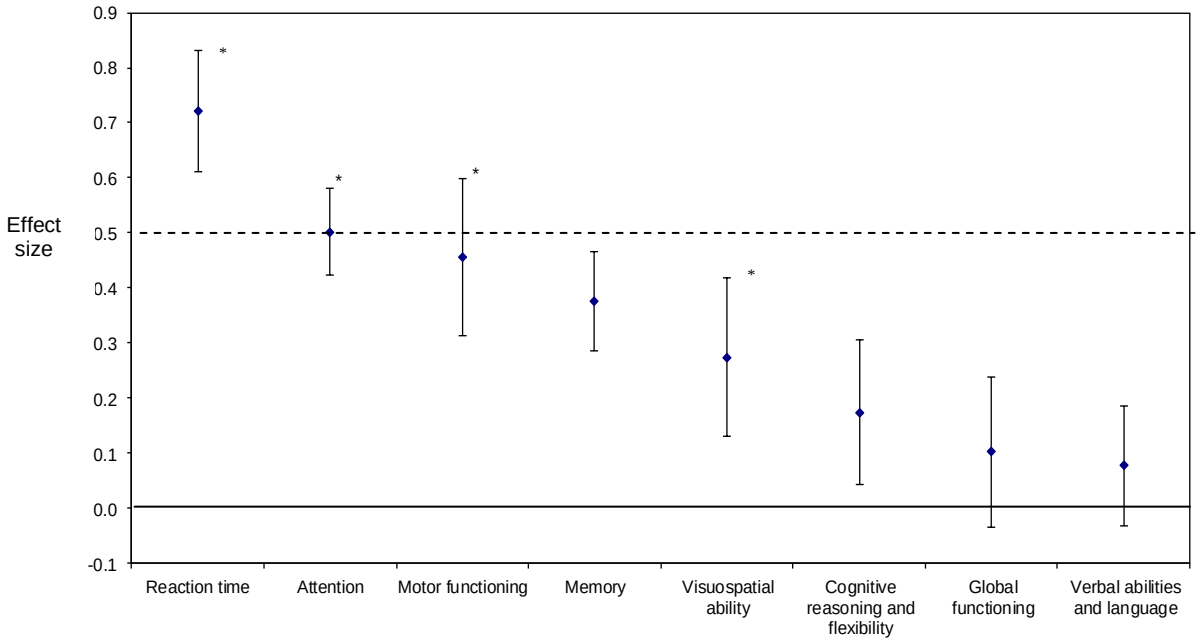

Figure 1. Cognitive domains: weighted Cohen's d effect sizes with 95% confidence intervals, in descending order from left to right. * Significant test of heterogeneity (Q statistic), $p < 0.05$.

Cognitive tests

The 50 studies examined here used a total of 43 cognitive tests, which yielded 79 different scores.

Attention, which encompasses attention span and working memory, was one of the most commonly assessed cognitive domains ($N_{studies}$ = 45; N_{tests} = 19). There were positive mean effect sizes for all tests, indicating that the CFS group showed deficits to varying degrees in this cognitive domain (see Table 2). Moderate to large and significant effect sizes with acceptable N_{fs} were evident for eight tests: the N-Back Memory Task, Stroop Colour Word Task, Paced Auditory Serial Addition Test (plus visual and threshold versions), Short Term Memory Scanning Task, Wechsler Adult Intelligence Scale – Revised (WAIS-R) Digit Symbol subtest, and Spatial Working Memory test. Although very commonly used ($N_{studies}$ = 9 to 13), the Trail Making Test and WAIS-R Digit Span only showed small, albeit significant, deficits.

Memory was assessed by the majority of studies ($N_{studies}$ = 32) using a large number of verbal and visual memory tests (N_{tests} = 29; see Table 3), the majority of which assessed memory for word lists (N_{tests} = 20). While the effect sizes for most tests of word list learning and recall were statistically significant, only seven were moderate to large in size, suggesting that some tests are more sensitive to memory deficits in CFS than others. The tests that met the study criteria were: single presentation Word List Learning Tasks (immediate recall, delayed recognition), the Auditory Verbal Learning Test (immediate recall, distraction list recall, delayed recall, recognition), and the Selective Reminding Test (number of trials). Whereas one of the least commonly used tests of memory for figures (WMS-R Visual Reproduction - immediate recall, $N_{studies}$ = 2) had a significant medium effect size with acceptable N_{fs}, a more commonly used test of memory for figures was only

Table 2. *Attention: weighted Cohen's d effect sizes for each test, in descending order*

Test name	**$N_{studies}$**	**N_{CFS}**	**Mean d_w**	**SD d_w**	**95%CI**	**N_{fs}**	**Study references**
N-Back Memory Task	2	37	**0.82**	1.04	0.30 - 1.33	6	Caseras et al., 2006; Dobbs et al., 2001
Stroop Colour Word Task	12	334	**0.73**	0.39	0.58 - 0.89	32	Claypoole et al., 2007; Creswell & Chalder, 2002; DiClementi et al., 2001; Fiedler et al., 1996; Fuentes et al., 2001; Mahurin et al., 2004; Marcel et al., 1996; Marshall et al., 1997; Metzger & Denney, 2002; Moss-Morris & Petrie, 2003; Short et al., 2002; Smith et al., 1996
Paced Visual Serial Addition Test	2	52	**0.70**	1.17	0.20 - 1.20	5	Johnson et al., 1996; Michiels et al., 1999
Short Term Memory Scanning	5	186	**0.63**	0.60	0.39 - 0.86	11	Chiaravalloti et al., 2003; DeLuca et al., 2004a; Mahurin et al., 2004; McCue et al., 2002; Michiels et al., 1999
Visual Threshold Serial Addition Test	2	96	**0.58**	0.01	0.25 - 0.92	4	Chiaravalloti et al., 2003; DeLuca et al., 2004a
WAIS-R Digit Symbol	9	228	**0.58**	0.16	0.39 - 0.77	17	Blackwood et al., 1998; Claypoole et al., 2007; Fiedler et al., 1996; Gaudino et al., 1997; Kane et al., 1997; Krupp et al., 1994; Lawrie et al., 2000; Michiels et al., 1996; Vercoulen et al., 1998
Paced Auditory Serial Addition Test	15	486	**0.52**	0.27	0.37 - 0.67	24	Chiaravalloti et al., 2003; Claypoole et al., 2007; DeLuca et al., 1993; DeLuca et al., 1995; DeLuca et al., 1997a, b; DeLuca et al., 2004b; Johnson et al., 1996; Kane et al., 1997; Lawrie et al., 2000; Marshall et al., 1997; Michiels et al., 1999; Schmaling et al., 2003; Short et al., 2002; Tiersky et al., 1998; Tiersky et al., 2003
Spatial Working Memory - strategy	3	121	**0.50**	0.15	0.27 - 0.74	5	Capuron et al., 2006; Joyce, 1996; Majer et al., 2008
Auditory Threshold Serial Addition Test	2	96	0.41	0.02	0.08 - 0.74	2	Chiaravalloti et al., 2003; DeLuca et al., 2004a
Stroop Colour Word Task - interference	3	84	0.39	0.03	0.08 - 0.69	3	Metzger & Denney, 2002; Michiels et al., 1998; Ray et al., 1993
Trail Making Test Part A	11	375	0.37	0.41	0.21 - 0.53	9	Claypoole et al., 2007; DeLuca et al., 1995; Dobbs et al., 2001; Krupp et al., 1994; Lawrie et al., 2000; Michiels et al., 1996; Michiels et al., 1998; Starr et al., 2000; Tiersky et al., 1998; Tiersky et al., 2003; Vercoulen et al., 1998
Trail Making Test Part B	12	400	0.36	0.32	0.21 - 0.52	10	Claypoole et al., 2007; DeLuca et al., 1995; Dobbs et al., 2001; Gaudino et al., 1997; Krupp et al., 1994; Lawrie et al., 2000; Michiels et al., 1996; Michiels et al., 1998; Starr et al., 2000; Tiersky et al., 1998; Tiersky et al., 2003; Vercoulen et al., 1998

Test name	$N_{studies}$	N_{CFS}	Mean d_w	SD d_w	95%CI	N_{fs}	Study references
WAIS-R Digit Span Backward	12	401	0.31	0.52	0.16 - 0.47	7	Blackwood et al., 1998; Claypoole et al., 2001; DeLuca et al., 1997a, b; Dobbs et al., 2001; Fiedler et al., 1996; Johnson et al., 1996; Lawrie et al., 2000; Michiels et al., 1996; Michiels et al., 1998; Tiersky et al., 1998; Tiersky et al., 2003; Vercoulen et al., 1998
WMS-R Mental Control	3	100	0.28	0.16	-0.03 - 0.59	1	DeLuca et al., 2004b; Grafman et al., 1993; Marcel et al., 1996
Short Term Memory Scanning - visuospatial	5	217	0.27	0.09	0.08 - 0.46	2	Capuron et al., 2006; Chiaravalloti et al., 2003; DeLuca et al., 2004a; Joyce, 1996; Majer et al., 2008
Continuous Performance Task	7	274	0.26	0.28	0.10 - 0.42	2	Capuron et al., 2006; Kane et al., 1997; Mahurin et al., 2004; Marcel et al., 1996; Marshall et al., 1997; Smith et al., 1996; Smith et al., 1999
Continuous Performance Task - reaction time	5	206	0.25	0.29	0.08 - 0.43	1	Capuron et al., 2006; Fiedler et al., 1996; Majer et al., 2008; Michiels et al., 1998; Smith et al., 1999
WAIS-R Digit Span Forward	13	430	0.25	0.31	0.10 - 0.40	3	Blackwood et al., 1998; Claypoole et al., 2001; DeLuca et al., 1997a, b; Dobbs et al., 2001; Fiedler et al., 1996; Johnson et al., 1996; Lawrie et al., 2000; Marcel et al., 1996; Michiels et al., 1996; Michiels et al., 1998; Tiersky et al., 1998; Tiersky et al., 2003; Vercoulen et al., 1998
WAIS-R Digit Span Total	9	220	0.25	0.19	0.06 - 0.43	2	Claypoole et al., 2007; DeLuca et al., 1993; DeLuca et al., 1995; Fiedler et al., 1996; Gaudino et al., 1997; Johnson et al., 1997; Johnson et al., 1998; Krupp et al., 1994; Short et al., 2002; Vercoulen et al., 1998

95%CI = 95% Confidence Interval; WAIS-R = Weschsler Adult Intelligence Scale - Revised

Tests with bold effect sizes met the study criteria

Table 3. *Memory: weighted Cohen's d effect sizes for each test, in descending order*

Test name	**$N_{studies}$**	**N_{CFS}**	**Mean d_w**	**SD d_w**	**95%CI**	**N_{fs}**	**Study references**
Word List Learning - verbal delayed recognition	2	44	**0.84**	0.43	0.40 - 1.27	6	Fuentes et al., 2001; McCue et al., 2002
Auditory Verbal Learning Test - delayed recognition	2	52	**0.67**	0.06	0.23 - 1.11	5	Claypoole et al., 2007; Lawrie et al., 2000
Selective Reminding Test - number of trials	3	125	**0.62**	0.03	0.33 - 0.90	6	Chiaravalloti et al., 2003; DeLuca et al., 2004b; Michiels et al., 1999
Auditory Verbal Learning Test - delayed recall	2	52	**0.61**	0.27	0.18 - 1.05	4	Claypoole et al., 2007; Lawrie et al., 2000
WMS-R Visual Reproduction - immediate recall	2	38	**0.57**	0.33	0.10 - 1.04	4	Fiedler et al., 1996; Grafman et al., 1993
Auditory Verbal Learning Test - immediate recall	2	52	**0.55**	0.01	0.12 - 0.99	4	Claypoole et al., 2007; Lawrie et al., 2000
Word List Learning - verbal immediate recall	2	96	**0.53**	0.62	0.26 - 0.79	3	Marcel et al., 1996; Smith et al., 1996
Auditory Verbal Learning Test - distraction	2	52	**0.51**	0.48	0.07 - 0.94	3	Claypoole et al., 2007; Lawrie et al., 2000
Selective Reminding Test - long-term retrieval	5	121	0.49	0.39	0.23 - 0.76	7	Kane et al., 1997; Krupp et al., 1994; Marshall et al., 1997; Michiels et al., 1996; Michiels et al., 1999
Selective Reminding Test - sum recall all trials	3	89	0.49	0.25	0.20 - 0.78	4	Gaudino et al., 1997; Michiels et al., 1996; Michiels et al., 1999
WMS-R Visual Reproduction - delayed recall	2	38	0.47	0.39	0.00 - 0.93	3	Fiedler et al., 1996; Grafman et al., 1993
Selective Reminding Test - delayed recall	6	172	0.45	0.35	0.22 - 0.68	8	DeLuca et al., 2004b; Kane et al., 1997; Krupp et al., 1994; Marshall et al., 1997; Michiels et al., 1996; Michiels et al., 1999
Selective Reminding Test - long-term storage	4	101	0.44	0.35	0.16 - 0.73	5	Kane et al., 1997; Marshall et al., 1997; Michiels et al., 1996; Michiels et al., 1999
California Verbal Learning Test - list A trials 1-5	8	310	0.44	0.46	0.26 - 0.62	10	DeLuca et al., 1995; DeLuca et al., 1997a, b; Fiedler et al., 1996; Johnson et al., 1994; Michiels et al., 1998; Tiersky et al., 1998; Tiersky et al., 2003; Vercoulen et al., 1998
California Verbal Learning Test - long delay cued recall	2	77	0.44	0.20	0.11 - 0.76	2	DeLuca et al., 1995; Vercoulen et al., 1998
WMS-R Logical Memory - delayed recall	4	98	0.43	0.19	0.13 - 0.73	5	Claypoole et al., 2007; DeLuca et al., 1995; Grafman et al., 1993; Tiersky et al., 1998
WMS-R Logical Memory - immediate recall	8	187	0.42	0.28	0.21 - 0.62	9	Claypoole et al., 2007; DeLuca et al., 1995; DiClementi et al., 2001; Gaudino et al., 1997; Grafman et al., 1993; Krupp et al., 1994; Short et al., 2002; Tiersky et al., 1998

Test name	$N_{studies}$	N_{CFS}	Mean d_w	SD d_w	95%CI	N_{fs}	Study references
California Verbal Learning Test - short delay cued recall	2	77	0.39	0.29	0.07 - 0.72	2	DeLuca et al., 1995; Vercoulen et al., 1998
California Verbal Learning Test - long delay free recall	7	292	0.39	0.32	0.21 - 0.57	7	DeLuca et al., 1995; DeLuca et al., 1997a, b; Johnson et al., 1994; Michiels et al., 1998; Tiersky et al., 1998; Tiersky et al., 2003; Vercoulen et al., 1998
Rey Osterreith Complex Figure - immediate recall	5	165	0.35	0.42	0.13 - 0.58	4	Claypoole et al., 2007; DeLuca et al., 1995; DeLuca et al., 1997a, b; Tiersky et al., 1998; Vercoulen et al., 1998
California Verbal Learning Test - short delay free recall	7	292	0.33	0.30	0.15 - 0.52	5	DeLuca et al., 1995; DeLuca et al., 1997a, b; Johnson et al., 1994; Michiels et al., 1998; Tiersky et al., 1998; Tiersky et al., 2003; Vercoulen et al., 1998
California Verbal Learning Test - recognition	5	149	0.31	0.16	0.07 - 0.55	3	DeLuca et al., 1995; Johnson et al., 1994; Lawrie et al., 2000; Michiels et al., 1998; Vercoulen et al., 1998
Rey Osterreith Complex Figure - delayed recall	4	107	0.30	0.37	0.03 - 0.58	2	Claypoole et al., 2007; DeLuca et al., 1995; DeLuca et al., 1997a, b; Short et al., 2002
Paired Associate Learning - verbal delayed recall	2	42	0.30	0.41	-0.15 - 0.74	1	Claypoole et al., 2007; Grafman et al., 1993
Paired Associate Learning - visual	3	88	0.24	0.28	-0.11 - 0.58	1	Grafman et al., 1993; Joyce, 1996; Wearden & Appleby, 1997
Selective Reminding Test - delayed recognition	2	64	0.23	0.07	-0.13 - 0.59	0	Michiels et al., 1996; Michiels et al., 1999
Paired Associate Learning - verbal	5	115	0.21	0.42	-0.07 - 0.49	0	Claypoole et al., 2007; Grafman et al., 1993; Joyce, 1996; Lawrie et al., 2000; Short et al., 2002
7/24 Test	2	96	0.16	0.04	-0.16 - 0.49	0	Chiaravalloti et al., 2003; DeLuca et al., 2004b
Pattern Recognition Test	5	181	0.04	0.24	-0.16 - 0.24	0	Capuron et al., 2006; Joyce, 1996; Mahurin et al., 2004; Majer et al., 2008; Marcel et al., 1996

95%CI = 95% Confidence Interval; WAIS-R = Weschsler Adult Intelligence Scale - Revised; WMS-R = Weschsler Memory Scale - Revised

Tests with bold effect sizes met the study criteria

Table 4. *Weighted Cohen's d effect sizes in descending order for reaction time tasks, tests of motor functioning, visuospatial ability, verbal abilities and language, cognitive reasoning and flexibility, and global functioning*

Cognitive Domain Test Name	$N_{studies}$	N_{CFS}	**Mean** d_w	**SD** d_w	**95%CI**	N_{fs}	**Study references**
Reaction Time							
Simple Visual Reaction Time - variable fore-period	9	303	**0.84**	0.49	0.67 - 1.00	29	DeLuca et al., 2004a; Fuentes et al., 2001; Mahurin et al., 2004; McCue et al., 2002; Michiels et al., 1998; Michiels et al., 1999; Sargent et al., 1997; Smith et al., 1999; Vercoulen et al., 1998
Choice Visual Reaction Time	14	480	**0.77**	0.43	0.64 - 0.90	40	Capuron et al., 2006; Chiaravalloti et al., 2003; DeLuca et al., 2004a; Fuentes et al., 2001; Hou et al., 2008; Mahurin et al., 2004; Majer et al., 2008; Marshall et al., 1997; McCue et al., 2002; Michiels et al., 1998; Sargent et al., 1997; Scheffers et al., 1992; Smith et al., 1996; Smith et al., 1999
Simple Auditory Reaction Time - variable fore-period	3	94	**0.61**	0.31	0.29 - 0.93	6	Davey et al., 2001; DeLuca et al., 2004a; McCue et al., 2002
Simple Visual Reaction Time	10	361	**0.58**	0.47	0.43 - 0.73	19	Capuron et al., 2006; Chiaravalloti et al., 2003; Claypoole et al., 2007; Fiedler et al., 1996; Lawrie et al., 2000; Majer et al., 2008; Marcel et al., 1996; Marshall et al., 1997; Michiels et al., 1999; Smith et al., 1999
Choice Auditory Reaction Time	4	139	**0.57**	0.17	0.30 - 0.83	7	Chiaravalloti et al., 2003; Davey et al., 2001; DeLuca et al., 2004a; McCue et al., 2002
Motor Functioning							
Motor Complex Reaction Time	5	185	**0.58**	0.40	0.38 - 0.78	9	Capuron et al., 2006; Davey et al., 2001; Majer et al., 2008; Marshall et al., 1997; Vercoulen et al., 1998
Motor Reaction Time	6	174	**0.53**	0.56	0.32 - 0.74	10	Capuron et al., 2006; Davey et al., 2001; Lawrie et al., 2000; Majer et al., 2008; Marshall et al., 1997; Sargent et al., 1997
Finger Tapping Test	4	113	0.31	0.63	0.05 - 0.58	2	Claypoole et al., 2007; Gaudino et al., 1997; Mahurin et al., 2004; Michiels et al., 1996
Hand-eye Coordination Test	2	47	0.24	0.07	-0.17 - 0.66	0	Fiedler et al., 1996; Marcel et al., 1996
Grooved Pegboard	2	40	0.15	0.10	-0.29 - 0.59	0	Claypoole et al., 2007; Fiedler et al., 1996
Visuospatial Ability							
Rey Osterreith Complex Figure - copy	6	188	0.30	0.31	0.09 - 0.51	3	Claypoole et al., 2007; DeLuca et al., 1995; DeLuca et al., 1997a, b; Short et al., 2002; Tiersky et al., 1998; Vercoulen et al., 1998
Pattern Matching	2	49	0.28	0.08	-0.13 - 0.68	1	Joyce, 1996; Marcel et al., 1996

WAIS Block Design	5	243	0.16	1.03	-0.05 - 0.36	0	Busichio et al., 2004; Claypoole et al., 2007; DeLuca et al., 1997a, b; Fuentes et al., 2001; Lawrie et al., 2000
Verbal Abilities & Language							
Category Fluency	3	70	**0.58**	0.01	0.23 - 0.92	6	Claypoole et al., 2001; Joyce, 1996; Marcel et al., 1996
Controlled Oral Word Association Test	9	194	0.35	0.38	0.14 - 0.55	7	Blackwood et al., 1998; Claypoole et al., 2001; Claypoole et al., 2007; Gaudino et al., 1997; Joyce, 1996; Kane et al., 1997; Krupp et al., 1994; Lawrie et al., 2000; Marcel et al., 1996
WAIS Vocabulary	8	432	0.00	0.20	-0.15 - 0.15	0	Busichio et al., 2004; DeLuca et al., 1997a, b; DeLuca et al., 2004b; Fuentes et al., 2001; Gaudino et al., 1997; Michiels et al., 1996; Short et al., 2002; Tiersky et al., 2003
Wide Range Achievement Test - Reading	2	76	-0.02	0.34	-0.31 - 0.27	0	Fiedler et al., 1996; Majer et al., 2008
National Adult Reading Test	2	73	-0.04	0.19	-0.43 - 0.35	0	Moss-Morris & Petrie, 2003; Wearden & Appleby, 1997
Boston Naming Test	2	59	-0.18	0.06	-0.59 - 0.23	0	Lawrie et al., 2000; Marcel et al., 1996
Cognitive Reasoning & Flexibility							
Tower of London	2	40	0.27	0.54	-0.18 - 0.73	1	Grafman et al., 1993; Joyce, 1996
Logical Reasoning	2	98	0.27	0.18	0.01 - 0.53	1	Mahurin et al., 2004; Smith et al., 1999
WAIS Arithmetic	2	58	0.19	0.18	-0.18 - 0.57	0	Claypoole et al., 2007; DeLuca et al., 1997a, b
Tower of London - perfect solutions	3	121	0.17	0.22	-0.06 - 0.40	0	Capuron et al., 2006; Joyce, 1996; Majer et al., 2008
Category Test	5	173	0.08	0.32	-0.13 - 0.28	0	Capuron et al., 2006; Claypoole et al., 2007; Krupp et al., 1994; Majer et al., 2008; Tiersky et al., 1998
WAIS Picture Completion	2	45	0.02	0.30	-0.39 - 0.43	0	Claypoole et al., 2007; Short et al., 2002
WAIS Similarities	2	34	-0.04	0.09	-0.52 - 0.44	0	Claypoole et al., 2007; DeLuca et al., 1993
Global Functioning							
Shipley Institute of Living Scale	2	34	0.25	0.22	-0.22 - 0.72	0	Kane et al., 1997; Ross et al., 2001
WAIS Information	3	70	0.12	0.12	-0.19 - 0.43	0	Claypoole et al., 2007; Gaudino et al., 1997; Short et al., 2002
North American Adult Reading Test - IQ estimate	4	77	0.07	0.56	-0.26 - 0.39	0	DiClementi et al., 2001; Fuentes et al., 2001; Johnson et al., 1998; LaManca et al., 1998
WAIS Vocabulary - verbal IQ	3	57	0.06	0.07	-0.33 - 0.46	0	Claypoole et al., 2007; DeLuca et al., 1993; Johnson et al., 1997
National Adult Reading Test - IQ estimate	4	127	0.03	0.30	-0.21 - 0.27	0	Blackwood et al., 1998; Joyce, 1996; Lawrie et al., 2000; Smith et al., 1999
Raven's Progressive Matrices	3	84	-0.03	0.25	-0.34 - 0.28	0	Michiels et al., 1996; Michiels et al., 1998; Michiels et al., 1999

95%CI = 95% Confidence Interval; IQ = Intelligence Quotient, WAIS = Weschsler Adult Intelligence Scale (all editions)
Tests with bold effect sizes met the study criteria

associated with small but significant group differences (Rey Osterreith Complex Figure – immediate recall, $N_{studies}$ = 5).

RT was significantly impaired for responses to both simple and complex (choice) stimuli in people with CFS, with all five tests showing medium to large and significant group differences and large N_{fs} (see Table 4). The visual domain was assessed more frequently than the auditory domain.

Motor functioning in CFS was assessed using three tests of manual dexterity (Finger Tapping Test, Grooved Pegboard, Hand-Eye Coordination Test) and the movement time of simple and complex RT tasks (see Table 4). Only the movement times revealed significant moderate group differences with good N_{fs} statistics, with the CFS group taking longer to perform the motor component of RT tasks.

Three tests of *visuospatial ability* were used to assess figure copying, pattern matching, and block construction ($N_{studies}$ = 12). However, these tests only revealed small effects (see Table 4), indicating minimal impairment in this domain.

Of the tests assessing *verbal abilities and language*, only the Category Fluency test revealed moderate and significant group differences and good N_{fs} (refer to Table 4). The most frequently used test was the Controlled Oral Word Association Test, which only showed small but significant group differences.

There was little overlap in the tests used to assess *cognitive reasoning and flexibility*, with most tests only evaluated by two studies (see Table 4). None of the results for these tests met the study criteria, yielding only small effect sizes. Additionally, all but one of the confidence intervals spanned zero, further indicating that this domain is not impaired in people with CFS.

Finally, measures of *global functioning* were used by 17 studies, with all tests producing small and non-significant effect sizes (see Table 4), indicating that people with CFS performed comparably to healthy controls on these measures.

Discussion

Overall, the data from 50 studies (N_{CFS} = 1,544; $N_{controls}$ = 1,487) were analysed in order to determine whether CFS is associated with deficits in cognitive functioning. The groups appeared well matched for gender, age and education, making it unlikely that differences in these variables were contributing to the findings. Persons with CFS were significantly more depressed than the controls, but it was not possible to directly analyse the contribution of depression to cognitive functioning because very few studies provided the necessary data. However, the majority of studies that examined the impact of self-reported depression in CFS on cognitive functioning failed to find a relationship (e.g. Busichio *et al.*, 2004, DeLuca *et al.*, 1995, Johnson *et al.*, 1997, Short *et al.*, 2002, Vercoulen *et al.*, 1998) although some studies did find an association (e.g. Krupp *et al.*, 1994, Marshall *et al.*, 1997). Additionally, using clinical interviews, those studies that categorised CFS participants on the basis of psychiatric diagnosis (most commonly Major Depressive Disorder or Dysthymia) found that cognitive impairment was greater for people *without* a co-existing psychiatric disorder than for those with a co-morbid diagnosis (e.g. DeLuca *et al.*, 1997a, Tiersky *et al.*, 2003). Hence, while the increased levels of depression in people with CFS may explain some of the cognitive problems found in this study, the results from a number of studies suggest that it is unlikely to account for all of the observed problems.

A large number of tests have been used to assess cognitive functioning in CFS and there is considerable variability in the extent to which performance on these measures is affected by this condition. This is likely to have hindered the integration of research findings to date. A total of 24 of the 79 test scores met the study criteria for impairment ($d \geq 0.5$, 95%CIs $\neq 0$, $N_{fs} > N_{studies}$), including tests of attention, memory, RT, motor functioning, and verbal abilities. In contrast, none of the tests of visuospatial ability, cognitive reasoning and flexibility, and global functioning met the study criteria.

Measures of both simple (RT tasks) and complex (Paced Auditory Serial Addition Test) information processing speed showed moderate to large and significant impairments in persons with CFS, confirming the findings of two previous literature reviews (Michiels & Cluydts, 2001, Tiersky *et al.*, 1997). It is also likely that information processing deficits contributed to the deficits noted in the movement time of RT tasks, which are reportedly not pure measures of motor speed (Smith & Carew, 1987, Vercoulen *et al.*, 1998). Moreover, fine motor speed was not impaired in persons with CFS, making it unlikely that motor functioning is predominately responsible for slower RTs.

In addition to deficits in information processing speed, persons with CFS were impaired on tests that assess working memory over a sustained period of time (i.e. N-Back Memory Task, Short Term Memory Scanning Task, Spatial Working Memory). Moderate and significant impairments were also found for the WAIS-R Digit Symbol Test and the Stroop Task, which showed only minimal impairment when the speed of reading patches and words was taken into account. Michiels and Cluydts (2001) have suggested that this pattern of performance on the Stroop Task may be due to an 'overall slowness' in persons with CFS. While this is consistent with the delays in

simple information processing, it is not clear why other simple tests of attention were not also impaired (e.g. Trail Making Test, WMS-R Mental Control).

Previous reviews of the literature have not been able to resolve the conflicting findings regarding verbal and non-verbal memory deficits in persons with CFS (Michiels & Cluydts, 2001, Tiersky *et al.*, 1997). With respect to verbal memory, moderate to large and significant deficits were found on several tests of word list learning (e.g. Auditory Verbal Learning Test and other Word List Learning Tasks). Immediate recall was impaired, as was delayed recall and recognition. DeLuca *et al.* (2004b) suggest that these memory problems may be due to poor initial learning. The deficits in information processing speed and working memory identified by this study may contribute to these problems with initial learning. In support of this, persons with CFS took more trials to learn on a task that controlled for initial learning (Selective Reminding Test) but had only minimally impaired immediate and delayed recall.

Non-verbal memory for complex figures and spatial location were not impaired, with only one test of memory for figures showing moderate and significant deficits (WMS-R Visual Reproduction - immediate recall). Thus, memory deficits associated with CFS may be predominately verbal, despite the absence of modality-specific impairments in RT and attention.

Verbal abilities and language were also largely preserved, except for Category Fluency which may be reliant on working memory for successful completion (Lezak *et al.*, 2004). Finally, higher order cognitive functions appear to be intact, consistent with the findings of previous reviews (Michiels & Cluydts, 2001, Tiersky *et al.*, 1997).

The magnitude of the deficits in persons with CFS is rarely reported. This study found that there were deficits of a half to one standard deviation below that of their

healthy peers. The practical impact this has on people with CFS appears to have only been explored by one study, which found that people with a greater number of deficits reported more days of inactivity (Christodoulou *et al.*, 1998).

Overall, the impairments identified by objective cognitive tests are congruent with the memory and concentration problems reported by persons with CFS. While most studies have not found a relationship between self-reported cognitive problems in persons with CFS and their test performance (e.g. Vercoulen *et al.*, 1998, Wearden & Appleby, 1997), their self-rating of performance on specific tests is reliable (Wearden & Appleby, 1997).

The cause of these cognitive deficits is uncertain. Depression may be a contributing factor but, as previously discussed, greater deficits have been found in people with CFS *without* co-morbid depression. Other research has investigated the role of a sudden versus gradual onset of the condition, with those who report a sudden onset being more impaired, possibly representing a subgroup with a viral cause for their condition (e.g. Claypoole *et al.*, 2007, DeLuca *et al.*, 1997b). Other factors that may contribute to the cognitive deficits, while not a cause, are the fluctuations that occur in CFS symptoms (Fuentes et al., 2001), such as fatigue, which may result in inconsistent levels of effort being applied during cognitive testing. Although the cause of cognitive deficits in CFS is still not known, treatments with cognitive behaviour therapy and graded exercise have resulted in some improvements (e.g. de Lange *et al.*, 2008, Thomas *et al.*, 2006).

Limitations

There are several limitations that may have influenced the study findings. Firstly, a large number of effect sizes were calculated due to the large number of tests that were used by researchers, which may result in some effect sizes being significant by

chance alone (i.e. Type 1 error). The requirement for an effect size of interest to meet multiple criteria ($d \geq 0.5$, 95% CIs $\neq 0$, $N_{fs} > N_{studies}$) should improve the robustness of our findings, however we cannot exclude the possibility that Type 1 errors have occurred.

Secondly, while publication bias may have influenced the findings of this study, we attempted to evaluate the potential robustness of our findings by calculating an N_{fs} statistic and ensuring that the number of studies contributing to a finding exceeded this value. Furthermore, nearly half of the studies reported small effect sizes for most tests, indicating that non-significant results are being reported in the literature, thereby reducing the likelihood of publication bias.

Thirdly, many studies did not report data on variables that may have influenced cognitive functioning, such as psychiatric status, depression and the nature of the onset of the condition (sudden versus gradual), thereby precluding an analysis of their impact on cognition. There was also considerable variability in the methods used to diagnosis CFS. Hence, there may be important differences between the CFS participants that may have contributed to the findings. Reeves *et al.* (2003) have provided guidelines to resolve some of the ambiguities in the CDC CFS criteria (Fukuda *et al.*, 1994), which may help to standardise the procedures used in future research. However, the cognitive tests that they proposed may need to be reconsidered based on the findings of this meta-analysis.

Finally, the impact of medication usage on cognitive functioning could not be explored in this study. However, individual studies suggest that its impact may be minimal, with one study finding no difference between the performance of medicated and un-medicated persons with CFS (Michiels *et al.*, 1998) and another finding

significant performance decrements in un-medicated (but not medicated) CFS participants compared to controls (Sargent *et al.*, 1997).

Conclusions

In conclusion, this study provides objective evidence of cognitive deficits in persons with CFS, primarily in the domains of attention, memory, and reaction time. In general, these deficits are consistent with those that are reported by patients. Both simple and complex information processing speed are impaired, along with working memory. The data also suggest that memory deficits may be due to the poor initial acquisition of information but more studies are needed to investigate this. The deficits in performance are around a half to one standard deviation below that of their healthy peers, which is likely to have an impact on day-to-day activities. In contrast, CFS does not appear to have an impact on perceptual abilities or fine motor speed; nor does it appear to affect higher order cognitive abilities, such as language, reasoning or intelligence.

Declaration of Interest

None.

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* Indicates studies that were included in the meta-analysis.

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Chapter 4: Study 2 (Part 1)

Test effort in persons with Chronic Fatigue Syndrome when assessed using the Validity Indicator Profile

This chapter consists of a published paper, reprinted with permission. The paper is presented in a format common with the body of the thesis in this chapter, and in the format of the journal in Appendix B.

Cockshell, S. J., & Mathias, J. L. (2012). Test effort in persons with Chronic Fatigue Syndrome when assessed using the Validity Indicator Profile. *Journal of Clinical and Experimental Neuropsychology, 34*(7), 679-687.

Preamble

The preceding meta-analysis (Study 1, Chapter 3) found that people with CFS were impaired in information processing speed and sustained working memory. The next study was designed to examine the cognitive deficits in CFS in greater detail and to evaluate some of the possible causes, correlates and consequences of these impairments (Study 2). To this end, a sample of people with CFS and matched healthy controls were assessed on measures of cognitive functioning - selected from the meta-analysis because they had shown sensitivity to cognitive impairment in people with CFS - and on measures of test effort, psychological status, everyday functioning, CFS symptoms and self-reported memory and concentration problems. The next three chapters analyse different aspects of this study (Chapters 4 - 6). It should be noted that this research was undertaken in a relatively small city of approximately one million people, hence a limited number of participants were available for research purposes. Therefore, it was necessary to design a single detailed study that examined a number of questions within the same sample. One advantage of this approach is that between sample variability did not contribute to the findings.

The first analysis examined the extent to which people with CFS were putting forth their best effort during cognitive testing and, hence, whether their results were valid (Study 2, Chapter 4). The Validity Indicator Profile (VIP) test was specifically chosen to assess test effort because it analyses patterns of performance to provide an indication of intention and effort. This contrasts with the effort tests that have previously been used in CFS research, which employ cut-off scores for poor effort, but may confound effort and ability. Additionally the relationship between test effort

and compensation was examined to investigate whether people with CFS may be exaggerating or fabricating symptoms for secondary gain.

Test effort in persons with Chronic Fatigue Syndrome when assessed using the Validity Indicator Profile

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Abstract

The current study examined the potential contribution of sub-optimal effort to the cognitive deficits that are associated with Chronic Fatigue Syndrome (CFS) using the Validity Indicator Profile (VIP). Unlike most tests of effort, the VIP distinguishes between intentional and unintentional poor performance, and does not assess cognitive functions that are affected by CFS; thereby reducing the risk of mistakenly attributing genuinely poor performance to reduced effort. The VIP was administered to 54 persons with CFS and 54 matched healthy community controls, and performance categorized into 1 of 4 response styles (valid: compliant; invalid: suppressed, irrelevant, inconsistent), based on the level of effort expended (high or low) and the intention to perform well or not. VIP performance was classified as valid for the majority of participants (CFS & Controls), indicating high levels of effort and an intention to perform well. Three participants in the CFS group and four in the control group showed low levels of effort but an intention to do well (invalid: inconsistent). No participant performed in a manner indicative of an intent to perform poorly (invalid: suppressed, inconsistent). These findings suggest that poor effort is unlikely to contribute to cognitive test performance of persons with CFS.

Keywords: Chronic Fatigue Syndrome; Validity Indicator Profile; Cognitive performance; Effort; Valid performance.

Introduction

Chronic Fatigue Syndrome (CFS) is characterized by a severe and unexplained fatigue of at least 6 months duration, combined with a range of other symptoms, including problems with memory and concentration (Fukuda, Straus, Hickie, Sharpe, Dobbins et al., 1994). While cognitive testing has consistently revealed deficits in reaction time, attention and memory (predominately verbal learning, Cockshell & Mathias, 2010), the underlying cause of these problems remains unclear. Psychological factors, such as depression, do not adequately account for observed cognitive deficits in CFS (e.g. Short, McCabe & Tooley, 2002; Busichio, Tiersky, DeLuca & Natelson, 2004; Thomas & Smith, 2009). Brain imaging studies have revealed inconsistent findings relating to the existence of abnormalities in persons with CFS (e.g. Cope, David, Pelosi & Mann, 1995; Fischler, D'Haenen, Cluydts, Michiels, Demets et al., 1996; Lange, Steffener, Cook, Bly, Christodoulou et al., 2005), possibly due to sampling differences, as some studies have only found abnormalities in the absence of co-morbid psychiatric disorders (Lange, DeLuca, Maldjian, Lee, Tiersky et al., 1999; Cook, Lange, DeLuca & Natelson, 2001). Functional imaging studies have also found a relationship between brain activity and mental fatigue in people with CFS (Tanaka, Sadato, Okada, Mizuno, Sasabe et al., 2006; Cook, O'Connor, Lange & Steffener, 2007), possibly suggesting a physiological basis to the disorder. With the current limited understanding of the basis for cognitive deficits in CFS and no clearly defined cause for these cognitive problems, it is important to consider whether reduced effort is a contributing factor (Binder & Campbell, 2004; Heilbronner, Sweet, Morgan, Larrabee, Millis et al., 2009).

The results of cognitive tests are only valid if a person applies their best effort during testing (Bush, Ruff, Troster, Barth, Koffler et al., 2005). However, sub-optimal

effort may occur for several reasons, including: anxiety associated with the test situation; illness-related factors that may interfere with performance, such as fatigue or depression; or deliberately poor performance motivated by some external reward, such as money or time away from work (American Psychiatric Association, 2000). Test performance may therefore be deliberately compromised (also called malingering or feigning), which often requires external incentives to be present (e.g. Slick, Sherman & Iverson, 1999; Bianchini, Greve & Glynn, 2005) or genuine attempts to perform well may also be affected by fatigue or test anxiety.

A number of tests are used to identify reduced effort during cognitive testing, the most common of which detect 'excessive impairment' caused by failures on very easy test items, and performance that falls below chance levels on forced-choice tests or below that of genuinely impaired groups (Rogers & Bender, 2003). However, these tests only provide a dichotomous categorization of performance as valid or invalid, with invalid performance often assumed to be intentional. That is, they are unable to differentiate between poor performance due to deliberate intention and reduced effort that occurs for more benign reasons (e.g., fatigue, disinterest, Frederick & Bowden, 2009). Moreover, they do not formally consider the extent to which a person's underlying cognitive capacity impacts on his/her test performance (Frederick, 2000). Less commonly, 'unexpected patterns' of performance on standard cognitive tests are used as a measure of effort, such as consistency across similar items and patterns of performance across items of varying difficulty. The latter measures are thought to provide a better indicator of deliberately poor performance because they provide more information about the reason for the poor performance (Rogers & Bender, 2003). However, unless specifically validated for the purposes of detecting malingering, they are likely to be ineffective (van Gorp, Humphrey, Kalechstein, Brumm, McMullen et

al., 1999) and risk confounding genuine deficits with effort. Validated tests, such as the Validity Indicator Profile (Frederick, 2003), which analyze patterns of performance to identify sub-optimal effort, are therefore likely to be more robust and assist in identifying the reason for poor performance. Moreover, the VIP classifies performance into one of four categories based on 'effort' and 'intention'; enabling poor performance due to reduced effort (an intention to perform well but low effort) to be distinguished from poor performance due to deliberate (intention to perform poorly, combined with high effort) or irrelevant (intention to perform poorly, but with low effort) responding. The VIP has also been shown to have better false-positive and true-positive rates than other well known effort tests (e.g., Rey 15-Item Memory Test, Word Memory Test, Frederick & Bowden, 2009).

Test effort has been the focus of only one study on CFS (van der Werf, Prins, Jongen, van der Meer & Bleijenberg, 2000), with several others including effort tests, either as part of a battery of cognitive tests (e.g., Schmaling, DiClementi, Cullum & Jones, 1994; Binder, Storzbach, Campbell, Rohlman & Anger, 2001; Fuentes, Hunter, Strauss & Hultsch, 2001; Busichio et al., 2004) or for screening purposes (van der Werf, de Vree, van der Meer & Bleijenberg, 2002). All studies used memory-based effort tests that detect 'excessive impairment'. Most found no evidence of reduced effort: one study each found that no CFS participant showed unsatisfactory effort on the Test of Memory Malingering (TOMM, Busichio et al., 2004), Rey 15-item Memory Test (Schmaling et al., 1994), Oregon Dual Task Procedure (a computerized version of the Portland Digit Recognition Test, Binder et al., 2001), and Dot Counting Test (Schmaling et al., 1994); one found no difference between CFS and Controls on the Victoria Symptom Validity Test (Fuentes et al., 2001); and another found that approximately 6% of their CFS participants (who also had Gulf War Syndrome)

showed performance suggestive of feigned impairment on the TOMM (Tiersky, Natelson, Ottenweller, Lange, Fiedler et al., 2000; results reported in DeLuca & Tiersky, 2003). In contrast, two studies reported that 23% and 30% of persons with CFS demonstrated reduced effort, suggestive of deliberately poor performance, using the Amsterdam Short Term Memory Test (van der Werf et al., 2002, van der Werf et al., 2000, respectively). These authors argued that their findings were unlikely to be due to the memory requirements of the test, citing two studies that failed to find memory deficits in persons with CFS on a similar memory task (Johnson, 1994; Vercoulen, Bazelmans, Swanink, Galama, Fennis et al., 1998). However, a recent meta-analysis of research examining the cognitive functioning of persons with CFS has reported consistent deficits in memory (Cockshell & Mathias, 2010). Hence, it is unclear whether the reduced effort identified by van der Werf et al. (2000; 2002) could be attributed to the memory deficits that are often associated with CFS, poor performance due to other confounding factors (e.g. fatigue, depression) or deliberately poor performance (due to external incentives or secondary gains). This question needs to be resolved using a validated test of effort that detects 'unexpected patterns' of performance in a cognitive domain that is unaffected by CFS in order to improve our understanding of whether sub-optimal test effort is a serious issue in this clinical group and the reasons for any poor performance.

It is also noteworthy that existing studies have not examined the impact of external incentives, particularly financial compensation, on effort in CFS samples, despite the fact it is estimated that 35% of people with chronic fatigue (defined as fatigue for ≥ 6 months, with no other symptoms) or fibromyalgia (a related condition) seek compensation for their illness (Mittenberg, Patton, Canyock & Condit, 2002). Moreover, Gervais (2001) reported that 30% of persons with fibromyalgia who were

not seeking compensation, but who were in receipt of disability benefits, failed tests of effort. Hence, both compensation and the receipt of benefits may influence effort and should therefore be explored in the CFS population.

The current study was designed to examine test effort, and the impact of compensation and disability allowances on performance, in a sample that was diagnosed with CFS. The Validity Indicator Profile (Frederick, 2003) was specifically chosen because it assesses test effort in the non-memory cognitive domains of problem-solving and verbal ability, which do not appear to be impaired by CFS (Cockshell & Mathias, 2010). In addition, the VIP classifies performance as 'valid' or 'invalid', independently of a person's ability-level; with invalid performance being further classified into one of three types (suppressed, irrelevant, or inconsistent), based on the person's level of effort (high or low) and motivation (intention to perform well or not).

Method

Participants

Fifty four persons who met the US Centers for Disease Control and Prevention criteria for a diagnosis of CFS (Fukuda et al., 1994) and were diagnosed on the basis of medical history, physical examination and laboratory tests to exclude other medical conditions, participated in this study. Participants were excluded if they did not meet this diagnostic criteria, were aged under 18 years or over 60, or they had a condition that may have independently impacted on cognitive performance, namely: prior loss of consciousness for more than five minutes; stroke; heart disease; uncontrolled high blood pressure; diabetes requiring insulin injections; seizures; and/or learning disorders (e.g. dyslexia). Forty one of these CFS participants were recruited from an

Australian CFS patient database containing 71 patients, which was created for research and clinical service development (see Clark, Del Fante & Beilby, 2006). A further thirteen CFS participants were recruited from 24 respondents to a letter, sent by two general practitioners and an endocrinologist to their CFS patients, inviting participation in this study (113 letters sent, 21% response rate). A total of 30 participants from the database and 11 from the mail-out responded but were not included in the study for the following reasons: 17 (41%) did not meet the study criteria, 19 (46%) were not available for testing, 2 (5%) were too unwell to participate, and 3 (7%) declined to participate. Psychiatric symptomatology was identified using the Mini International Neuropsychiatric Interview (MINI) modules for Major Depressive Episode, Dysthymia, and Generalized Anxiety Disorder (v5.0.0, Sheehan, Lecrubier, Sheehan, Amorim, Janavs et al., 1998); with the modules for alcohol and substance abuse (Alcohol Dependence and Abuse and Substance Dependence and Abuse modules) additionally used to exclude any participants that met those criteria (which none did). Two CFS participants met the criteria for dysthymia and a further two for generalized anxiety disorder.

Fifty four healthy controls, who were individually matched to the CFS participants on the basis of age, gender and educational level, were recruited from the family and friends of the CFS participants and from the general community. No participant in this group had a past or present diagnosis of CFS and all met the above exclusion criteria. Nine controls were excluded during the recruitment process because they met one of the exclusion criteria. No one in the control group met the criteria for the aforementioned psychiatric disorders when screened using the MINI. The study was approved by The University of Adelaide Human Research Ethics Committee and all participants were part of a larger study into CFS.

Measures

Effort was assessed using the Validity Indicator Profile (Frederick, 2003), which consists of two subtests: Nonverbal (problem solving) and Verbal (word definition). The Nonverbal subtest is based on the Test of Nonverbal Intelligence (TONI, Brown, Sherbenou & Johnsen, 1982). Participants are presented with a series of 100 matrices and must select one of two options that complete the matrix (e.g. matching, next in sequence). For the VIP Verbal subtest, participants are given a series of 78 target words and must select the word that is most similar in meaning from a choice of two words. The items in both subtests vary in their level of difficulty but are not ordered in terms of difficulty until they are electronically scored.

A total score (correct responses) and a performance curve (which reflect performance as a function of increasing item difficulty) are calculated by computer and these are used to classify participants into one of four response styles, only one of which is valid (Frederick, 2003). Valid performance (termed 'Compliant') occurs when a person correctly responds to items that are within his/her level of ability but guesses the answer when the items exceed his/her ability level (chance level performance). In contrast, there are three response styles that are classified as invalid. 'Suppressed' performance, which is the opposite of 'Compliant', occurs when a series of incorrect responses occur when items are within an individual's ability level (deliberate poor performance). 'Irrelevant' performance reflects random responding to items with little regard to question content. Finally, 'Inconsistent' performance tends to capture temporary performance problems, such as inattention, distraction or fatigue (Frederick, 2002); hence some easy items are answered incorrectly, even within an individual's range of ability, and other more difficult ones may be answered correctly

if they are still within the person's ability level. The response styles for both the Nonverbal and Verbal subtest were both used to assess effort.

In addition, a measure of a participant's ability was obtained for each subtest by calculating the absolute value of the difference between the number of items answered correctly and incorrectly. This latter score (referred to as the 'Adjusted Score') was used to determine whether there were any differences in the levels of ability between the CFS and healthy control groups.

The VIP has been validated in a variety of samples (e.g., brain injury, suspected and 'coached' malingerers, Frederick & Crosby, 2000; Frederick, Crosby & Wynkoop, 2000; Frederick, 2002; Frederick, 2003) and has good sensitivity (Nonverbal: 74%, Verbal: 67%) and specificity (Nonverbal: 86%, Verbal: 83%); better than other measures of malingering that have previously been used in CFS research (i.e. Portland Digit Recognition Test, Rey 15-Item Memory Test, Dot Counting Test, Frederick & Crosby, 2000).

Moreover, some of the factors that may independently impact on effort and cognitive performance were also assessed. Specifically, depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), which requires participants to rate the extent to which they experience seven symptoms each of depression and anxiety (scores range from 0 to 21). A cut-off score of ≥ 11 is frequently used to identify clinical levels of depression and anxiety in the general population (Zigmond & Snaith, 1983); this was used to determine the number of clinical cases in the Control group. A lower cut-off score of ≥ 9 has been recommended for use with CFS patients (Morriss & Wearden, 1998) and was adopted for this group. Estimates of pre-morbid intelligence were also obtained using the National Adult Reading Test (NART, Nelson & Willison, 1991) in order to ensure

that the CFS and Control groups were comparable in terms of pre-illness cognitive ability. As an adjunct to the objective measures of response style, self-reported levels of effort and energy were additionally obtained for each VIP subtest, with participants rating effort and energy during completion of the VIP on a 5-point Likert scale from very low (-2) to very high (2). Finally, CFS participants were asked if they were in receipt of, or had ever been denied, compensation or disability payments for their CFS or another related condition in order to examine the effect of external financial incentives on effort.

Procedure

Participants attended a testing session as part of a larger study into CFS. The VIP, NART and MINI were administered in either the first or second half of the testing session according to one of two test schedules, which were counter-balanced between participants. Self-ratings of effort and energy during the task were obtained immediately after each of the VIP subtests. The HADS and other demographic information were completed in the few days immediately prior to the testing session.

Results

Participant characteristics

Of the 54 people with CFS and their 54 matched controls, most were middle-aged females ($N_{females}$ = 42, N_{males} = 12) with a tertiary education (see Table 1). The median duration of CFS was 7.3 years (range 1.3 to 48.0 years; M = 11 years, SD = 10 years). The two groups did not differ significantly in terms of age, education or predicted IQ (refer to Table 1), indicating that they were successfully matched. Similarly, when the measures of ability provided by the VIP (Adjusted Scores) were

compared between groups, neither the Nonverbal or Verbal subtests (see Table 1) differed significantly, again indicating that the two groups were comparable in terms of cognitive ability. However, the CFS group was significantly more depressed than the healthy control group (see Table 1). Although the majority of CFS participants scored within the normal range on the HADS (0 - 8), there was a subset (N = 11, 20%) whose responses suggested clinical levels of depression (≥ 9), compared with none of the healthy controls (≥ 11). The CFS group was also significantly more anxious than the healthy control group (see Table 1), with the responses of 30% (N = 16) of CFS participants suggestive of clinical levels of anxiety using the recommended cut-off scores for CFS (≥ 9) compared with 7% (N = 4) of healthy controls (cut-off ≥ 11).

Table 1. Study participant characteristics

	CFS		***Healthy***		***t test***		
	Mean	SD	Mean	SD	df	t	p
Age (years)	43.0	12.2	42.7	12.2	106	0.15	0.88
Education (years)	14.9	3.1	15.3	2.9	106	0.68	0.50
NART Predicted IQ	112.5	5.4	112.6	4.5	106	0.08	0.94
HADS							
Depression	5.9	3.3	1.9	2.1	106	7.42	0.00
Anxiety	7.1	4.0	5.2	3.7	106	2.59	0.01
VIP Nonverbal Adjusted Score	87	7	88	8	103	0.63	0.53
VIP Verbal Adjusted Score	65	4	65	3	106	0.05	0.96

Validity Indicator Profile performance

For the Nonverbal subtest of the VIP, the data for three CFS participants were excluded. In two cases, there were problems with the test materials due to no fault of the participant and their responses could not be scored, and one participant selected both responses (instead of a single response) to 12 items, rendering this data unusable (VIP scoring only tolerates missing data for ≤ 5 items). This latter respondent was also in receipt of compensation, hence it is possible that they were demonstrating reduced effort, however all three participants were 'Compliant' for the Verbal subtest.

Performance on the VIP Nonverbal subtest was classified as 'Compliant' (valid) for the majority of participants in the CFS (94%) and Control (96%) groups, with only 3 (6%) people in the CFS group and 2 (4%) in the control group responding inconsistently. Similarly, the Verbal subtest performance of most of the participants in both groups were classified as 'Compliant' (valid), with none in the CFS group and only 2 people (4%) in the healthy group responding inconsistently. None of the invalid responders indicated an intention to perform poorly (i.e. 'Suppressed' or 'Irrelevant'), rather they were suggestive of inconsistent effort. Base rates of 'Inconsistent' performance on the VIP for 'honest normals' are 7% for the Nonverbal subtest and 5% for the Verbal subtest (Frederick & Crosby, 2000). When the *categorization* of VIP responses were compared between the CFS and healthy control groups, there were no significant differences for the Nonverbal (Fisher's Exact test 1-sided, $p = 0.47$) or Verbal (Fisher's Exact test 1-sided, $p = 0.25$) subtests.

Of the 'Inconsistent' responders in each group, two of the three CFS participants and none of the four control participants had clinical levels of depression and/or anxiety (see Table 2). Of the 48 'Compliant' responders in the CFS group, nine and 15 of the participants showed clinically significant levels of depression and

anxiety, respectively. None of the 50 'Compliant' responders in the healthy control group had HADS depression scores in the clinically significant range and four had clinically significant levels of anxiety. Further analysis within the CFS group did not find any significant differences for categorization of response for those who had clinical levels of depression or anxiety (Fisher's Exact test two-sided, $p = 0.56$); hence mood does not adequately account for the inconsistent responses.

Self-reported effort & energy levels

As can be seen in Figure 1, there were no between-group differences in the self-reported levels of *effort* that were exerted while completing the Nonverbal ($t(105) = -0.01$, $p = 1.00$) and Verbal VIP subtests ($t(105) = -0.72$, $p = 0.47$). In contrast, CFS participants reported significantly lower *energy* levels than the healthy controls during completion of both of these subtests (Nonverbal: $t(105) = -7.7$, $p = 0.00$), Verbal: $t(105) = -6.2$, $p = 0.00$). However, given that the two groups performed comparably on the VIP, these reduced energy levels did not appear to impact on performance.

Table 2. The number of people with clinical levels of depression and anxiety on the HADS for the VIP response types in CFS and healthy control groups.

	CFS HADS		**Healthy HADS**	
VIP Category	**Depression**	**Anxiety**	**Depression**	**Anxiety**
Compliant	9 of 48 (19%)	15 of 48 (31%)	0 of 50 (0%)	4 of 50 (8%)
Inconsistent	2 of 3 (67%)	1 of 3 (33%)	0 of 4 (0%)	0 of 4 (0%)

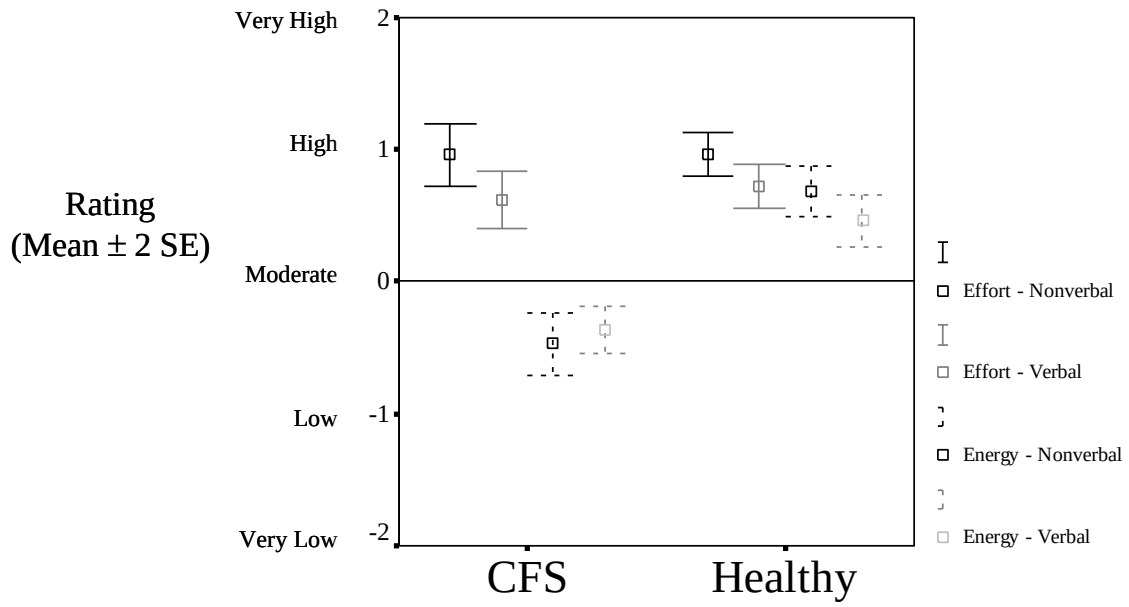

Figure 1: Self-reported ratings of effort and energy during the VIP subtests

Compensation

Within the CFS group, nearly half of all participants were receiving some form of compensation (*n* = 24), predominately for CFS, although one participant was receiving it for depression and another did not state the reason. The most common form of compensation was a government disability allowance (*n* = 17), followed by unemployment benefits (*n* = 4) and insurance payments (*n* = 3). Of all the CFS participants, eight reported having been declined compensation for their CFS (e.g. symptoms being considered insufficient for a claim, claim made prior to a formal diagnosis of CFS, or excessive financial assets), half of whom were subsequently receiving benefits.

As seen in Table 3, there were no significant differences in the VIP 'Compliant' and 'Inconsistent' response types for the Nonverbal subtest between those people with CFS who were receiving compensation and those were not (Fisher's Exact test 1-sided, $p = 0.40$) or between those who had initially been declined compensation but

now either were or were not receiving it (Fisher's Exact test 1-sided, $p = 0.50$). All CFS responses to the Verbal subtest were compliant, making it unnecessary to assess the impact of compensation for this subtest.

Table 3. VIP response types for each subtest for people with CFS either receiving compensation or not.

	Nonverbal subtest		**Verbal subtest**	
VIP Category	**No Compensation**	**Compensation**	**No Compensation**	**Compensation**
Compliant	28 [4]	20 [3]	34	20
Inconsistent	1 [0]	2 [1]		

[ ] Indicates the number of people within the group who had been declined compensation for CFS

Discussion

The current study found that, in a clinical sample who met the US Centers for Disease Control and Prevention for a diagnosis of CFS (Fukuda et al., 1994), the majority of people performed in a manner that indicated high levels of effort and an intention to perform well, as measured by the VIP (valid response style). This finding is consistent with that of a number of previous studies (i.e. Tiersky et al., 2000; Binder et al., 2001; Fuentes et al., 2001; Busichio et al., 2004), but contrasts with the findings of two others that reported reduced levels of effort in 23%-30% of their samples (van der Werf et al., 2000; van der Werf et al., 2002). Notably, all previous studies measured effort using a test of memory, which has since been shown to be impaired in persons with CFS (Cockshell & Mathias, 2010). The VIP, on the other hand, has the advantage of measuring effort when performing non-memory cognitive tasks, while also assessing effort independently of a person's underlying ability-level (by using items of varying difficulty), and differentiating between intentionally and

unintentionally poor performance. Importantly, the CFS samples in the above-mentioned studies had similar rates of depression (e.g. 25% in van der Werf et al., 2000, 20% in the current study) and recruited participants from relatively similar sources (hospital outpatients, clinics), making it unlikely that these variables contributed to the difference in findings.

Only a small number of CFS and Control group participants performed in a manner that was indicative of reduced effort. However, the performance of these individuals was categorized as being 'inconsistent', suggesting an intention to perform well but with reduced effort, possibly due to fatigue or depression, rather than reflecting deliberately poor (classified as 'Suppressed' by the VIP) or random (classified as 'Irrelevant') performance. Not all inconsistent responders were clinically depressed or anxious, and many people who were depressed and anxious provided valid (compliant) responses. This suggests that depression does not adequately explain an inconsistent response style, and demonstrates that depressed or anxious individuals will not necessarily perform sub-optimally. This is also consistent with the only other study to have investigated the relationship between depression and effort, which found that they were not significantly correlated (van der Werf et al., 2000). Moreover, the rate of reduced effort observed here (CFS 6%, Controls 7%) is comparable to that of "honest normals" in the VIP standardisation studies (Frederick & Crosby, 2000). Unfortunately, due to the small numbers who showed reduced effort, it was not possible to provide a more detailed analysis of some of the variables that may have contributed to this performance (e.g., fatigue).

The present study also examined self-reports of the amount of effort that were exerted during completion of the VIP subtests and found no difference between people with CFS and healthy controls, suggesting that the task was equally effortful

for both groups. In contrast, the CFS group reported experiencing significantly reduced energy levels while completing the VIP, compared to the Control group. This may be because the CFS group had lower perceived energy levels to begin with, felt more depleted of energy while performing at a similar level to the controls, were more sensitive to energy level, or were over-reporting symptoms.

Also important is the finding that the receipt of compensation or a disability pension by persons with CFS did not have an impact on effort in the current sample. This contrasts with the findings of a study of fibromyalgia (a related condition), which found that 30% of persons who were in receipt of disability benefits (and, like this study, were not being tested to determine compensation) failed tests of effort (Gervais et al., 2001). The impact of compensation on effort now needs to be examined in a sample of people with CFS who are undergoing cognitive testing for the purposes of compensation, and for whom compensation status can be independently verified, in order to determine whether the current findings are replicated. In addition, whether CFS participants meet the criteria for definite, probable or possible malingering neurocognitive dysfunction (Slick et al., 1999) remains to be investigated.

There are a number of limitations that warrant consideration when considering the results of this study. Firstly, while the VIP has been extensively validated using clinical samples, computer-generated random responses were also included as a 'participant' group; when these responses are removed, the sensitivity and specificity of the VIP are reduced (Ross & Adams, 1999). Hence, the VIP may not be as sensitive as it claims to be and, consequently, may not have detected all instances of suboptimal performance. Only a single test of effort was used due to its lengthy administration time (approximately 50 minutes). If shown to have greater classification accuracy, the inclusion of additional tests of effort may increase the

certainty of these findings. The fact that all participants volunteered for this study also suggests a certain level of motivation that may not be evident in groups tested for other reasons. Finally, the single item self-report measures of effort and energy used in this study have not been independently validated.

Conclusion

The VIP performance of a group of people diagnosed with CFS, 44% of whom were currently in receipt of compensation, suggested that they intended to perform well with high levels of effort ('compliant' VIP response style). Moreover, the three people who performed sub-optimally did not intend to do so; rather their performance was more likely to be indicative of other factors, such as fatigue. Thus, in clinical settings where persons with CFS are referred for cognitive testing, it is likely their test performance will provide a valid assessment of their cognitive ability.

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Chapter 5: Study 2 (Part 2)

Cognitive deficits in Chronic Fatigue Syndrome and their relationship to psychological status, symptomatology and everyday functioning.

This chapter consists of a published paper, reprinted with permission. The paper is presented in a format common with the body of the thesis in this chapter, and in the format of the journal in Appendix C.

Cockshell, S. J., & Mathias, J. L. (2013). Cognitive deficits in Chronic Fatigue Syndrome and their relationship to psychological status, symptomatology and everyday functioning. *Neuropsychology, 27*(2), 230-242.

Preamble

The meta-analysis (Study 1, Chapter 3) identified deficits in simple and complex information processing speed and sustained working memory. In the current paper, people with CFS and matched healthy controls were compared on measures of cognitive functioning that were selected from the preceding meta-analysis. Test were selected from domains in which deficits had been identified, as well as from several domains in which the CFS group had not shown impairment, to assess the possibility of effects of a more global impairment due to fatigue and/or depression. Only data from participants demonstrating high levels of effort and an intention to perform well (see Chapter 4) were analysed. Those test scores on which the CFS group was impaired were correlated with measures of psychological status, CFS symptomatology and daily functioning to study their relationship with cognitive functioning.

Cognitive Deficits in Chronic Fatigue Syndrome and Their Relationship to Psychological Status, Symptomatology and Everyday Functioning

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Abstract

Objective: To examine cognitive deficits in people with Chronic Fatigue Syndrome (CFS) and their relationship to psychological status, CFS symptoms, and everyday functioning.

Method: The current study compared the cognitive performance (reaction time, attention, memory, motor functioning, verbal abilities and visuospatial abilities) of a sample with CFS (n = 50) with that of a sample of healthy controls (n = 50), all of whom had demonstrated high levels of effort and an intention to perform well, and examined the extent to which psychological status, CFS symptoms, and everyday functioning were related to cognitive performance.

Results: The CFS group showed impaired information processing speed (reaction time), relative to the controls, but comparable performance on tests of attention, memory, motor functioning, verbal abilities and visuospatial abilities. Moreover, information processing speed was not related to psychiatric status, depression, anxiety, the number or severity of CFS symptoms, fatigue, sleep quality, or everyday functioning.

Conclusion: A slowing in information processing speed appears to be the main cognitive deficit seen in persons with CFS whose performance on effort tests is not compromised. Importantly, this slowing does not appear to be the consequence of other CFS-related variables, such as depression and fatigue, or motor speed.

Keywords: chronic fatigue syndrome, cognitive problems, depression, symptoms, everyday functioning

Introduction

Chronic Fatigue Syndrome (CFS) is characterized by severe and unexplained fatigue that is present for at least 6 months, does not reduce with rest, and results in a substantial reduction in work and leisure activities (Fukuda et al., 1994). Secondary symptoms include problems with memory and concentration, which are reported by 89% of people (Jason et al., 1999), as well as postexertional malaise, unrefreshing sleep, tender lymph nodes, muscle pain, multijoint pain, sore throat and headaches. Moreover, medical and psychiatric explanations for these symptoms must be excluded before a diagnosis of CFS can be made (Fukuda et al., 1994).

Given the high prevalence of self-reported memory and concentration problems, research has focused on whether CFS is associated with deficits on objective cognitive tests and some of the variables that may contribute to the development of these problems (for reviews see Cockshell & Mathias, 2010; Michiels & Cluydts, 2001; Tiersky, Johnson, Lange, Natelson, & DeLuca, 1997). Although some studies have found deficits on cognitive testing (e.g. Claypoole et al., 2007; DeLuca et al., 2004a; Thomas & Smith, 2009), others have not (e.g. Krupp, Sliwinski, Masur, Friedberg, & Coyle, 1994; Short, McCabe, & Tooley, 2002); suggesting that between-study differences in methodology may be contributing to these findings. More specifically, small samples, which may limit statistical power, and the use of different diagnostic criteria, methods of diagnosis, and types of control groups (or poorly matched controls), may contribute to the divergent findings (see Michiels & Cluydts, 2001; Tiersky et al., 1997).

Recent research has begun to address some of these limitations by more clearly describing the diagnostic procedures that are used to establish CFS and by using well-matched control groups and larger samples (e.g. Claypoole et al., 2007; Thomas & Smith, 2009); however a number of important issues have yet to be addressed. In particular, a wide variety of different cognitive tests have been used to assess cognition and very few studies have reported effect sizes, making it difficult to compare findings. To this end, Cockshell and Mathias (2010)

meta-analyzed data from 50 studies that compared the cognitive functioning of CFS and healthy control groups. They concluded that CFS is associated with moderate to large deficits in information processing speed and working memory, as assessed by tests of reaction time (RT), attention and verbal memory. Fine motor speed, vocabulary, cognitive reasoning and global functioning, on the other hand, all appear to be unaffected by CFS. Although this and a number of previous reviews have consolidated the research literature (e.g. Michiels & Cluydts, 2001; Moss-Morris, Petrie, Large, & Kydd, 1996; Tiersky et al., 1997), the contribution of other potentially confounding variables, such as psychological problems (e.g., depression and anxiety), CFS symptoms (e.g., fatigue, sleep) and test effort, to the cognitive performance of persons with CFS remains poorly understood. Furthermore, the real-world impact of these cognitive problems on the everyday functioning of persons with CFS has not been adequately addressed. Importantly, while these variables have all been investigated in separate studies, no single study has examined all of them in the same sample.

Psychological status

Community studies have found high rates of psychological problems, predominately major depression, in people with CFS (36-55%, Fuller-Thomson & Nimigon, 2008; Jason et al., 1999), but the relationship between depression and cognitive problems in CFS remains unclear. Although the majority of studies have reported that depression and anxiety were *not* related to the cognitive problems of their CFS sample (e.g. Busichio, Tiersky, DeLuca, & Natelson, 2004; DeLuca, Johnson, Beldowicz, & Natelson, 1995; Johnson, Lange, DeLuca, Korn, & Natelson, 1997; Short et al., 2002; Thomas & Smith, 2009; Vercoulen et al., 1998), some studies have found that depression was related to cognition (Krupp et al., 1994; Marshall, Forstot, Callies, Peterson, & Schenck, 1997) and, paradoxically, others have found *fewer* cognitive problems in CFS samples *with* co-morbid depression than CFS samples without depression (Claypoole et al., 2007; DeLuca et al., 2004a; DeLuca, Johnson, Ellis, & Natelson, 1997a). Given the high frequency of depression in CFS samples and the potential for depression to independently affect cognition in those with major depression (e.g. Porter,

Bourke, & Gallagher, 2007; Zakzanis, 1998), it is important to evaluate the relationship between the two in any study of CFS.

CFS symptoms and onset

Very few studies have investigated whether the CFS symptoms, themselves, are related to cognition, with symptom severity, particularly fatigue, and sleep quality being potentially important variables. Two early studies found no relationship between fatigue and cognitive performance (Grafman et al., 1993; Vercoulen et al., 1998), but there has been limited research since that time. One exception is a study by Thomas and Smith (2009), which found that as symptom severity increased, performance on both a simple RT task and the Stroop task worsened. However, symptom severity was not related to performance on a word recall or vigilance task, despite the fact that the CFS group performed significantly more poorly on these tests. Why symptom severity is related to some cognitive deficits, but not others, remains unclear.

Sleep disturbances are reported by between 81% and 88% of people with CFS (Jason et al., 1999; Unger et al., 2004) and sleep disorders, such as sleep apnea and restless legs, have been diagnosed using objective measures (polysomnography) in 51% to 58% of people with CFS (Fossey et al., 2004; Le Bon et al., 2000), although a twin study reported a much lower rate of diagnosed disorders (5%, Ball et al., 2004). Few studies have examined the relationship between sleep and cognitive functioning despite the high frequency of sleep problems. One study reported cognitive deficits in people with CFS who had abnormal sleep (abnormal duration, problems going to sleep and/or waking up early) when compared with a CFS group with no sleep difficulties and healthy controls (Smith, Pollock, Thomas, Llewelyn, & Borysiewicz, 1996). More recently, Thomas and Smith (2009) found that poor sleep quality was associated with poor performance on a vigilance task; however when this was statistically controlled, group differences between the CFS and healthy controls remained. Hence, sleep quality may impact on cognitive functioning and should be examined in research on CFS.

Finally, two studies have examined whether the cognitive performance of persons with CFS who had a gradual onset of their symptoms differed from those who had a sudden onset (Claypoole et al., 2007; DeLuca, Johnson, Ellis, & Natelson, 1997b). Both studies found that those who had a sudden onset had greater cognitive deficits, suggesting that this variable should also be considered.

Everyday functioning

Despite reports that cognitive problems are one of the most disabling CFS symptoms (Abbey & Garfinkel, 1991; Moss-Morris et al., 1996), the relationship between cognitive status and everyday functioning has rarely been investigated. One study that examined this is that of Christodoulou et al. (1998), which found that CFS participants who failed more cognitive tests also reported more days of inactivity. In addition, a longitudinal study by Tiersky et al. (2001) found a relationship between the number of cognitive tests that were failed by participants with CFS and their overall level of disability, but not their employment status. Thus, the functional impact of CFS-related cognitive problems requires further investigation.

Effort

Cognitive testing relies on persons having both the intention to perform well and applying their best effort during the test session. However, intent and effort may be compromised by test anxiety, illness-related variables (e.g., fatigue, depression), or the motivation to gain an external reward (e.g., compensation, time off work; American Psychiatric Association, 2000), all of which may be relevant to CFS. Several studies have assessed test effort in CFS samples using purpose-designed memory tests but have revealed mixed findings. Some have found no evidence of reduced effort (Binder & Campbell, 2004; Busichio et al., 2004; Fuentes, Hunter, Strauss, & Hultsch, 2001) or that only a small proportion of participants demonstrated reduced effort (Tiersky et al., 2000; results reported in DeLuca & Tiersky, 2003), and two studies found that 23% to 30% of their CFS participants showed evidence of reduced effort (van der Werf, de Vree, van der Meer, & Bleijenberg, 2002; van der Werf, Prins, Jongen, van

der Meer, & Bleijenberg, 2000). However, it is not clear whether the memory deficits that are often associated with CFS (Cockshell & Mathias, 2010), other confounding factors (e.g. fatigue, depression), and/or intentionally poor performance (motivated by external incentives or secondary gains) are responsible for the latter findings, suggesting the need to examine test effort using measures that assess other cognitive domains and in a way that can tease apart effort and intent.

Study aims

The current study was designed to assess the cognitive functioning of persons with CFS to improve our understanding of the nature and extent of the cognitive problems associated with CFS, while also addressing the aforementioned issues. Specifically, this study (a) selected cognitive tests that have been shown to be sensitive to the deficits experienced by persons with CFS, based on a meta-analysis by Cockshell and Mathias (2010); (b) included tests of cognitive domains that do not appear be affected by CFS to ensure that any observed deficits were not merely due to the pervasive effects of fatigue or depression on cognition; (c) used strict criteria and methods to diagnose CFS to improve sample quality (Fukuda et al., 1994); (d) restricted the age range to 18-60 years to reduce the likelihood of including persons who were cognitively compromised due to other undiagnosed causes (e.g., dementia) or medical conditions (e.g., cardiovascular problems); (e) matched CFS participants with healthy controls on a pairwise basis, using age, gender and education; (f) assessed the presence of comorbid psychiatric conditions, depression and anxiety levels, CFS symptoms, level of fatigue, sleep quality, the onset and duration of CFS, everyday functioning and employment status; (g) excluded any participant who demonstrated poor test effort (as described in Cockshell & Mathias, 2012); and (h) reports effect sizes to enable direct comparisons between the different tests used by this and other existing research.

Method

Participants

The CFS sample consisted of 50 people (see Table 1) who met the Centers for Disease Control (CDC) criteria for a diagnosis of CFS (Fukuda et al., 1994) and were diagnosed on the basis of medical history, physical examination, and laboratory tests to exclude other medical conditions. Potential participants were excluded if they did not meet this diagnostic criteria, were younger than 18 years or older than 60 years of age, or had a condition that may have independently impacted cognitive performance, namely prior loss of consciousness for more than 5 min, stroke, heart disease, uncontrolled high blood pressure, diabetes requiring insulin injections, seizures, and/or learning disorders (e.g. dyslexia).

Fifty-four persons were initially tested, 41 of whom were recruited from an Australian CFS patient database, which was created both for research and clinical service development and contained 71 patients (see Clark, Del Fante, & Beilby, 2006), and 13 of whom were recruited via a letter, which was sent by two general practitioners and an endocrinologist to all of their CFS patients, inviting them to participate in the study (113 letters sent, 24 responded: 21% response rate). An additional 41 participants responded but were not included (CFS database $n = 30$; letter $n = 11$) for the following reasons: Seventeen (41%) did not meet one or more of the inclusion criteria, 19 (46%) were not available for testing, two (5%) were too unwell to participate, and three (7%) declined to participate after being contacted. Four of the 54 CFS participants who underwent cognitive testing were excluded because their performance on an effort test (Validity Indicator Profile) was classified as being 'invalid', reflecting poor effort but an intention to do well (see Cockshell & Mathias, 2012), leaving valid data for the final sample of 50 CFS participants. This sample size is in the upper range of those reported by other studies of CFS ($M = 30$ CFS participants, averaged across 50 studies; Cockshell & Mathias, 2010).

Fifty-four healthy controls (see Table 1) were individually matched to the CFS participants on the basis of age, gender, and educational level. They were recruited from the

family and friends of the CFS participants (n = 13, 24%), to assist in finding suitable sociodemographic matches, and the general community (e.g. government employees, community groups; n = 41, 76%). No participant in this group had a past or present diagnosis of CFS and none met any of the aforementioned exclusion criteria. However, during the recruitment process, 11 potential controls had to be excluded: Seven (64%) did not meet one or more of the inclusion criteria, two (18%) were not suitable matches for anyone in the CFS group, and two (18%) were not available when it came to scheduling the test sessions. As was the case for the CFS group, four of the 54 healthy controls who initially underwent cognitive testing were excluded because their performance on the Validity Indicator Profile was classified as 'invalid' (see Cockshell & Mathias, 2012), resulting in a final sample of 50 healthy controls.

Measures

Cognitive tests.

Tests were selected to assess cognitive domains that have been shown to be impaired by CFS (RT, attention and memory), based on the findings of a recent meta-analysis (Cockshell & Mathias, 2010), as well as domains that do not appear to be impaired by CFS (motor, verbal abilities, visuospatial abilities) to ensure that any resultant deficits were not simply reflecting the general effects of fatigue and/or depression. Similarly, when tests provided multiple alternative scores, the aforementioned meta-analysis was used to select those scores that best differentiated between CFS and healthy controls.

Visual RT was assessed using a simple task (simple RT), modeled on that of Western and Long (1996), and a two-choice task (choice RT), based on that of DeLuca et al. (2004a). Briefly, the task presented a cross in the centre of the screen (prime), after which either a circle or square appeared in the same location (following a 0.5-, 1.0-, 1.5-, 2.0-, or 2.5-s delay). For the simple RT task, participants pressed the *spacebar* whenever the circle or square appeared (10 practice trials, 50 trials). The choice RT task required participants to

respond with the *spacebar* when a circle randomly appeared and then when the square appeared (10 practice trials, 100 trials for each choice), or vice versa. Thus, the same response was required for both simple and choice RT tasks.

Attention was assessed using the Stroop Color-Word Interference Test from the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) and the Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977). The Stroop task requires participants to name color patches, read color words printed in black, and then name the color of color words which are printed in a different color, with the score for the final trial measuring "interference" (maximum = 180 seconds). The PASAT uses 50 prerecorded strings of single-digit numbers (1-9), which are presented at four different speeds (2.4, 2.0, 1.6, 1.2 s). Every new number must be added to the last and the answer verbalised (e.g., "4" "5", 4 + 5 = answer 9, next number is "1", 5 + 1 = answer 6). The PASAT score represents the sum of the total correct responses over the four intervals (range = 0–196).

Memory was assessed using both verbal (California Verbal Learning Test II, CVLT II; Delis, Kramer, Kaplan, & Ober, 2000) and visual (Rey-Osterreith Complex Figure Test; ROCFT) tests. Only the short-delay (postinterference trial) and long-delay (20 min) free and cued recall and recognition trial scores of the CVLT were used for present purposes. The ROCFT provides a copy score (used to measure visuospatial ability), as well as a 3-min recall, and 20-min delayed recall.

The Finger Tapping Test (FTT; Reitan & Wolfson, 1993) was used to assess fine motor skill. Participants were required to use their index finger (dominant hand only) to press a key as many times as they could in 10 s, with the number of taps per trial averaged across five trials (if within 10 taps of each other), with up to 10 trials offered to achieve this or the 10 trials averaged.

The D-KEFS Verbal Fluency Test provided a measure of verbal ability, with participants required to provide as many words as they could in 60 s for each of the letters F, A, and S,

and then the categories of animals and boys' names. The total number of correct responses for both the letters and categories were analysed.

Psychological status.

Psychiatric symptomatology was examined using the Mini-International Neuropsychiatric Interview (MINI) Major Depressive Episode, Dysthymia, and Generalized Anxiety Disorder modules (Version 5.0.0; Sheehan et al., 1998) with the Alcohol Dependence and Abuse and the Substance Dependence and Abuse modules additionally used to exclude any participants who met these criteria (no CFS or control participant was excluded on this basis).

Depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), which requires participants to rate their depression and anxiety symptoms (scores range from 0 to 21). A cut-off score of ≥ 11 is frequently used to identify clinical levels of depression and anxiety in the general population (Zigmond & Snaith, 1983); this cut-off was used for the control group. However, a lower cut-off of ≥ 9 has been recommended for use with CFS participants (when compared to gold standard measures; Morriss & Wearden, 1998) and was adopted here.

CFS symptoms.

CFS symptomatology was assessed using the CDC CFS Symptom Inventory, which measures the presence, frequency, severity and duration of each of eight CFS symptoms over the past month (sore throat, tender lymph nodes, fatigue after exertion, muscle aches and pains, joint pain, unrefreshing sleep, headache, and memory and concentration problems). A case definition score for this measure was calculated by multiplying the frequency of each symptom by its severity and then summing the scores (range = 0-128; Wagner et al., 2005). The severity of each CFS symptom was also captured on the day of testing (0 = *not present*, 1 = *mild*, 2 = *moderate*, 3 = *severe*). Fatigue severity during the previous 2 weeks was assessed using the eight-item Fatigue subscale of the Checklist of Individual Strength (Vercoulen et al., 1994), with scores ranging between 0 (*no fatigue*) and 7 (*high level of fatigue*). Sleep quality was assessed using the Pittsburgh Sleep Quality Index, which involves rating 19 sleeping

habits (e.g., quality, duration, medication usage) over the past month in order to provide an overall measure of sleep quality that ranges between 0 (*no difficulty*) and 21 (*severe difficulties*), with a score over 5 indicating that a person is a poor sleeper (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989).

Everyday functioning.

Everyday functioning during the previous month was assessed using the Medical Outcomes Study Short Form 36 (SF-36; Ware & Kosinski, 2001), which asks 11 questions about physical and mental health and its impact on daily functioning, work and social activities. Scores were calculated for two primary scales (Physical and Mental Component scales) and eight subscales (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, Mental Health). Finally, employment status was classified as full or part time (working or studying), home duties, unemployed, or unable to work.

Procedure

All participants were administered the cognitive tests and the MINI structured interview in a single session, either at The University of Adelaide or in the participants' homes. Tests were ordered in one of two ways, which were counterbalanced across participants. Questionnaires were posted to participants and completed in the few days immediately prior to testing and then returned to the researcher (SJC) on the day of testing. The study protocol was approved by The University of Adelaide Human Research Ethics Committee and written informed consent was obtained from each participant.

Analysis

One-way analyses of variance (ANOVAs) were used to compare the demographic data for the CFS and healthy control groups and their performance on the cognitive tests, with a significance level of .01 chosen to control for an increased likelihood of Type I errors due to

multiple comparisons, while also limiting the risk of Type II errors. Cohen's *d* effect sizes were also calculated for the cognitive tests to provide a standardized measure of the magnitude of differences with $d = 0.2$, $d = 0.5$ and $d = 0.8$ indicating small, medium, and large effects, respectively (Cohen, 1988). All effect sizes were standardized to ensure that a positive effect reflected impaired performance in the CFS group.

Additional analyses were conducted for the cognitive tests that showed significant group differences. Specifically, the cognitive scores for the CFS group were correlated (Pearson *r*) with their self-report measures of psychological status, CFS symptoms and everyday functioning, again using an alpha of .01 to balance the risk of making Type I and II errors. Correlations were additionally interpreted in terms of their associated effect size, with $r = .1$, .3 and .5 equating to small, medium, and large effects, respectively (Cohen, 1992). Where there were significant correlations, these variables were entered as independent variables into a regression analysis of the cognitive score (dependent variable) in order to determine their relative contribution to cognitive performance. Furthermore, the cognitive performance of a number of CFS subgroups (gradual vs sudden onset; co-morbid psychiatric diagnosis: yes/no; employment status: yes/no) were compared using one-way ANOVAs to determine whether there were specific CFS subgroups that experienced more problems.

Results

As can be seen from Table 1, the study participants were primarily middle-aged women, with a tertiary-level education and high-average intelligence. Importantly, the CFS and control groups did not differ in terms of gender, age, education and National Adult Reading Test-estimated IQ, indicating that they were well matched, and demographically comparable. The majority of people with CFS reported a sudden onset of the condition, as opposed to a gradual development over weeks or months (see Table 1), and many had lived with the condition for over a decade (see Table 1; *Mdn* = 7.3 years, range = 1.3-48 years).

Table 1. CFS and Healthy control group characteristics. Scores are means (and SDs) unless indicated as a percentage.

	CFS (*n* = 50)		**Healthy (*n* = 50)**		**Test Statistic**	***p***	**Cohen's *d***
Gender					χ^2 (98) = 0.00	1.00	
Female	78%		80%				
Male	22%		20%				
Age (years)	42.2	(12.2)	42.0	(12.2)	*F*(98) = 0.01	0.93	-0.02
Education (years)	15.1	(3.1)	15.5	(2.9)	*F*(98) = 0.62	0.43	0.16
NART estimated IQ	112.7	(4.9)	112.8	(4.6)	*F*(98) = 0.01	0.93	0.02
CFS onset							
Sudden	64%						
Gradual	36%						
CFS Duration (years)	11.3	(10.0)					

CFS symptoms

Over the preceding month, participants reported experiencing an average of six out of eight symptoms (*SD* = 1.6) on the CDC CFS Symptom Inventory, with the most common symptoms being fatigue after exertion, muscle aches and pains, and unrefreshing sleep (see Table 2). Problems with memory and concentration were also reported by the majority of CFS participants, compared with none in the healthy control group. Overall, the severity of CFS symptoms (CDC case definition score) was high in CFS participants, and all were experiencing one or more symptoms on the day of testing (see Table 2). As expected, the number and severity of symptoms were significantly greater and worse, respectively, in the CFS participants than the healthy controls, with very large differences in general and on the day of testing.

Table 2. Self-report data for CFS and Healthy control group. Scores are means (SDs) unless indicated as a percentage.

	CFS		Healthy		*F* test (df = 98)	*p*	Cohen's *d*
CFS Symptoms							
CDC CFS Symptom Inventory							
Fatigue after exertion	94%		2%				
Muscle aches and pains	90%		30%				
Unrefreshing sleep	90%		36%				
Concentration	82%		0%				
Headaches	72%		26%				
Joint	70%		16%				
Memory	62%		0%				
Lymph nodes	54%		6%				
Sore throat	42%		4%				
No. of symptoms	6.0	(1.6)	1.2	(1.4)	247.91	0.00**	-3.15
Case Definition score	41.3	(19.3)	4.6	(7.2)	157.80	0.00**	-2.51
No. of CFS symptoms - day of testing	5.2	(2.0)	0.8	(1.1)	194.43	0.00**	-2.79
Fatigue							
Checklist of Individual Strength							
Fatigue subscale	5.7	(0.8)	2.8	(1.3)	202.28	0.00**	-2.84
Sleep							
Pittsburgh Sleep Quality Index	9.4	(3.4)	5.0	(3.0)	47.16	0.00**	-1.37
Poor sleepers (> 5)	92%		34%				
Everyday Functioning							
Employment Status ˜							
Employed – full time/part time	10/18%		70/16%				
Studying – full time/part time	8/10%		8/0%				
Home duties	14%		4%				
Unable to work	42%		0%				
Other (retired)	0%		2%				
Medical Outcomes Study Short Form 36 (SF-36)							
Physical Component Scale	30.3	(9.0)	55.3	(6.8)	245.22	0.00**	3.13
Mental Component Scale	45.7	(9.0)	50.7	(8.8)	8.17	0.01**	0.57
Physical Functioning	44.1	(21.9)	92.3	(13.4)	176.25	0.00**	2.66
Role-Physical	10.5	(22.1)	90.0	(24.2)	294.31	0.00**	3.43
Bodily Pain	50.3	(22.4)	83.8	(17.7)	68.62	0.00**	1.66
General Health	31.0	(14.7)	80.0	(14.5)	281.97	0.00**	3.36
Vitality	23.1	(13.9)	62.2	(20.4)	125.68	0.00**	2.24
Social Functioning	46.3	(21.6)	91.0	(16.9)	132.73	0.00**	2.30

	CFS		Healthy		*F* test (df = 98)	*p*	Cohen's *d*
Role-Emotional	64.7	(40.1)	87.3	(28.5)	10.63	0.00**	0.65
Mental Health	72.00	(14.5)	77.7	(15.0)	3.71	0.06	0.39
Psychological Status							
Mini International Neuropsychiatric Interview							
Major Depressive Episode	8%		0%				
Dysthymia	6%		0%				
Generalized Anxiety Disorder	10%		0%				
Hospital Anxiety & Depression Scale							
Clinical Depression ^	18%		0%				
Clinical Anxiety ^	30%		8%				
Depression Score	5.8	(3.2)	2.0	(2.1)	45.88	0.00**	-1.35
Anxiety Score	7.0	(4.0)	5.3	(3.6)	5.03	0.03	-0.45

˜ Note: CFS participants total 102% as one participant was employed part time and studying part time
^ Note: CFS ≥ 9; Controls ≥ 11; 10% of CFS participants scored in the clinical range for both Depression and Anxiety, resulting in a total of 38%
**$p < 0.01$

The CFS group also had significantly more fatigue and poorer quality of sleep than healthy controls, with large effect sizes evident for both measures (Checklist of Individual Strength Fatigue subscale and Pittsburgh Sleep Quality Index; see Table 2). Sleep problems were identified in almost all CFS participants, with 92% classified as poor sleepers (score > 5) on the Pittsburgh Sleep Quality Index. In contrast, only 34% of controls were classified as poor sleepers.

Everyday functioning.

Everyday functioning was measured using employment status and the SF-36. Although over half of the CFS participants were employed, studying or engaged in home duties, the majority of employed people worked only on a part-time basis and a very large number were unable to work (see Table 2). These results contrast strongly with those of the control group, in which the majority was employed and none were unable to work. In line with this, there were significant differences between the two groups in terms of their ability to work (χ^2 (1, N = 100) = 24.11, p = .00, phi = -0.52, with Yates continuity correction). CFS participants were also significantly more impaired than the healthy controls on the SF-36 Physical and Mental

Component scales, with these differences equating to very large and moderate effect sizes, respectively. Mental Health was the only SF-36 subscale that did not differ between the two groups, with the CFS group showing significantly more impairments on the remaining subscales. Moreover, these group differences were very large with one exception: The Role-Emotional subscale showed a moderate difference (see Table 2).

Psychological status.

Psychological status was captured using the MINI (Sheehan et al., 1998) and the HADS. A total of 11 CFS participants had one or more psychiatric conditions, based on their responses to the MINI (see Table 2). Four CFS participants met the criteria for a major depressive episode, however, a number of these criteria overlap with CFS symptoms (i.e., feeling tired and without energy, difficulty concentrating), possibly confounding the two. When affirmative responses to these two items were removed, none of the participants continued to meet the criteria for major depressive episode. The removal of these symptoms also reduced the number of CFS participants meeting the criteria for dysthymia from three to two, and for generalized anxiety disorder from five to four. None of the control group met the criteria for any psychiatric disorder.

Although the majority of participants scored within the normal range on the HADS, the CFS group had significantly higher mean scores on the Depression subscale than the healthy controls, equating to a large group difference (see Table 2), but were not significantly more anxious (low-moderate *d*). Of the 11 CFS participants who were identified as possibly having a psychiatric condition on the MINI, eight had clinical levels of depression or anxiety on the HADS. However, a further 11 CFS participants scored within the clinical range on the HADS without meeting the MINI criteria for a diagnosis of depression, anxiety or dysthymia.

Cognitive performance

Summary cognitive data for the CFS and control groups are provided in Table 3, where it can be seen that both simple and choice RTs were significantly slower in the CFS group. Moreover, these differences do not appear to be due either to simple motor slowing or to the groups differentially trading speed for accuracy, as there were only small to low-moderate and non-significant group differences in finger tapping (motor) performance and the mean number of errors on the choice RT task. In addition, the group differences on the simple and choice RT tests remained after controlling for motor performance using FTT scores as a covariate in an analysis of covariance (ANCOVA): simple RT, F (1, 96) = 18.2, p = .00, partial eta squared = .16; choice RT, F (1, 96) = 13.7, p = .00, partial eta squared = .13. The group difference in choice RT appears to be due to a slowing in basic information processing speed, as this difference was no longer significant after entering simple RT as a covariate in an ANCOVA, F (1, 96) = 0.7, p = .42, partial eta squared = .00. There were no other significant differences in performance on the measures of attention (PASAT, Stroop), verbal (CVLT) or visual (ROCFT) memory, verbal fluency (FAS, Category), or visuospatial ability (ROCFT copy), and all were associated with small effects.

Relationship between cognition, psychological status, symptoms and functioning in CFS

The scores for the two cognitive tests that were impaired in the CFS group (simple RT, choice RT) were then correlated with demographic data (age, education, IQ estimate), CFS-specific information (CFS duration and symptoms), and the self-report measures (HADS, Pittsburgh Sleep Quality Index, SF-36 Physical and Mental Component subscales) to determine whether they were related. These analyses revealed that simple RT and choice RT were significantly related to age, and simple RT was significantly related to National Adult Reading Test-estimated IQ, such that slower RT speed was related to higher IQ (see Table 4). All other correlations were non-significant at the .01 level. An examination of the scatterplot for simple RT and IQ suggests that this relationship appeared to be influenced by the performance of a single CFS participant who had the highest IQ (124) but had a mean RT of

Table 3. Cognitive scores for the CFS and Healthy control groups

Cognitive Domain **Test Name (units)**	**CFS**		**Healthy**		***F* test**[+]		**Cohen's *d***
	Mean	**(SD)**	**Mean**	**(SD)**	***F***	***p***	
Reaction Time							
Simple RT (ms)	345.5	(60.9)	295.4	(53.3)	18.97	0.00**	**0.88**
Choice RT (ms)	464.9	(87.4)	406.9	(60.8)	14.78	0.00**	**0.77**
Choice RT Errors (count)	1.8	(1.8)	2.7	(2.9)	3.94	0.05	0.40
Motor Functioning							
Finger Tapping Test (count)	46.0	(8.4)	47.5	(7.9)	0.84	0.36	0.18
Attention							
Paced Auditory Serial Addition Test (correct)	160.2	(21.5)	165.9	(19.9)	1.87	0.18	0.27
Stroop (seconds)	52.8	(11.8)	48.4	(9.6)	4.20	0.04	0.41
Memory							
California Verbal Learning Test II (correct)							
- List A Trials 1-5	52.7	(10.2)	54.8	(7.3)	1.37	0.25	0.23
- Short Delay Free Recall	11.4	(2.7)	12.0	(2.7)	1.49	0.23	0.24
- Short Delay Cued Recall	12.5	(2.5)	12.7	(2.4)	0.17	0.68	0.08
- Long Delay Free Recall	12.0	(2.8)	12.2	(2.8)	0.18	0.67	0.09
- Long Delay Cued Recall	12.5	(2.6)	12.9	(2.6)	0.64	0.43	0.16
- Recognition	15.0	(1.2)	15.2	(1.0)	0.85	0.36	0.18
Rey Osterreith Complex Figure Test (correct)							
- Recall 3min	16.6	(5.6)	18.3	(5.0)	2.39	0.13	0.31
- Long Delay Recall 20min	16.5	(5.1)	17.7	(5.2)	1.34	0.25	0.23
Verbal Ability							
Verbal Fluency (correct)							
- FAS	43.4	(10.1)	43.0	(10.0)	0.03	0.87	-0.03
- Category	45.5	(8.7)	46.7	(8.6)	0.49	0.48	0.14
Visuospatial Ability							
Rey Osterreith Complex Figure Test (correct)							
- Copy	27.6	(2.3)	28.2	(2.8)	1.43	0.24	0.24

[+] *df* =98 for all ANOVAs except all Reaction Time measures, the PASAT and ROCF Recall where *df* = 97
**$p < 0.01$

Table 4. Simple and Choice RT for CFS participants related to demographic information, CFS symptoms, everyday functioning and psychological status

	Simple RT (*n* = 49)		Choice RT (*n* = 49)	
	r	***p***	***r***	***p***
Age	0.37	0.01**	0.59	0.00**
Education	0.21	0.15	0.14	0.35
Estimated IQ	0.40	0.00**	0.30	0.03
CFS Symptoms				
CDC CFS Symptom Inventory				
No. of symptoms	0.03	0.88	0.04	0.78
Case Definition score				
No. of CFS symptoms - day of testing	-0.14	0.35	-0.06	0.70
Fatigue				
Checklist of Individual Strength				
Fatigue subscale	-0.09	0.52	-0.14	0.34
Sleep				
Pittsburgh Sleep Quality Index	0.03	0.85	0.07	0.64
Everyday Functioning				
Medical Outcomes Study Short Form 36 (SF-36)				
Physical Component Scale	0.03	0.83	-0.03	0.84
Mental Component Scale	-0.11	0.45	-0.14	0.34
Physical Functioning	-0.16	0.28	-0.27	0.06
Role-Physical	-0.06	0.69	0.00	0.98
Bodily Pain	0.07	0.64	-0.06	0.70
General Health	0.03	0.82	0.06	0.71
Vitality	0.36	0.01	0.28	0.05
Social Functioning	-0.14	0.34	-0.21	0.15
Role-Emotional	-0.25	0.08	-0.32	0.02
Mental Health	-0.03	0.82	-0.01	0.97
Psychological Status				
Hospital Anxiety & Depression Scale				
Depression Score	0.03	0.82	0.05	0.74
Anxiety Score	-0.05	0.71	-0.15	0.31

**$p < 0.01$

612ms (nearly double the group mean). This person also had the second slowest FTT performance. When the data was reanalyzed with this outlier removed, the correlation between simple RT and IQ was rendered non-significant (r = .26, n = 48, p = .08), but the relationship between simple RT and age (r = .37, n = 48, p = .01) and the difference in simple RT performance between the CFS and healthy controls, F (1, 96) = 19.0, p = .00, remained significant.

Next, we performed a series of analyses to determine whether there were specific subgroups of CFS participants that had slower simple and choice RTs. These analyses examined onset (gradual vs. sudden), work status (employed/studying/home duties vs. unable to work), and psychological status (MINI psychiatric diagnosis vs. no psychiatric diagnosis; HADS depressed vs. nondepressed, anxious vs. nonanxious). As can be seen in Table 5, these analyses revealed that there were no significant differences in cognition for any of the subgroup comparisons, suggesting that differences in symptom onset and both psychiatric and employment status were not contributing to the slower RTs of the CFS group. This was also confirmed by the small Cohen's *d* effect sizes.

Contrary to our original statistical plan, we did not perform a regression analysis exploring the relative influence of CFS symptomatology, psychological status, and everyday functioning on cognitive functioning, as Tabachnick and Fidell (2007) suggest that correlations above .3 are needed to reliably perform such an analysis. As seen in Table 5, almost all correlations fell below this threshold.

Discussion

The current study assessed the cognitive functioning of persons with CFS using tests that have previously been shown to be sensitive to the deficits experienced by persons with CFS while also examining domains that are not affected by CFS to ensure that any observed deficits were not due to the pervasive effects of fatigue or depression on cognition. It used strict criteria and methods to diagnose CFS to improve sample quality and restricted the age

Table 5. Reaction Time performance for CFS subgroups: CFS onset, employment status and psychiatric status

	M	**(SD)**	**M**	**(SD)**	**ANOVA**		**Cohen's**
					***F*(1,47)**	***p***	***d*[+]**
	CFS onset						
	Sudden (N = 32)		Gradual (N = 17)				
Simple RT	345.9	(71.7)	344.7	(34.0)	0.00	0.95	0.02
Choice RT	460.9	(96.4)	472.5	(68.5)	0.19	0.66	-0.13
	Employment status						
	Employed (*n* = 29)		Unable to work (*n* = 20)				
Simple RT	351.6	(74.0)	336.6	(34.1)	0.71	0.40	0.25
Choice RT	470.1	(93.6)	457.3	(78.5)	0.25	0.62	0.15
	Psychiatric status						
	MINI psychiatric diagnosis (*n* = 11)		MINI no psychiatric diagnosis (*n* = 38)				
Simple RT	338.1	(63.6)	347.6	(60.8)	0.20	0.66	-0.15
Choice RT	452.2	(93.6)	468.6	(86.1)	0.30	0.59	-0.19
	HADS clinical depression (*n* = 9)		HADS no clinical depression (*n* = 40)				
Simple RT	354.8	(57.8)	343.4	(62.1)	0.26	0.62	0.19
Choice RT	493.0	(87.5)	458.6	(86.9)	1.15	0.29	0.40
	HADS clinical anxiety (*n* = 15)		HADS no clinical anxiety (*n* = 34)				
Simple RT	340.6	(66.2)	347.6	(59.3)	0.13	0.72	-0.11
Choice RT	448.2	(89.8)	472.2	(86.3)	0.79	0.38	-0.27

[+] Positive effect sizes indicate RTs of the groups in the first column (sudden onset, employed and with a psychiatric condition) were slower than that of the groups in the second column, and negative effect sizes indicate the reverse.

range (18-60 years), thereby reducing the likelihood of including persons who were cognitively compromised because of other undiagnosed conditions (e.g., dementia, cardiovascular problems). The controls were carefully matched on a pairwise basis (age, gender, education) and a variety of potentially confounding variables were examined (e.g., comorbid psychiatric conditions, depression & anxiety, CFS symptomatology, fatigue, sleep, onset and duration of CFS, everyday functioning, and employment status). Moreover, participants who demonstrated poor test effort were excluded to ensure that suboptimal performance did not contribute to the study findings (Cockshell & Mathias, 2012).

Overall, the CFS group showed large and significant impairments in simple and choice RTs, compared to healthy controls, with normal functioning in all other cognitive domains (attention, memory, motor functioning, verbal ability, visuospatial ability). Interestingly, RT was also identified as being the most impaired cognitive domain in a recent meta-analysis (Cockshell & Mathias, 2010), with the current study finding effect sizes similar to those reported for both simple RT (current: d = 0.88, meta-analysis: d = 0.84) and choice RT (current and meta-analysis: d = 0.77). Deficits in RT do not appear to be due to a slowed motor response, as there was no group difference in motor speed (FTT) and statistically controlling for motor speed did not alter the simple or choice RT findings. However, the slowing in choice RT does appear to be the consequence of a basic slowing in information processing speed, as opposed to more complex decision making, further clarifying the nature of the problem. These findings therefore appear to be robust, especially given the strict inclusion criteria for the current study, criteria that have not been adopted by previous studies.

Contrary to expectation, there were only small and nonsignificant differences in attention between CFS and healthy controls, as measured by the Stroop and PASAT. This is consistent with the findings of some studies (e.g., Kane, Gantz, & DiPino, 1997; Mahurin et al., 2004; Short et al., 2002), but not a recent meta-analysis (Cockshell & Mathias, 2010). However, this is consistent with a factor analysis of test performance in people with CFS, which identified a three-factor structure consisting of simple speed (simple and choice RTs),

complex information processing speed (PASAT), and working memory (spatial and verbal tests; Chiaravalloti, Christodoulou, Demaree, & DeLuca, 2003). Chiaravalloti et al. (2003) concluded that complex information processing speed can be distinguished from RT and working memory; hence, it is possible for one domain to be impaired and not the others. No deficits were found using the CVLT to assess verbal memory, which is consistent with a number of studies (e.g., Fiedler, Kipen, DeLuca, Kelly-McNeil, & Natelson, 1996; Johnson, DeLuca, Fiedler, & Natelson, 1994; Tiersky, Matheis, DeLuca, Lange, & Natelson, 2003), although not all of them (e.g., DeLuca et al., 1995; Michiels, Cluydts, & Fischler, 1998; Tiersky, Cicerone, Natelson, & DeLuca, 1998), and the meta-analyzed data (Cockshell & Mathias, 2010). As expected, the current study found that the CFS group was not impaired in fine motor speed, verbal ability, and visuospatial ability.

Notably, depression did not account for the slowing in simple and choice RTs that is associated with CFS, which is also consistent with the majority of study findings (e.g., DeLuca et al., 1995; Thomas & Smith, 2009; Vercoulen et al., 1998). Moreover, CFS participants who had a comorbid psychiatric disorder did not differ in their cognitive performance from those who did not (small effect size), which is consistent with the findings of Claypoole et al. (2007), but not of DeLuca et al. (1997a), who found greater cognitive impairments in a CFS subgroup without a psychiatric disorder. Further studies are needed to clarify how psychiatric status impacts on cognitive functioning in CFS.

CFS onset (sudden vs. gradual) did not have an impact on the RT performance of this group. Two previous studies have reported poorer cognitive performance when CFS had a sudden onset; however, they found differences on the PASAT (Claypoole et al., 2007) and verbal memory (DeLuca et al., 1997b), neither of which were impaired in the current study. It is possible that the difference reported by DeLuca et al. (1997b) was confounded with psychiatric status, as there were fewer psychiatric problems in people who had a sudden onset of CFS. A related study by DeLuca et al. (1997a) found that people with CFS who did not have psychiatric problems had greater cognitive deficits, which the current study did not

replicate. Thus, there appear to be many complex elements that are involved in CFS, with psychiatric status and illness onset shown by other studies to have a role, although not supported by the current study.

The frequency and severity of CFS symptoms were also not related to RT performance. This is consistent with a longitudinal study, which found that improvements on some cognitive tests over time were not related to CFS severity (Tiersky et al., 2001); however, the authors did find a corresponding improvement in fatigue, which the current study did not replicate. Moreover, the deficits in RT were not related to sleep quality; however, it was not possible to examine whether cognitive deficits were restricted to CFS participants with a sleep disorder (as was found by Smith et al., 1996), as only four CFS participant were not classified as poor sleepers. Although high, the finding that 34% of controls were classified as poor sleepers is comparable to the 40% reported for healthy Australian adults of an equivalent age (Magee, Caputi, Iverson, & Huang, 2008).

In addition, the current study failed to find a relationship between everyday functioning (employment status, SF-36) and RT performance, which contrasts with the finding of Christodoulou et al. (1998), who found that greater inactivity was associated with poorer verbal memory (but not poorer visual memory or attention). Memory was not impaired in the current group, which may explain why this finding was not replicated. Alternatively, Tiersky et al. (2001) found that performance on some cognitive measures improved over time, and although they found that level of disability improved, employment status did not change. Hence, despite anecdotal reports that cognitive deficits are among the most disabling CFS symptoms (Abbey & Garfinkel, 1991; Moss-Morris et al., 1996), it is possible that factors other than impaired cognition may have a greater impact on everyday functioning in CFS.

Finally, many studies do not screen for test effort (e.g., Claypoole et al., 2007; Thomas & Smith, 2009), making it difficult to determine whether this has contributed to their findings (Binder & Campbell, 2004; Heilbronner et al., 2009). In the current study, 7% of the CFS and healthy control group participants were excluded from the analyses because of performance

that suggested reduced effort, although not due to intentional factors. Deficits in information processing speed were still evident when these participants were removed from the analysis, suggesting that they were not due to reduced effort.

The current study found that people with CFS are impaired in information processing speed, but not on tests of memory and attention, despite the fact that problems with memory and concentration are commonly reported in this population (Jason et al., 1999). There are a number of explanations for the incongruence between test performance and self-reported problems. First, it has been suggested that reduced information processing speed may contribute to poorer early learning on memory tasks, which people with CFS may report as memory problems (DeLuca et al., 2004; DeLuca, Johnson, Beldowicz, & Natelson, 1995). Another explanation is that objective and subjective measures may capture slightly different problems, with the two measures often only broadly similar in content. Some studies have attempted to address this by choosing measures that assess more comparable cognitive domains. This led to a closer alignment between the two types of measures in one study (e.g., actual and self-reported reading problems; Wearden & Appleby, 1997), although only for a subgroup of people with CFS who were also depressed; and not in another study (e.g., actual and self-reported addition for the PASAT; Short et al., 2002). Alternatively, it may be that people overestimate their pre-CFS abilities when rating their current performance (good-old-days phenomenon; Sullivan & Edmed, 2012) or underestimate their current ability; although, in the latter case, it has been found that CFS and healthy control groups underestimate their abilities by equal amounts (Metzger & Denney, 2002). Importantly, the disconnect between self-reported problems and objective cognitive testing is not unique to CFS, having been noted in other clinical groups, including people who have suffered a stroke (e.g., Duits, Munnecom, van Heugten, & van Oostenbrugge, 2008) or mild traumatic brain injury (e.g., Stulemeijer, Vos, Bleijenberg, & van der Werf, 2007). The relationship between objective and subjective measures of cognitive performance in CFS warrants further attention and is the subject of another study by the current investigators.

A number of limitations with the current study have been identified. First, the CFS participants may not be representative of a community sample, as the majority of them were sourced from a clinical research database. Despite this, the demographic data and clinical characteristics of the current CFS sample appear similar to those described in other studies (see Cockshell & Mathias, 2010, for a review). Secondly, psychiatric status was assessed using the MINI, which, although used in other studies of CFS, has not been validated in this population. It was selected for its short administration time; however, the current study found differences between the classification of psychiatric status for the MINI and the HADS Depression and Anxiety scales, which have been validated with CFS groups (Henderson & Tannock, 2005; Morriss & Wearden, 1998). Further research is recommended to determine whether the MINI is suitable for use in CFS research and, until such a time, psychiatric classifications that are based on the MINI should be treated with caution. Lastly, while not examined here, the relationship between personality disorders and cognitive functioning should be considered in future research. Relatively high rates of comorbid personality problems have been reported in some studies of CFS (e.g., Deary & Chalder, 2010; Henderson & Tannock, 2004; Nater et al., 2010; van Geelen, Sinnema, Hermans, & Kuis, 2007), although this finding is not universal (e.g., Courjaret, Schotte, Wijnants, Moorkens, & Cosyns, 2009; Harvey, Wadsworth, Wessely, & Hotopf, 2007; Wood & Wessely, 1999). Research with other groups (e.g., young and older adults) suggests this relationship may be worth investigating (Ayotte, Potter, Williams, Steffens, & Bosworth, 2009; Beaver, Vaughn, DeLisi, Barnes, & Boutwell, 2012; Cassimjee & Murphy, 2010), with two studies reporting a relationship between personality measures and cognitive performance in young adults (Beaver et al., 2012; Cassimjee & Murphy, 2010), and another study finding that some personality characteristics were related to better cognitive test performance in a group of depressed older adults, but not in non-depressed older adults (Ayotte et al., 2009).

Conclusion

In conclusion, the current evidence suggests that people with CFS have impaired information processing speed, when compared to healthy controls, which do not appear to be attributable to reduced test effort, depression, anxiety, fatigue, or sleep problems. Moreover, these impairments in information processing speed were not the result of motor slowing and were not related to psychological status; the number, frequency or severity of CFS symptoms; or everyday functioning.

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Chapter 6: Study 2 (Part 3)

Cognitive functioning in people with Chronic Fatigue Syndrome: A comparison between subjective and objective measures

This chapter consists of a published paper, reprinted with permission. The paper is presented in a format common with the body of the thesis in this chapter, and in the format of the journal in Appendix D.

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Preamble

The previous chapters (Chapters 3-5) have focussed on cognitive functioning in CFS and factors that may be related to deficient performance. Cognitive testing has been employed to quantify the problems with memory and concentration that form part of the diagnostic criteria for CFS (Fukuda et al., 1994). The current paper compared self-reported problems with cognitive performance, specifically matching the questionnaires to tests in the domains of memory and attention (Study 2). Participants who demonstrated suboptimal performance on a test of effort (Chapter 4) were again excluded from this analysis. Fatigue, sleep, depression and anxiety were also assessed to examine their relationship to subjective and objective measures of cognitive functioning, and the impact of cognitive testing on fatigue during and after the testing session was explored.

Cognitive functioning in people with Chronic Fatigue Syndrome:

A comparison between subjective and objective measures

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Abstract

Objective: To examine the relationship between subjective and objective assessments of memory and attention in people with chronic fatigue syndrome (CFS), using tests that have previously detected deficits in CFS samples and measures of potential confounds.

Method: Fifty people with CFS and fifty healthy controls were compared on subjective (memory and attention symptom severity, Cognitive Failures Questionnaire, Everyday Attention Questionnaires) and objective (California Verbal Learning Test, Rey-Osterreith Complex Figure Test, Paced Auditory Serial Addition Test, Stroop task) measures of memory and attention. Fatigue, sleep, depression and anxiety were also assessed.

Results: The CFS group reported experiencing more cognitive problems than the controls, but the two groups did not differ on the cognitive tests. Scores on the subjective and objective measures were not correlated in either group. Depression was positively correlated with increased severity of cognitive problems in both the CFS and control groups.

Conclusions: There is little evidence for a relationship between subjective and objective measures of cognitive functioning for both people with CFS and healthy controls, which suggests that they may be capturing different constructs. Problems with memory and attention in everyday life are a significant part of CFS. Depression appears to be related to subjective problems, but does not fully explain them.

Keywords: chronic fatigue syndrome, cognition, self-report, cognitive tests

Introduction

Chronic Fatigue Syndrome (CFS) is characterized by severe and disabling fatigue, which persists for over 6 months, does not reduce with rest, and cannot be explained by other medical or psychiatric causes (Fukuda et al., 1994). In order to meet the diagnostic criteria for CFS, this fatigue must be coupled with at least four out of eight additional symptoms: memory and attention problems, tender lymph nodes, muscle pain, multi-joint pain, sore throat, headaches, unrefreshing sleep, and post-exertional malaise (Fukuda et al., 1994). A diagnosis of CFS is therefore primarily based on self-reported symptoms and the exclusion of other differential diagnoses.

Nearly 90% of people with CFS report experiencing problems with memory and attention (Jason et al., 1999); a figure that is significantly higher than that seen in healthy samples (e.g. Ray, Phillips, & Weir, 1993; Thomas & Smith, 2009) and other clinical groups (e.g. multiple sclerosis, depression, DeLuca, Johnson, Beldowicz, & Natelson, 1995), suggesting that these problems are an important feature of CFS. This is further supported by CFS research which has found that self-reported cognitive problems predict outcomes one year later (Ray, Jefferies, & Weir, 1997) and that these problems reportedly reduce a person's ability to work and function at normal levels (Abbey & Garfinkel, 1991; Moss-Morris, Petrie, Large, & Kydd, 1996).

Research that has used objective tests to examine the cognitive problems of people with CFS has revealed mixed findings, with some studies finding significant deficits (e.g. Constant et al., 2011; Dickson, Toft, & O'Carroll, 2009; Majer et al., 2008; Van Den Eede et al., 2011) but others failing to do so (e.g. Krupp, Sliwinski, Masur, Friedberg, & Coyle, 1994; Mahurin et al., 2004; Short, McCabe, & Tooley, 2002). However, there are some notable methodological differences that may account for some of the variability in these findings (Michiels & Cluydts, 2001; Tiersky, Johnson, Lange, Natelson, & DeLuca, 1997). For example, a number of studies have failed to use either published criteria to diagnose CFS (e.g.

Krupp et al., 1994; Prasher, Smith, & Findley, 1990; Smith, Behan, Bell, Millar, & Bakheit, 1993) or matched control groups (e.g. Altay et al., 1990; McDonald, Cope, & David, 1993; Schmaling, DiClementi, Cullum, & Jones, 1994), or have only recruited very small samples, which limits statistical power (e.g. Sargent, Anderson, & Budek, 1997; Scheffers, Johnson, Grafman, Dale, & Straus, 1992). When Cockshell and Mathias (2010) meta-analyzed the data from 50 CFS studies, all of which had used published diagnostic criteria and matched control groups, they reported moderate to large deficits in processing speed, memory and attention. However, deficits were only noted for specific tests within each of these cognitive domains (e.g. attention: Stroop but not Digit Span). Hence, formal testing of people with CFS has confirmed the presence of selected deficits in the areas of memory and attention.

Interestingly, numerous studies have failed to identify a relationship between subjective (self-reports) and objective (cognitive tests) assessments of cognition in CFS samples (e.g. DeLuca et al., 1995; Short et al., 2002; Vercoulen et al., 1994; Wearden & Appleby, 1997). Nevertheless, there are only a small number of good quality studies that have explicitly analyzed this relationship (Ray et al., 1993; Short et al., 2002; Vercoulen et al., 1998; Wearden & Appleby, 1997), with the others failing to use published diagnostic criteria (Cope, Pernet, Kendall, & David, 1995; McDonald et al., 1993; Smith et al., 1993) or matched control groups (Altay et al., 1990; McDonald et al., 1993; Schmaling et al., 1994); or failing to directly examine the relationship between their self-report and test data (e.g. DeLuca et al., 1995; Fischler et al., 1996; Knoop, Prins, Stulemeijer, van der Meer, & Bleijenberg, 2007). Of these studies, none have found a relationship between subjective and objective measures of cognition (Ray et al., 1993; Short et al., 2002; Vercoulen et al., 1998; Wearden & Appleby, 1997), with all four studies finding that their CFS samples reported experiencing cognitive problems in the absence of objective deficits. Importantly, two of these studies failed to examine equivalent constructs, instead comparing an aggregate rating of different aspects of cognitive functioning with scores from specific tests of memory and attention (Ray et al., 1993) or vice versa (Vercoulen et al., 1998). Although the remaining two studies used more

comparable measures, they failed to find a relationship between the two in *both* the CFS and control groups (Short et al., 2002; Wearden & Appleby, 1997), suggesting that this dissociation may not be unique to CFS.

Several explanations have been given to explain why people with CFS report cognitive problems that are not confirmed by formal testing. Firstly, people with CFS may overestimate their pre-morbid cognitive ability ('good-old-days' phenomenon, Sullivan & Edmed, 2012) or the impact of CFS on it, leading them to underestimate their current cognitive ability and report more problems (Knoop, Prins, Moss-Morris, & Bleijenberg, 2010; Ray et al., 1993; Short et al., 2002; Wearden & Appleby, 1996). Some researchers believe that this indicates a problem with self-perception (e.g., Knoop et al., 2007; Prins, van der Meer, & Bleijenberg, 2006). However, two studies that investigated self-assessments of cognitive performance found that CFS samples were either accurate in their evaluations (Wearden & Appleby, 1997) or underestimated their performance to the same extent as that of a healthy control group (Metzger & Denney, 2002), suggesting that people with CFS either do not have a problem with self-perception or that the problem is not specific to CFS.

Alternatively, it has been proposed that people with CFS perform comparably to controls in a test situation by expending additional cognitive effort (Capuron et al., 2006; Grafman et al., 1993; Ray et al., 1993; Short et al., 2002; Wearden & Appleby, 1997), possibly contributing to the post-exertional malaise that is a defining characteristic of CFS (Fukuda et al., 1994). Consistent with this, Schmaling *et al*., (2003) found that people with CFS performed comparably to healthy controls on the Paced Auditory Serial Addition Test but exerted more cognitive effort in order to achieve this level of performance. However, another study found that CFS and control groups both rated their level of cognitive effort as high while doing a cognitive task (Scheffers et al., 1992). Of the two studies that have specifically explored the impact of cognitive testing on fatigue, one concluded that cognitive effort did not impact on cognitive functioning or fatigue when testing occurred on consecutive days (Marshall, Forstot, Callies, Peterson, & Schenck, 1997) and the other reported that all CFS

participants found the examination tiring, but debilitating fatigue was only experienced by a subgroup on the day after testing (Grafman et al., 1993). Hence, people with CFS may perform comparably to their peers by expending additional cognitive effort, and this may subsequently impact on their levels of fatigue.

Finally, both cognitive performance and perceived cognitive problems may be influenced by a number of other variables, such as fatigue, sleep, depression and anxiety; which may further complicate the relationship between the objective and subjective measures. Specifically, fatigue has been associated with poorer performance on selected cognitive tests (Thomas & Smith, 2009) and with more self-reported cognitive problems (Ray et al., 1993; Vercoulen et al., 1998), although not all studies support these findings (Grafman et al., 1993; Short, McCabe, & Tooley, 2002; Vercoulen et al., 1998). Few studies have examined sleep: one found that poor sleep was related to cognitive problems (Smith, Pollock, Thomas, Llewelyn, & Borysiewicz, 1996) and another that these problems remained after controlling for sleep quality (Thomas & Smith, 2009), but its relationship to subjective problems has yet to be investigated. Lastly, while the majority of studies have found that depression and anxiety are not related to the cognitive performance of persons with CFS (e.g. Busichio, Tiersky, DeLuca, & Natelson, 2004; DeLuca, Johnson, Beldowicz, & Natelson, 1995; Thomas & Smith, 2009; Vercoulen et al., 1998), depression/emotional distress has repeatedly been associated with cognitive complaints (Ray et al., 1993; Vercoulen et al., 1998; Wearden & Appleby, 1997). In contrast, anxiety was not found to be related to self-reported cognitive problems; albeit in samples with low levels of anxiety (Short et al., 2002; Wearden & Appleby, 1997). Thus, there are either inconsistent findings or data that indicates that these variables may have a differential impact on the cognitive performance and self-reports of cognitive problems of persons with CFS; highlighting the need to consider these variables when examining the relationship between objective and subjective measures of cognition in CFS samples.

Given the frequency of self-reported cognitive problems and their role in the diagnosis of CFS, it is important to understand the basis of these reports and whether they reflect objectively measured cognitive deficits or perceived problems that are better accounted for by other factors. However, much of the existing research has failed to use comparable measures (i.e., general reports correlated with specific tests), published CFS diagnostic criteria and matched control groups, and/or failed to examine important confounding variables (e.g., fatigue, depression). The current study examined this topic, addressing each of these limitations, as part of a broader study investigating the cognitive deficits that are experienced by persons with CFS and their relationship with psychological status, CFS symptoms, and everyday functioning (Cockshell & Mathias, 2013). Memory and attention were the focus of this study because they are a part of CFS diagnostic criteria (Fukuda *et al.*, 1994), people with CFS frequently report problems in these domains (Fukuda et al., 1994; Jason et al., 1999), and a recent meta-analysis concluded that there is objective evidence of deficits in these domains (Cockshell & Mathias, 2010). In addition, participants rated their test performance in order to assess the accuracy of their self-perceptions, and ratings of cognitive effort and mental fatigue were obtained to examine cognitive exertion and its relationship to post-exertional malaise. Finally, variables that may be related to both objective and subjective assessments of cognitive ability were also investigated (fatigue, sleep, depression, anxiety).

Method

Participants

A total of 50 people who had been diagnosed with CFS (39 females, 11 males) and 50 matched healthy controls (40 females, 10 males) aged between 18 and 60 years participated in this study. Participants in the CFS group were recruited from an Australian CFS database and from the practice of two General Practitioners and an Endocrinologist (refer to Cockshell & Mathias, 2013, for further details). All met the Centre for Disease Control criteria for a diagnosis of CFS (Fukuda et al., 1994) and were diagnosed on the basis of medical history,

physical examination and laboratory tests to exclude other medical conditions. Healthy controls were recruited from the family and friends of the CFS group and from the general community, and were individually matched to the CFS participants on the basis of age, gender and education. No participant in either group reported having any condition that could independently affect cognitive performance when specifically asked about the following: previous loss of consciousness (> 5 minutes), stroke, heart disease, uncontrolled high blood pressure, insulin-dependent diabetes, seizures, and/or learning disorders (e.g. dyslexia). In addition, healthy controls were ineligible if they had a history of CFS, which was determined by a series of questions asking about the presence or absence of the major and minor CFS symptom criteria (Fukuda et al., 1994). A total of 54 participants were initially tested in each group, however the Validity Indicator Profile scores of four people in each group were classified as 'invalid', reflecting poor effort but with an intention to perform well. These participants were excluded from all further analyses (for further details see Cockshell & Mathias, 2012).

Measures

Cognitive tests.

Memory and attention tests which have shown deficits in people with CFS were selected from a recent meta-analysis (Cockshell & Mathias, 2010). Verbal memory was assessed using the California Verbal Learning Test II (CVLT II, Delis, Kramer, Kaplan, & Ober, 2000), which is a word list-learning task. The short-delay (free and cued recall), long-delay (free and cued recall), and recognition trial scores were used for present purposes (score range: 0-16). Visual memory was examined using the Rey-Osterreith Complex Figure Test (ROCFT) and scored using the Taylor criteria (Strauss, Sherman, & Spreen, 2006), which involves copying a geometric figure (non-memory task) and then recalling it after a delay of 3 minutes and 20 minutes (score range: 0–26).

Attention was assessed using both the Paced Auditory Serial Addition Test (PASAT, Gronwall, 1977) and the Stroop Color-Word Interference Test from the Delis-Kaplan

Executive Function System (D-KEFS, Delis, Kaplan, & Kramer, 2001). The PASAT presents four trials of 50 pre-recorded strings of single-digit numbers (1-9) at four different speeds (2.4, 2.0, 1.6, 1.2 sec). Every new number must be added to the last and the answer verbalised (e.g. "4" "5", 4+5 = answer 9, next number "1", 5+1 = answer 6), with the score being the total number of correct responses over the four trials (range: 0–196). The Stroop requires participants to name color patches, read color-words printed in black, and then name the color of color-words that are printed in a different color. The latter trial provides a measure of 'interference' (maximum = 180 seconds) and was used here.

Pre-morbid IQ was estimated using the National Adult Reading Test (NART, Nelson & Willison, 1991) in order to ensure that the CFS and control groups were comparable in terms of their general intellectual ability.

Self-report.

A summary of the self-reported measures, the timing of administration and the timeframes which they assess, is provided in Figure 1. The Centre for Disease Control CFS Symptom Inventory (Wagner et al., 2005) was used to assess the extent to which participants' experienced 8 core CFS symptoms over the *preceding month* (not present = 0, mild = 1, moderate = 2.5 or severe = 4). The scores for the 'Memory' and 'Concentration' problems only were analyzed for present purposes. Participants were also asked to rate the severity of these two symptoms on the *day of testing* (not present = 0, mild = 1, moderate = 2.5, severe = 4). In addition, participants completed the 25-item Cognitive Failures Questionnaire (Broadbent, Cooper, FitzGerald, & Parkes, 1982), where they rated the frequency with which they experienced minor problems with perception, memory and motor functioning over the *previous 6 months* (never = 0, very rarely = 1, occasionally = 2, quite often = 3, very often = 4; total score range 0-100); and the 18-item Everyday Attention Questionnaire (Martin, 1986), where they rated the ease with which they could generally do a number of concurrent tasks (ratings 1-5; total score range: 18-90, higher scores indicate better attention).

Subjective Measure	Prior to Test Session						Test Session			Post Session	
	undefined	-6mths	-1mth	-2wks	-1wk	-1-2days	Start	Middle	End	3hrs	24hrs
Memory											
Cognitive Failures Questionnaire		——	——	——	——	*					
CFS Symptom Inventory - Memory			——	——	——	*					
Symptom Severity - Memory							*				
Attention											
Everyday Attention Questionnaire	——	——	——	——	——	*					
CFS Symptom Inventory - Concentration			——	——	——	*					
Symptom Severity - Concentration							*				
Fatigue											
Checklist of Individual Strength - Fatigue				——	——	*					
Mental Fatigue							*	*	*	*	*
Sleep											
Pittsburgh Sleep Quality Index			——	——	——	*					
Depression & Anxiety											
Hospital Anxiety & Depression Scale					——	*					

* Time of test administration

Figure 1. Timing of administration (indicated by astericks) of the subjective measures of cognitive functioning, fatigue, sleep and mood, and the time period over which the questionnaires apply (indicated by lines if not at the time of administration)

Fatigue was measured by the Fatigue subscale from the Checklist of Individual Strength (Bultmann et al., 2000), which requires participants to indicate their level of agreement (1 = "yes, that is true", 7 = "no, that is not true") with eight statements describing their experience over the *preceding 2 weeks* (e.g. 'I feel tired'; total scores range: 8-56). Depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS, Zigmond & Snaith, 1983), which is designed to assess these symptoms in a general medical population, and hence somatic items that may be attributable to either emotional or physical disorders are excluded (Smarr, 2003). The HADS requires participants to rate the extent to which they have experienced seven symptoms each of depression and anxiety on a 4-point scale (0 to 3), over the *past week*. HADS scores can additionally be used to identify clinical levels of depression and anxiety using published cut-off scores (subscale scores range from 0 to 21). Although scores ≥ 11 are thought to indicate clinically significant depression and anxiety in the general community (Zigmond & Snaith, 1983), a cut-off of ≥ 9 has been recommended in order to maximize sensitivity and specificity with CFS samples (Morriss & Wearden, 1998). These cut-offs were used to identify 'caseness' in the control and CFS groups, respectively. Sleep quality was assessed using the Pittsburgh Sleep Quality Index, which involves rating 19 sleeping habits (e.g., quality, duration, medication usage) over the past month to provide an overall measure of sleep quality that ranges between 0 (*no difficulty*) and 21 (*severe difficulties*), with a score over 5 indicating that a person is a poor sleeper (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989).

Finally, participants rated: (1) how well they performed (very poor = -2, poor = -1, average = 0, good = 1, very good = 2) immediately after the cognitive tests (CVLT II short-delay cued recall, Stroop Interference trial, PASAT, ROCFT copy) in order to examine the accuracy with which they could evaluate their performance; and (2) both the level of cognitive effort that was expended during each task (very low = -2, low = -1, moderate = 0, high = 1, very high = 2) and the mental fatigue (very low = -2, low = -1, moderate = 0, high = 1, very high = 2) experienced at

various time-points (*start, middle* and *end* of the test session, and *3*- and *24-hours after* testing) in order to evaluate the impact of cognitive exertion on mental fatigue. In the latter case, participants were also asked to indicate how long it took to recover to their pre-test mental energy levels (*3*- and *24-hour* ratings, and recovery time, returned by mail).

Procedure

Participants were recruited and assessed as part of a broader study into cognitive functioning in people with CFS (Cockshell & Mathias, 2013). Cognitive assessments were completed during a single session, lasting approximately 3 hours. Each session was divided into two blocks, with the tests in each block presented in the same order to ensure that the memory tests did not overlap with each other and that the interspersed tests did not contain content that could interfere with performance on the memory tests. The blocks were presented in one of two counter-balanced orders. One block contained the ROCFT copy and immediate recall, a test of verbal ability, a psychiatric screening interview, ROCFT delayed recall, and a test of effort; the other block contained a test of motor performance, reaction time tasks, CVLT II immediate and short-delay recall, Stroop, PASAT, and CVLT II long-delay recall. All assessments were conducted in the participant's home or at the University. Participants completed the questionnaires in the few days immediately prior to testing, except for the CFS symptom scale (completed at the start of the session), and evaluations of mental fatigue (completed at the aforementioned time-points), test performance and cognitive effort (completed after each test).

Analysis

The demographic, cognitive and self-reported data for the CFS and control groups were firstly compared using one-way ANOVAs (or chi-square), using an alpha of 0.01 to reduce the likelihood of Type I errors caused by multiple comparisons, while also limiting the risk of Type II errors. Cohen's *d* effect sizes additionally provide a standardized measure of the magnitude of the group differences; with $d = 0.2$, $d = 0.5$ and $d = 0.8$ indicating small, medium and large effects,

respectively (Cohen, 1988). A positive *d* indicates that the performance of the CFS group was *impaired* relative to the controls.

Pearson correlation coefficients were then calculated to examine the relationship between: the self-report and objective measures, and these measures and self-evaluations of test performance, fatigue, sleep, depression, and anxiety. An alpha of 0.01 was again used and correlations of r = 0.1, 0.3 and 0.5 interpreted to reflect small, medium and large effects, respectively (Cohen, 1992). A repeated-measures ANOVA was used to analyse changes in mental fatigue over time and one-way ANOVAs were used to determine whether the order in which the cognitive tests were completed influenced the findings by comparing the results from participants who completed the test in the first half with those that completed it in the second half.

Results

As seen in Table 1, the CFS and Control groups did not differ in terms of age, education, estimated IQ (NART) and gender, indicating that they were well-matched on important demographic variables. On average, participants were middle-aged females with a tertiary-level education and high-average intelligence (see Table 1).

Table 1. Participant characteristics

	CFS (n = 50)		Healthy (n = 50)		Statistical test		Cohen's *d*
	Mean	*SD*	*Mean*	*SD*	*F*	*p*	
Age (years)	42.2	12.2	42.0	12.2	0.01	0.93	-0.02
Education (years)	15.1	3.1	15.5	2.9	0.62	0.43	0.13
NART estimated IQ	112.7	4.9	112.8	4.6	0.01	0.93	0.02
	N	%	N	%	χ^2	*p*	
Gender					0.00	1.00	
Female	39	78%	40	80%			
Male	11	22%	10	20%			

Note. NART, National Adult Reading Test; IQ, Intelligence Quotient.

Cognitive tests

When the cognitive performance of the CFS and Control groups was compared, they were not found to differ in terms of their verbal (CVLT II) or visual (ROCFT) *memory* performance, with the differences equating to small effects (see Table 2). Similarly, there were small to low-moderate and non-significant differences in the measures of *attention* (PASAT, Stroop; see Table 2).

Table 2. Cognitive Test Scores for the CFS and Healthy control groups.

Cognitive Domain Test	CFS		Healthy		Statistical test[+]		Cohen's *d*	Cohen's *d* 95% CIs	
	Mean	*SD*	*Mean*	*SD*	*F*	*p*			
Memory									
CVLT II									
short-delay free recall	11.4	2.7	12.0	2.7	1.49	0.23	0.24	-0.15	0.63
short-delay cued recall	12.5	2.5	12.7	2.4	0.17	0.68	0.08	-0.31	0.47
long-delay free recall	12.0	2.8	12.2	2.8	0.18	0.67	0.09	-0.30	0.48
long-delay cued recall	12.5	2.6	12.9	2.6	0.64	0.43	0.16	-0.23	0.55
recognition trial	15.0	1.2	15.2	1.0	0.85	0.36	0.18	-0.21	0.57
ROCFT									
3-min recall	16.6	5.6	18.3	5.0	2.39	0.13	0.31	-0.09	0.70
20-min recall	16.5	5.1	17.7	5.2	1.34	0.25	0.23	-0.17	0.63
Attention									
PASAT	160.2	21.5	165.9	19.9	1.87	0.18	0.27	-0.13	0.67
Stroop Interference (secs)	52.8	11.8	48.4	9.6	4.20	0.04	0.41	0.01	0.81

Note. CI, Confidence Interval; CVLT II, California Verbal Learning Test II; ROCFT, Rey Osterreith Complex Figure Test; PASAT, Paced Auditory Serial Addition Test.
[+] *df* =98 for *F* tests of CVLT II measures and *df* = 97 for ROCFT and PASAT.

Self-report measures

The majority of participants in the CFS group reported experiencing problems with memory and attention over the preceding month (CFS Symptom Inventory), which contrasted with the Controls, none of whom reported experiencing problems (see Table 3). On the day of testing,

Table 3. Self-report measures of CFS symptoms, cognitive problems, fatigue, sleep, depression and anxiety

	CFS		Healthy		Statistical Test		Cohen's *d*
	Mean	*SD*	*Mean*	*SD*	*F*	*p*	
CFS Symptoms							
CFS Symptom Inventory-Memory	62%		0%				
CFS Symptom Inventory-Concentration	82%		0%				
Symptom Severity-Memory	76%		6%				
Symptom Severity-Concentration	86%		12%				
Memory							
Cognitive Failures Questionnaire	54.9	12.5	32.7	11.4	86.0	0.00**	1.86
Attention / Concentration							
Everyday Attention Questionnaire	39.9	10.3	49.8	7.9	28.9	0.00**	1.08
Fatigue, Sleep, Depression & Anxiety							
Checklist of Individual Strength - Fatigue	46.0	6.1	22.2	10.1	202.3	0.00**	2.85
Pittsburgh Sleep Quality Index	9.4	3.4	5.0	3.0	47.16	0.00**	1.37
HADS							
Depression Score	5.8	3.2	2.0	2.1	45.88	0.00**	1.40
Anxiety Score	7.0	4.0	5.3	3.6	5.03	0.03	0.45
Clinical Depression ^	18%		0%				
Clinical Anxiety ^	30%		8%				

Note. HADS, Hospital Anxiety and Depression Scale
^ Note: CFS ≥ 9; Controls ≥ 11; 10% of CFS participants scored in the clinical range for both Depression and Anxiety, resulting in a total of 38%
**$p < 0.01$

most CFS participants (N = 38, 76%) reported experiencing memory problems (Symptom Severity-Memory), which were described as being mild in 55% of cases (N = 21), moderate in 40% of cases (N = 15) and severe in 5% (N = 2). Moreover, 86% (N = 43) of participants in this group reported having problems with attention (Symptom Severity-Concentration; mild problems: 49% [N = 21], moderate: 46% [N = 20], severe: 5% [N = 2]). In total, 90% (N = 45) of people with CFS reported experiencing problems with either memory or attention on the day of testing,

compared to only 12% (N = 6) of Controls, who were experiencing mild problems. As seen in Table 3, the CFS group also reported significantly more memory problems in the previous 6 months and poorer attention in general, as measured by the Cognitive Failures and Everyday Attention Questionnaires; with large differences evident on both measures. Thus, the CFS group reported experiencing substantially more problems with memory and attention than their healthy peers, both on the day of testing and over the preceding 6 months.

The CFS group also reported significantly higher levels of fatigue than the Controls over the preceding fortnight (Checklist of Individual Strength - Fatigue subscale), with this difference equating to a very large effect, but the mean HADS depression and anxiety scores were low for both groups (Table 3). Eighteen percent (N = 9) and 30% (N = 15) of CFS participants reported clinical levels of depression and anxiety, respectively, compared to 0% and 8% (N = 4) of the Controls. Overall, the CFS group was significantly more depressed, with the difference equating to a large effect, but they were not significantly more anxious (moderate effect). The CFS group reported significantly poorer sleep quality than the Controls over the past month, equating to a large effect (Pittsburgh Sleep Quality Index, Table 3).

Relationship between objective and subjective measures of cognitive performance

Pearson *r* correlations were calculated to examine the relationship between the objective and subjective measures of memory and attention in the CFS and Control groups (see Table 4). Specifically, correlations were calculated between (1) both the CVLT II and ROCFT and subjective reports of memory problems on the day of testing (Symptom Severity-Memory) and over the past month (CFS Symptom Inventory-Memory), and a more general measure of cognitive errors over the past 6 months (Cognitive Failures Questionnaire) and (2) both the PASAT and Stroop tests and subjective reports of attention on the day of testing (Symptom Severity-Concentration) and over the past month (CFS Symptom Inventory-Concentration), and with the Everyday Attention Questionnaire. As seen in Table 4, none of the correlations were

Table 4. Pearson correlations between objective and subjective measures of cognitive performance for the CFS and Healthy control groups.

	CFS			Healthy		
	Symptom severity -Memory	CFS Symptom Inventory -Memory	Questionnaire Cognitive Failures	Symptom severity -Memory	CFS Symptom Inventory -Memory	Questionnaire Cognitive Failures
Memory Test Performance						
CVLT II short delay free recall	-0.12	-0.12	0.10	0.03	-	0.19
CVLT II short delay cued recall	-0.02	0.07	0.18	-0.01	-	0.16
CVLT II long delay free recall	-0.08	-0.04	0.05	-0.05	-	-0.06
CVLT II long delay cued recall	-0.13	0.06	0.09	0.04	-	-0.03
CVLT II recognition	-0.08	0.07	0.03	-0.15	-	-0.02
ROCFT recall ^	0.16	-0.08	0.17	-0.10	-	0.19
ROCFT long delay recall	0.13	0.13	0.20	-0.02	-	0.17
	-Concentration	-Concentration	Everyday Attention	-Concentration	-Concentration	Everyday Attention
Attention Test Performance						
PASAT ^	-0.02	0.19	0.01	-0.02	-	-0.05
Stroop Interference	0.24	0.26	-0.21	0.02	-	0.15

CVLT II, California Verbal Learning Test II; ROCFT, Rey Osterreith Complex Figure Test; PASAT, Paced Auditory Serial Addition Test.
^ CFS: $n = 49$

significant for either the CFS or Control group, with all *r* values being small to low-moderate in size. Hence, the objective and subjective assessments of memory and attention were not related but this was not specific to CFS.

Self-evaluations of performance, cognitive effort, mental fatigue, and recovery time

The CFS and Control groups rated their performance on the CVLT II, PASAT and Stroop tests and these scores were correlated with their scores on these tests. The ratings of the CFS group showed moderate to large correlations with performance on the CVLT II ($r = 0.41$, $p < 0.01$), PASAT ($r = 0.50$, $p < 0.01$), and Stroop ($r = -0.27$, $p = 0.06$), although the latter was not significant. In contrast, the ratings of the Control group were not related to performance on the CVLT II ($r = 0.34$, $p = 0.02$) or Stroop ($r = -0.09$, $p = 0.54$), but were significantly related to performance on the PASAT ($r = 0.64$, $p < 0.01$, large effect). Hence, both groups accurately evaluated their performance on at least one test, but not all of them.

As indicated, the CFS and Control groups performed comparably on the cognitive tests (Table 2) but additional cognitive effort may have been required by the CFS group to achieve this which could, in turn, lead to greater mental fatigue in this sample. The CFS and Control groups rated their cognitive effort during the CVLT II, PASAT and Stroop tests, and an ANOVA was used to compare between the groups. There were no significant differences between the groups in cognitive effort expended during the CVLT II ($F(1,98) = 1.14$, $p = 0.29$, $d = -0.21$), PASAT ($F(1,97) = 5.30$, $p = 0.02$, $d = -0.46$) or Stroop ($F(1,98) = 1.11$, $p = 0.29$, $d = -0.21$) tests; with small to low-moderate effects.

A repeated-measures ANOVA was used to examine changes in mental fatigue over time (start, middle and end session, 3 and 24 hours post session). There were significant main effects for Time (Wilks' Lambda = 0.59, $F(4,79) = 13.87$, p = 0.00; partial eta squared = 0.41), with the mental fatigue of both groups increasing over time; and Group, with the CFS group showing significantly higher levels of mental fatigue ($F(1,82) = 84.74$, $p = 0.00$; partial eta squared =

0.51). However, the interaction between Time and Group was not significant (Wilks' Lambda = 0.91, $F(4,79) = 2.00$, $p = 0.10$, partial eta squared = 0.09), indicating that both groups showed a similar pattern over time, albeit at different levels, with a gradual increase in mental fatigue while being tested and in the 3-hours after, and improving over the following 24 hours (see Figure 2). The mental fatigue of the CFS group was significantly greater 24-hours after testing than at the start of testing (Start vs 24hrs Post: $t(39) = -3.59$, $p < 0.01$), but this was not the case for the healthy group (Start vs 24hrs Post: $t(44) = -0.84$, $p = 0.40$), indicating only the Control group had recovered within this time period. Finally, there was a significant difference in the time it took the two groups to return to their pre-test mental energy levels ($F(1,71) = 40.15$, $p < 0.01$), with the CFS group taking an average of 57 hours (SD = 46 hours, range 0-168 hours), compared to 7 hours for the Controls (SD = 10 hours, range 0-48 hours). Hence, although people with CFS may not expend more effort than Controls, they are differentially impacted by cognitive exertion, as demonstrated by their longer recovery times.

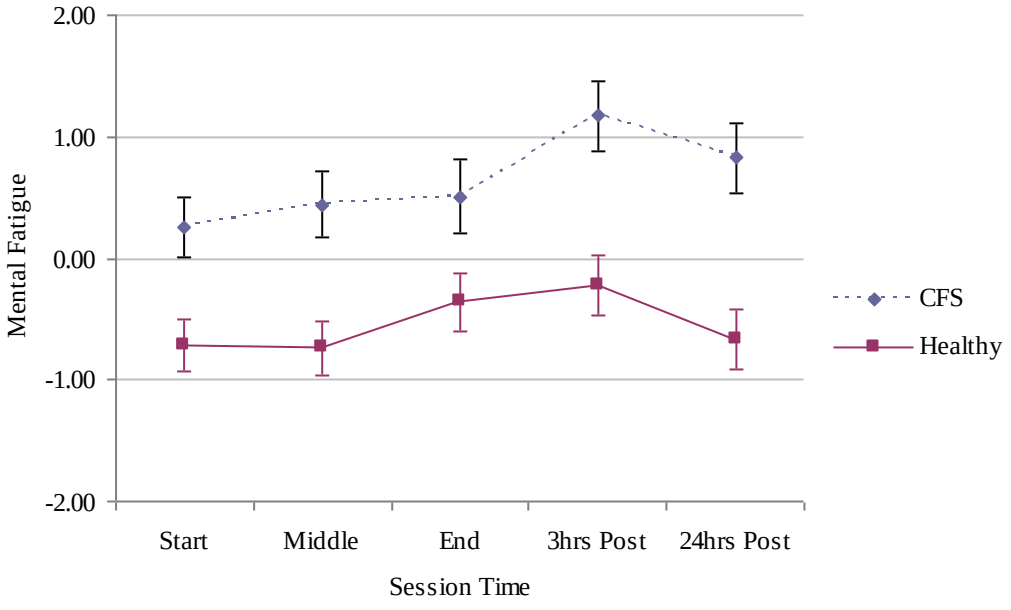

Figure 2. Mean ratings of mental fatigue with 95% confidence intervals, during and after the cognitive testing session for the CFS and Healthy Control groups.

Impact of test order on cognitive performance

ANOVAs comparing participants who completed a cognitive test (CVLT II, ROCFT, PASAT and Stroop) in the first half of a session with those who completed it in the second half were additionally undertaken to determine whether performance was worse for the latter group of participants, due to greater fatigue. These analyses were performed separately for the CFS and healthy control groups. All differences were non-significant, with the exception of the ROCFT 20-min recall in the Control group ($F(1,48) = 8.2$, $p < 0.01$, $d = 0.81$). Contrary to expectation, Controls who completed the ROCFT in the second half of the session performed slightly better than those who completed it in the first half (moderate-large effect equating to an average of 4 points or two correctly drawn elements). Thus, whether a test was completed in the first or last half of the session did not have a negative impact on performance, which is particularly notable for the CFS group who were more prone to fatigue.

Fatigue, sleep, depression and anxiety.

Lastly, fatigue, sleep, depression and anxiety were correlated with the objective and subjective cognitive measures for each group in order to investigate the influence of potential confounds on cognitive functioning. For the objective measures, only one correlation was significant in either group, with the remainder equating to small or low-moderate effects (see Table 5). The significant correlation was found for the Control group, such that worse sleep was associated with better PASAT performance ($r = 0.38$, $p = 0.006$, small-medium effect size). For the subjective measures, fatigue, sleep, depression and anxiety were not related to self-reported symptoms on the day of testing (Symptom Severity-Memory/Concentration) or over the past month (CFS Symptom Inventory-Memory/Concentration) for the CFS group; and similarly for the Controls with the exception that higher levels of depression showed a small to moderate correlation with concentration problems on the day of testing (Table 5). The memory and attention questionnaires were not significantly correlated with fatigue, sleep or anxiety, but they

Table 5. Pearson correlations between the measures of cognitive performance (objective and subjective) and fatigue, sleep, depression and anxiety for the CFS and Healthy control groups.

	CFS				Healthy			
	CIS - Fatigue	Sleep - PSQI	HADS Depression	HADS Anxiety	CIS - Fatigue	Sleep - PSQI	HADS Depression	HADS Anxiety
Memory Tests								
CVLT II short delay free recall	0.10	0.04	-0.09	0.19	0.10	0.23	0.21	0.19
CVLT II short delay cued recall	0.23	0.02	-0.09	0.10	0.03	0.12	0.15	0.08
CVLT II long delay free recall	0.23	-0.04	-0.13	0.12	0.00	0.15	0.06	0.00
CVLT II long delay cued recall	0.22	0.01	-0.13	0.11	-0.02	0.09	0.00	0.02
CVLT II recognition	0.24	0.12	-0.18	-0.06	-0.07	0.18	-0.01	0.06
ROCFT recall ^	0.26	0.07	-0.25	0.09	0.06	0.05	0.08	0.15
ROCFT long delay recall	0.31	0.07	-0.18	0.10	0.12	0.06	0.08	0.09
Self-Reported Memory Problems								
Symptom Severity-Memory	0.19	-0.08	0.13	-0.19	0.26	-0.25	0.35	0.08
CFS Symptom Inventory-Memory +	0.42	0.01	0.34	0.14	-	-	-	-
Cognitive Failures Questionnaire	0.33	0.00	0.43**	0.16	0.45**	0.27	0.56**	0.51**
Attention Tests								
PASAT ^	0.00	0.06	0.05	0.14	0.25	0.38**	0.22	0.33
Stroop Interference	0.07	0.06	0.15	0.06	-0.20	-0.21	-0.16	-0.19
Self-Reported Attention Problems								
Symptom Severity-Concentration	0.19	-0.23	0.15	0.10	0.31	-0.02	0.37**	0.08
CFS Symptom Inventory-Concentration˜	0.29	0.03	0.27	0.14	-	-	-	-
Everyday Attention Questionnaire	-0.10	0.09	-0.36**	-0.06	-0.29	-0.11	-0.29	-0.16

CIS, Checklist of Individual Strength; CVLT II, California Verbal Learning Test II; ROCFT, Rey Osterreith Complex Figure Test; PASAT, Paced Auditory Serial Addition Test; HADS, Hospital Anxiety and Depression Scale; PSQI, Pittsburgh Sleep Quality Index.
^ CFS: $n = 49$; + CFS: $n = 31$; Healthy: $n = 0$; ˜ CFS: $n = 41$, Healthy: $n = 0$; ** $p < 0.01$

were correlated with depression (moderate-large effect) in the CFS group (see Table 5). Only the memory questionnaire was significantly related to reports of fatigue, depression and anxiety in the healthy controls (moderate to large effects; Table 5). Hence, in the CFS group, fatigue was not related to either subjective or objective assessments of cognition, and only depression was related to subjective reports of memory and attention problems.

Discussion

The current study examined the relationship between subjective and objective measures of memory and attention in people with CFS in order to improve our understanding of the cognitive deficits that are associated with CFS. Although the CFS sample reported significantly more memory and attention problems than healthy controls, they did not show more deficits when tested. Moreover, the subjective and objective measures of cognitive functioning were not related, but more problems were reported by people with higher levels of depression. This is consistent with the findings of both Short, McCabe and Tooley (2002) and Wearden and Appleby (1997), but builds on this and other existing research by using: (1) a CFS sample that met established diagnostic criteria, (2) a carefully matched control group, (3) subjective and objective assessments of comparable cognitive constructs, and (4) samples whose test performance was shown to reflect a genuine effort to perform well (Cockshell & Mathias, 2012). The selection of cognitive tests was also evidence-based, having been guided by a recent CFS meta-analysis (Cockshell & Mathias, 2010), and it examined the potential contribution of a variety of frequently neglected variables (accuracy of self-perceptions, cognitive exertion, fatigue, sleep, depression, anxiety) to performance on both subjective and objective measures of cognitive problems.

Consistent with previous studies (e.g., Jason et al., 1999; Thomas & Smith, 2009), the current study found that the CFS group reported a large number of problems with memory and attention. However, the CFS group did not show significant deficits on objective tests of memory and attention. Although consistent with the findings of some studies (e.g., Krupp et

al., 1994; Mahurin et al., 2004; Short et al., 2002), it contrasts with others (Claypoole et al., 2007; DeLuca et al., 1995; DeLuca, Johnson, Ellis, & Natelson, 1997; DeLuca, Johnson, & Natelson, 1993; Lawrie, MacHale, Cavanagh, O'Carroll, & Goodwin, 2000; Tiersky, Cicerone, Natelson, & DeLuca, 1998). It also differs from the findings of a recent meta-analysis (Cockshell & Mathias, 2010), which was used as the basis for selecting the current tests of memory and attention. The reasons for this are unclear, however an examination of the confidence intervals around the effect sizes for the memory (CVLT II) and attention (PASAT, Stroop) tests used in the current study revealed that they overlap with the 95% confidence intervals from the equivalent effect sizes reported in this meta-analysis. Moreover, when we re-ran the meta-analysis, with the current data added to that of the previous studies it did not substantially alter the effect sizes (e.g., CVLT II short-delay free recall: $d = 0.32$ with current data vs $d = 0.33$; PASAT: $d = 0.49$ with current data vs $d = 0.52$; Stroop: $d = 0.69$ with current data vs $d = 0.73$). This suggests that the current findings, although not significant, do not provide strong support that these cognitive functions are not impaired in CFS. The fact that our results failed to reach significance may reflect normal variation in study findings, rather than a meaningful difference from the findings of previous studies (for further details see, Cumming, 2012). It should also be noted that this CFS group did have impaired information processing speed (see Cockshell & Mathias, 2013) and so were not entirely free of objectively measured cognitive problems.

The current study found that fatigue, sleep, depression and anxiety were not related to performance on the cognitive tests for either the CFS or healthy control groups, with the exception that worse sleep was related to better PASAT performance in the Control group. This is counter-intuitive, with the medium effect size indicating that this was not a strong effect. It is also possible that cognitive performance may have been influenced by fatigue that worsened during the test session, such that participants who took a particular test in the second half of the session performed worse than those who took it in the first half. However, the current study did not find that the performance of the CFS or Control groups was negatively affected when a test was administered in the latter part of the session.

The finding that the subjective and objective measures of cognition were not related in people with CFS is compatible with those of previous studies (Ray et al., 1993; Short et al., 2002; Vercoulen et al., 1998; Wearden & Appleby, 1997). It has been suggested that people with CFS may overestimate their cognitive problems (e.g. Knoop et al., 2010; Short et al., 2002; Wearden & Appleby, 1996). However this is not supported by Metzger and Denney (2002), Wearden and Appleby (1997) or the current study, in which the CFS group accurately evaluated their performance on 2 out of 3 tests; which was better than the controls. It has also been suggested that people with CFS perform comparable to healthy controls by expending additional effort (Capuron et al., 2006; Grafman et al., 1993), which may manifest as post-exertional malaise (a key symptom of CFS, Fukuda et al., 1994). In the current study, cognitive effort was comparable between the groups, but mental fatigue was greater and took longer to return to pre-test levels in the CFS group. Depression was related to greater reports of cognitive problems in both the CFS and control groups, but it is not possible to determine the cause of this relationship from this study.

When considering the relationship between subjective and objective measures of cognitive functioning, it is important to note that similar findings have been reported in other groups, including healthy participants from different age groups (Mantyla, Ronnlund, & Kliegel, 2010; Martin, 1983; Tucker-Drob, 2011), stroke patients (Duits, Munnecom, van Heugten, & van Oostenbrugge, 2008) and mild traumatic brain injury samples (Stulemeijer, Vos, Bleijenberg, & van der Werf, 2007); hence this discrepancy is not unique to CFS, and may indicate that they are measuring different things (Ray et al., 1993). Many questionnaires ask about general cognitive functioning (e.g. memory when doing everyday tasks), which has the advantage of capturing a broad range of activities and functions in a realistic environment, but may not be compatible with tests that assess specific cognitive functions in a structured and controlled test environment (Wearden & Appleby, 1996). Some researchers have dealt with this by asking questions that are more closely aligned with the tests, however they too have failed to find a relationship in both CFS and control groups (Short et al., 2002; Wearden

& Appleby, 1997), which may, in part, be because it is difficult to provide a rating before being exposed to the task (Short et al., 2002).

In addition, it has been found that the cognitive abilities of persons with CFS vary over time (Fuentes, Hunter, Strauss, & Hultsch, 2001), hence scales that rate problems over the previous weeks or months may not reflect those on the day of testing. This was addressed in the current study by having participants provide ratings of their problems on the day of testing and over the past month; however neither were related to test performance, suggesting that this does not adequately explain why the two are not related.

Finally, turning to the limitations of the study, it must be noted that the majority of the CFS participants were drawn from a clinical and research database and, therefore, may differ from the broader CFS population. However, the fact that the demographic and clinical characteristics of the current sample were very similar to those used in other studies (see Cockshell & Mathias, 2010) suggests that they are comparable to other research participants. Secondly, the ratings of memory and attention were taken from a scale that was designed to assess CFS symptoms (Wagner et al., 2005), which meant that there were limited items and a restricted range of scores; thereby limiting the size of the correlation between these and other scores. This needs to be addressed by developing a scale that contains more items that are relevant to CFS (e.g., forgetfulness, word–finding problems, problems thinking clearly, inability to concentrate, distractibility, Friedberg, Dechene, McKenzieII, & Fontanetta, 2000) and provides a better assessment of the cognitive problems that are experienced by this group. Thirdly, participants were required to evaluate their own performance after completing a cognitive test (once per test) but this meant that, in some cases, these evaluations did not always adequately align with the measures that were of interest to this study (e.g. ROCFT performance was evaluated after completing the 'copy' part of the task and not after the immediate or delayed recall). This could be overcome by having participants evaluate their performance after each individual task (e.g., ROCFT – copy, immediate and delayed recall). Finally, contrary to previous research (Cockshell & Mathias, 2010) and despite carefully selecting the tests for the current study, the CFS participants did not show deficits on tests of

memory and attention, which restricted the range of scores on these measures and, hence, the likelihood of finding a relationship between our subjective and objective measures. Indeed, this sample only showed evidence of impaired information processing speed on a reaction time task (Cockshell & Mathias, 2013) but, because reduced speed is not central to the diagnosis of CFS, we did not include self-report measures of this construct and so are unable to determine whether subjective and objective assessments of speed are related.

Conclusion

The CFS sample reported significantly more attention and memory problems than healthy controls, but they did not show comparable deficits on cognitive testing, nor were the two types of measures related. Self-reported problems were not due to people with CFS overestimating their problems, as they were able to accurately evaluate their performance on most cognitive tests; but they were related to higher levels of depression (but not fatigue, sleep or anxiety). Importantly, the subjective and objective measures of cognition were also not related in the healthy control group, and their subjective problems were related to higher levels of depression. Hence, it appears that these different types of measures are capturing different constructs.

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Chapter 7: Discussion

This thesis presents four papers that examined cognitive functioning in CFS, motivated by a need to more clearly understand and objectively assess the often severe and disabling cognitive problems reported by people with CFS (Abbey & Garfinkel, 1991; Jason, Richman, et al., 1999). The first aim was to identify the nature of cognitive deficits in people with CFS, and the second aim was to investigate some of the possible causes, correlates and consequences of cognitive impairment. The specific objectives were to: (1) meta-analyse existing research to identify the type and magnitude of cognitive deficits in people with CFS; (2) assess test effort in people with CFS, and identify possible causes of poor performance; (3) examine the relationship between impaired performance on cognitive tests and psychological status, CFS symptoms and everyday functioning; and (4) investigate the relationship between self-reported memory and attention problems and test performance.

Summary of Findings

Cognitive deficits in CFS.

The meta-analysis examined the cognitive performance of people with CFS compared to healthy controls (Study 1, Chapter 3) and found moderate to large and significant deficits in simple and complex information processing speed in people with CFS. The majority of narrative reviews had previously concluded that the most consistent deficit in people with CFS was in complex information processing speed, which includes elements of working memory (e.g. PASAT) and inhibition of response (e.g. Stroop Colour Word Task) (DeLuca & Tiersky, 2003; Tiersky et al., 1997). Therefore, while this thesis supported the existence of deficits in complex information

processing speed, it also identified the presence of large deficits in simple information processing speed.

In the area of memory, people with CFS were predominately impaired when learning lists of words, showing moderate to large deficits, but small to moderate deficits in their ability to remember figures and patterns. Moderate to large impairments in recognition of previously learnt lists of words was also found, however studies that have controlled for initial learning found that recall and recognition performance was comparable between CFS and control groups, suggesting initial learning is the primary deficit (DeLuca, Christodoulou, Diamond, Rosenstein, Kramer, Ricker, et al., 2004). Therefore, the meta-analysis clarified what were previously considered to be inconsistent findings regarding memory (DeLuca & Tiersky, 2003), particularly for non-verbal impairment (Michiels & Cluydts, 2001), and provided evidence that word-list learning is impaired, in contrast to previous claims that it was not (DiPino & Kane, 1996).

Motor functioning was moderately impaired in the meta-analysis, however, an examination of the individual tests revealed that tests of fine motor speed showed only small deficits, compared to the moderate deficits on tests that assessed motor functioning as part of a reaction time (RT) task. The movement time of a reaction time task has been shown to contain decision time; hence the delays on this task may not reflect a distinct motor impairment (Vercoulen, Bazelmans, et al., 1998). The meta-analysis therefore clarified the type and magnitude of impairment in motor functioning in CFS, for which previous reviews have concluded that the findings are inconsistent (DeLuca & Tiersky, 2003; Tiersky et al., 1997) or that the CFS group is not impaired (Moss-Morris et al., 1996).

The slowing on information processing tasks that require a motor response may also partly explain the slowing found when copying a figure, which was the only visuospatial task that was impaired in people with CFS. While there was a small deficit across all tests of cognitive reasoning and flexibility, the CFS group performed comparably to their healthy peers on each test, indicating a slight overall impairment for the domain, but no specific deficits on tests. Similarly, global functioning and vocabulary were preserved in people with CFS, although the generation of words was moderately impaired compared to their healthy peers. Such deficits may be related to self-reported problems, such as difficulty in finding the right word (Friedberg et al., 2000).

The empirical study found deficits in simple information processing speed (as measured by simple and choice RT; Study 2, Chapter 5) that were of similar magnitude to the meta-analysis. However, by directly analysing the contribution of motor speed to reaction time, it was revealed that motor speed was not responsible for the slowed reaction times. Further analyses revealed that the deficits in choice RT primarily appeared to be the consequence of the slowed simple RTs. Hence, this study further clarified the primacy of the deficit in simple information processing speed in people with CFS.

The current study did not find that complex information processing speed (as measured by the PASAT and Stroop) was impaired. This contrasts with the findings of previous reviews that have suggested that the primary deficits in CFS are complex information process speed and efficiency (Moss-Morris et al., 1996; Tiersky et al., 1997). Similarly, only small to moderate, non-significant deficits in memory were found. These findings highlight the fact that deficits in these and other areas in people

with CFS are subtle and may not occur in all persons, as has been suggested by a previous review (Moss-Morris et al., 1996), and demonstrates the challenges of researching memory and attention in people with CFS. Similarly, motor functioning and visuospatial ability were not impaired, and vocabulary and word generation was comparable between the groups, suggesting that small to moderate deficits may not be identified in single studies because of the large number of participants that would be required to obtain statistical power, but that the aggregation of study findings may provide insight into the deficits found in people with CFS.

Potential causes, correlates and consequences of cognitive impairments.

An examination of test effort revealed that the majority of people with CFS demonstrated high levels of effort and an intention to perform well (Study 2, Chapter 4), hence their test performance was likely to reflect their ability (Bush et al., 2005; Rogers, 1997). Four people in each of the CFS and healthy control groups (7%) demonstrated suboptimal performance, which is comparable to the percentage found in other healthy groups (Frederick & Crosby, 2000). The pattern of response of these people indicated an intention to perform well but with low effort expended, hence no instances of deliberate poor performance were found. Moreover, receipt of compensation did not influence the validity of CFS performance in the current study, despite it being related to suboptimal effort in a similar condition (Gervais et al., 2001).

The empirical study found that people with CFS showed impairment only in slowed information processing (simple and choice RT), and that this slowing was not related to psychological status (the presence or absence of a psychiatric diagnosis, level of depression or anxiety), CFS symptomatology (overall symptom severity,

fatigue, poor sleep) and the type of CFS onset (sudden or gradual development of symptoms) (Study 2, Chapter 5). This contrasts with the findings of previous CFS studies, which have found cognitive performance to be related to psychiatric diagnosis (DeLuca et al., 1997b) and type of CFS onset (Claypoole et al., 2007), but is consistent with most of the research findings on depression, anxiety, symptom severity, fatigue and poor sleep (Busichio et al., 2004; DeLuca et al., 1995; Short et al., 2002; Vercoulen, Bazelmans, et al., 1998). In the absence of a relationship between cognitive performance and these other factors, it was not possible to analyse their relative influence, however it suggests that cognitive deficits exist independently of other symptoms and co-morbidities in persons with CFS.

By definition, the cognitive problems reported by people with CFS must be severe enough to have a significant impact on work and leisure activities (Fukuda et al., 1994). The majority of people with CFS in the current study were unable to work full-time and were severely to moderately physically impaired (Study 2, Chapter 5). This functional impairment in employment status and level of functioning however, was not directly related to impaired cognitive performance. Previous studies have failed to find a relationship between cognitive performance and employment status (Tiersky et al., 2001), but have found cognitive impairment to be related to high levels of disability (Tiersky et al., 2001) and low levels of physical activity (Christodoulou et al., 1998; Vercoulen, Bazelmans, et al., 1998). This thesis did not identify an explicit relationship between impaired performance and everyday functioning, suggesting that cognitive tests may have limited utility in predicting the functional ability of people with CFS.

A preliminary investigation into the consequences of cognitive testing on fatigue was also undertaken (Study 2, Chapter 6). Fatigue as a consequence of exertion (post-exertional malaise) is one of the secondary criteria for a diagnosis of CFS (Fukuda et al., 1994) and is reported by 75% of people with CFS in the community (Jason, Richman, et al., 1999). Research on post-exertional malaise has predominately focussed on the effects of physical exertion (e.g., Blackwood et al., 1998; Claypoole et al., 2001; Cook & Nagelkirk, 2005; LaManca et al., 1998; VanNess et al., 2010; Yoshiuchi et al., 2007), with only a few studies investigating the consequences of cognitive testing (Capuron et al., 2006; Constant et al., 2011; Grafman et al., 1993; Marshall et al., 1997). The current study found that reported recovery times after an extended cognitive testing session were significantly longer for people with CFS, compared to their peers (an average of 57 vs. 7 hours, respectively), with some individuals taking up to one week to recover to their pre-test levels. This is consistent with the findings of two studies, one of which noted that some participants reported debilitating fatigue after 2 days of testing had been completed (Grafman et al., 1993), and another that found that people with CFS reported more fatigue after complex cognitive tasks than after simple ones (Capuron et al., 2006). This is the first study to explore the reported severity of fatigue and time-frames for recovery beyond one day after testing. The findings indicate that people with CFS are differentially affected by cognitive exertion and that it has a considerable impact on their functioning, which suggests that the disabling effects of cognitive exertion may need to be considered in addition to the cognitive deficits themselves.

Self-reported cognitive problems and performance.

This thesis failed to find a relationship between the self-reported problems and test performance of people with CFS (Study 2, Chapter 6). This is consistent with

previous findings (Ray et al., 1993; Short et al., 2002; Vercoulen, Bazelmans, et al., 1998; Wearden & Appleby, 1997), but expands upon previous research by matching attention and memory tests with subjectively reported problems in these areas across different timeframes (from the period prior to testing to the time of testing), and also by explicitly examining this relationship in healthy people.

Similarly, subjective and objective measures were not related in the healthy group, which was consistent with previous findings (Short et al., 2002; Wearden & Appleby, 1997), although not highlighted by the authors; and consistent with other studies of healthy groups (Righi, Mecacci, & Viggiano, 2009). This indicates that there may be problems with the questionnaires and/or tests employed. Early research into several questionnaires that are commonly used in the assessment of cognitive problems in CFS (e.g., Cognitive Failures Questionnaire, Everyday Attention Questionnaire) shows that they were not related to test performance (Martin, 1983). Hence their usefulness is questionable. This is further confirmed by the failure to find a relationship between subjective and objective measures of cognition across a range of conditions, including bipolar disorder (Miskowiak, Vinberg, Christensen, & Kessing, 2012), affective disorder (Svendsen et al., 2012) and people suffering from a stroke (Duits, Munnecom, van Heugten, & van Oostenbrugge, 2008). This is a broader research problem that needs to be resolved. These questionnaires may, however, continue to provide insight into the subjective experience of CFS. Alternatively, the development of questionnaires to assess simple information processing speed, which was the largest deficit identified by this thesis, may assist in clarifying the relationship between subjective and objective measures of cognitive functioning in CFS.

Implications of Findings and Recommendations for Future Research

Although the meta-analysis identified 'large' deficits in information processing speed, the practical implications of a large deficit needs to be determined. The empirical study found that people with CFS were, on average, 50 milliseconds slower in processing simple information than their healthy peers, which represents a 17% increase in response time. Practically, this delay is likely to be noticeable, with a visual image able to be comprehended in 13 milliseconds (Potter, Wyble, Hagmann, & McCourt, 2013) and a web page judged for its appeal in 50 milliseconds (Lindgaard, Fernandes, Dudek, & Brown, 2006). It may also affect a range of tasks that require people with CFS to process visual and auditory information from the world around them.

More general measures of daily functioning, such as employment status and overall functional ability, are unable to be predicted by cognitive test performance based on the findings of this and another study (Tiersky et al., 2001). Instead, test performance appears to be related to more specific measures of functioning, such as daily activity (Christodoulou et al., 1998; Vercoulen, Bazelmans, et al., 1998). It has also been suggested that cognitive tests may differ in important ways from the problems experienced in daily life (Wearden & Appleby, 1997). To that end, a number of tests have recently been developed that more closely capture daily activities, such as navigating a virtual map or building to undertake activities that include shopping, collecting and delivering objects (Jovanovski et al., 2012; Logie, Trawley, & Law, 2011; Smilek, Carriere, & Cheyne, 2010). These tests may provide a more realistic assessment of the problems that are experienced by people with CFS in everyday life and, hence, may be more strongly related to subjective complaints.

Further research into the type and severity of subjective complaints in CFS may also provide insight into how cognitive functioning could be better assessed objectively.

The assessment of test effort in people with CFS has generated some conflicting findings, with a number of studies finding up to a third of people with CFS demonstrating reduced effort (van der Werf, de Vree, van der Meer, et al., 2002; van der Werf et al., 2000). Using a more sophisticated test of effort, the current study found that fewer people with CFS demonstrated poor performance and that none showed evidence of deliberate under-performance. The VIP assessed vocabulary and problem solving, which are areas that are not usually impaired in CFS, however it may be argued that informed test-takers may be aware of the expected areas of impairment in CFS, and hence only display impaired performance on tests of those areas. To that end, the development of more complex effort tests in the areas of memory and attention that analyse the pattern of performance may be beneficial. The ability to screen CFS participants for underperformance is important for research into cognitive ability and also for investigating people with CFS who are seeking compensation. It has been reported that clinicians estimate that approximately 35% of people with chronic fatigue (fatigue for greater than six months duration without secondary symptoms) or Fibromyalgia who are seeking compensation may be malingering or exaggerating their symptoms (Mittenberg, Patton, Canyock, & Condit, 2002). Hence further research should investigate test effort in people with CFS seeking compensation.

People with CFS showed the greatest impairment relative to their peers in the area of information processing speed, however while the difference in test scores between the groups was statistically significant, there was still a 53% overlap in the scores of

the groups, meaning that approximately half of the CFS participants scored the same as the healthy controls (Zakzanis et al., 1999). This precludes the use of test scores as diagnostic markers for CFS, as this would require minimal overlap (< 5%) (Zakzanis, 2001) between the scores of those who do and do not have the condition. For clinicians, this overlap limits the ability to identify deficits in an individual with CFS, as approximately half of all people with CFS are likely to score within a healthy range. Hence, currently cognitive tests cannot be used to discriminate between people with CFS and their healthy peers.

A few studies have attempted to estimate the percentage of individuals with CFS who were impaired relative to their healthy peers by determining the number of tests that they 'failed' or the number of test scores that were one or more standard deviations below their estimated premorbid ability (Krupp et al., 1994) or healthy controls (Busichio et al., 2004; Vercoulen, Bazelmans, et al., 1998). Therefore, there is no standardised approach to determine the percentage of individuals that are impaired; and results cannot easily be compared between studies. To that end, the current study compared the mean performance of people with CFS and their peers, to enable effective comparison of findings. Future research into identifying individual impairment in CFS may be beneficial to clinicians.

The meta-analysis provides a list of the magnitude of deficits in CFS associated with different areas of cognitive functioning, which can be used to guide test selection by researchers and clinicians. Tests can be identified based on whether people with CFS have either previously shown deficits or that appear to be preserved. Within a particular cognitive domain, for example memory, this may result in tests being selected which show moderate to large deficits (e.g., working memory, learning of

word lists) instead of tests that do not appear to be impaired in CFS (e.g., memory span, sequencing). The pattern and magnitude of deficits found in the test results of individuals or groups of people with CFS can also be compared and contrasted with the meta-analysis findings, thereby facilitating the integration of findings between studies (Cohen, 1994; Oliver & Spokane, 1983; Schmidt, 1996; Zakzanis, 2001). Researchers may also be able to identify tests that require further study in CFS, such as tests on which large deficits have been found by a limited number of studies, hence the reliability of the findings are uncertain, for example, the N-Back Working Memory Test (Braver et al., 1997) and the Selective Reminding Task (Buschke, 1973). It may also be used to evaluate the utility of test batteries for CFS studies, including the extent to which the test battery assesses the range of deficits identified in people with CFS or whether other tests need to be included; and to provide an estimate of the effect size for each test.

For research studies where cognitive functioning is only one of a number of variables that are being assessed, a single measure of cognitive ability may be required. The meta-analysis and empirical study both indicate that the most appropriate measure is likely to be a simple reaction time task with a variable fore-period before the stimulus (as distinct from a fixed time when the stimulus will appear). This test has consistently shown the largest group differences of all the measures that have been used to study cognitive functioning in CFS. It can also be administered easily and relatively quickly, requiring minimal researcher involvement. Before this measure is used extensively, however, it is recommended that further research be conducted to identify the sensitivity of this measure to changes in symptom state within an individual, either as part of the natural course of the

condition or in response to treatment. Specifically, improvement in CFS symptoms would need to be associated with a corresponding improvement in reaction time.

More generally, it has been over 20 years since the last research definition for CFS was updated, with a revision long overdue. Revised clinical criteria for CFS have been developed in this time (e.g., Carruthers et al., 2003; Jason, Evans, Porter, et al., 2010; NICE (National Institute for Health Care and Excellence), 2007). However, as discussed in Chapter 1, clinical criteria are more inclusive because they are designed to identify all possible cases of CFS, instead of the more restrictive research definitions that must ensure all participants definitely have CFS. The revised clinical criteria show how the conceptualisation of CFS has evolved, with the most notable being the merging of the criteria for CFS and myalgic encephamyelitis (ME). In a considerable deviation from previous definitions, the Institute of Medicine recently released new clinical criteria, which propose that the central criteria for CFS is a reduction in functioning accompanied by fatigue, post-exertional malaise and unrefreshing sleep, with additional symptoms of either cognitive impairment or orthostatic intolerance (Institute of Medicine, 2015). This represents a shift from a diagnosis of CFS by excluding other conditions, to enabling a positive diagnosis of CFS through the use of a limited number of discriminating symptoms. They have also proposed re-naming the condition to "Systemic Exertion Intolerance Disease". Consequently, research criteria should be developed that enable the study of the people identified by these clinical criteria, and that facilitate research into how CFS findings may be relevant. The early development of a single, well-established definition for research will avoid many of the problems identified in this thesis, such as uncertainty about whether different findings are due to comparing different groups of people. Previous research, which has attempted to operationalise the criteria for

ME/CFS through the use of questionnaires, should provide a strong empirical base from which a new definition may be developed (Jason, Evans, Porter, et al., 2010; Jason et al., 2015).

This thesis has also provided some preliminary evidence that people with CFS experience significant fatigue after cognitive exertion, and further research should examine the nature of this fatigue and attempt to quantify it. This may be a particularly important area of research given that the updated clinical criteria for CFS has proposed that post-exertional malaise is a discriminating factor in the diagnosis of CFS (Institute of Medicine, 2015).

Key strengths and limitations

Study 1: Meta-analytic review.

A key strength of the meta-analysis is that it is the first quantitative review of cognitive functioning in people with CFS. Results were presented by cognitive domains to show the overall pattern of impairment in CFS and by individual measures to examine the types of impairment within each domain. The standardisation of test scores enabled different measures to be directly compared in order to examine the relative magnitude of deficits; and for results to be aggregated across studies to provide greater statistical power. Furthermore, all study authors were contacted to obtain data on tests that were administered but details were not provided to enable the calculation of effect sizes, which strengthened the comprehensiveness of this review. The meta-analysis selected studies using inclusion criteria, such as published CFS research criteria and healthy control groups, to create comparable groups for analysis and reduce ambiguity in findings due to poorly designed studies.

The exclusion of studies that had methodological limitations, such as the use of unpublished CFS criteria and the absence of healthy controls, may have limited the generalisability of the results. However, the advantages of analysing cognitive functioning in a more homogeneous group was considered necessary to attempt to reduce uncertain findings from previous narrative literature reviews, which were partly attributed to the inclusion of studies with methodological flaws (e.g., Michiels & Cluydts, 2001; Moss-Morris et al., 1996; Tiersky et al., 1998). However, the meta-analysis still included studies that had used four different research definitions of CFS, hence it is possible that the groups were not sufficiently homogenous. The authors planned to analyse the impact of CFS definitions on cognitive performance, but this was not possible because the majority of studies used the Fukuda criteria ($N_{studies}$ = 27) or met multiple criteria ($N_{studies}$ = 11), hence most definitions were not independent. The few studies that used different definitions ($N_{studies}$ = 12) did not use similar cognitive measures, hence the findings could not be directly compared. As discussed in Chapter 1, the four CFS research definitions included in the meta-analysis have important characteristics that distinguish them from other definitions of unknown fatiguing conditions, and overlapping symptoms that make them likely to identify similar groups. Thus, while there may be differences in the populations identified by the four research definitions, they are likely to represent groups that are frequently studied under the label of CFS.

A further limitation is that it has now been several years since the meta-analysis was conducted and published, with a number of new studies - including the findings from this thesis – adding to the literature on cognitive functioning in CFS (e.g., Constant et al., 2011; Hou et al., 2014; Togo et al., 2013; Van Den Eede et al., 2011). The findings from these studies appear to be consistent with the meta-analysis

findings, showing deficits in Simple and Choice RT (Constant et al., 2011; Hou et al., 2014; Togo et al., 2013; Van Den Eede et al., 2011), working memory and word-list learning (Constant et al., 2011) and the movement time of a task requiring cognitive processing (Van Den Eede et al., 2011), but additionally showing deficits on a visual working memory task (Constant et al., 2011). As more studies are published with findings that differ from the meta-analysis or include tests that are new, it is likely to be necessary to update the meta-analysis.

Study 2: Empirical study of cognitive deficits.

Effort.

A key strength of the empirical study was that the investigation of suboptimal performance in people with CFS used a test of effort that analyses the pattern of responses to enable possible causes of poor performance to be identified (Frederick, Crosby, & Wynkoop, 2000). Most effort tests are very simple and employ a cut-off score that reflects chance performance or performance achievable by a person with a brain injury confirmed by medical imaging; hence it is assumed that performance below that cut-off value must reflect a deliberate attempt to perform poorly (Heilbronner et al., 2009; Rogers & Bender, 2003). However, as the complexity of effort tests have increased in an attempt to identify those who are more subtle in their deception (e.g., Schagen, Schmand, de Sterke, & Lindeboom, 1997), the tests may require a certain level of cognitive ability which may be susceptible to impairment and, consequently, poor performance cannot be clearly attributed to either deliberate deception or actual impairment. This empirical study used the Validity Indicator Profile test (Frederick, 2003), which assesses cognitive domains that are not impaired in CFS, thereby reducing the risk of poor performance due to reduced ability. This study also provided an initial evaluation of the relationship between test performance

of people with CFS and their receipt of compensation, which has not been previously investigated.

A limitation of this study is that it only investigated effort in people with CFS who were drawn from primary and tertiary care centres and who had volunteered to participate in a research project. Performance by people with CFS seeking disability support may differ from that observed here, with a survey of neuropsychologists estimating that 35% of people with chronic fatigue (fatigue ≥ 6 months, but no other symptoms) or fibromyalgia who were seeking compensation were probably malingering or exaggerating their symptoms (Mittenberg et al., 2002). The current study did not find any indication of deliberate poor performance in those receiving benefits and, although this is only an initial investigation into the role of compensation in the cognitive performance of people with CFS, this measure has been found to identify people with reduced effort in a condition related to CFS (i.e. Fibromyalgia, Gervais et al., 2001). Additionally, it was not possible to explore the impact of reduced effort on cognitive performance as very few participants demonstrated deliberately poor performance.

Potential causes and consequences of cognitive deficits.

A key strength of the empirical study was that it was designed to assess psychological status, symptomatology and everyday functioning in a single group of people with CFS, to investigate the relative contribution of these factors to cognitive deficits. Many studies have investigated a subset of these variables; however few studies have investigated all factors in a single sample. None of the factors in this study were related to cognitive impairment; hence it was not possible to assess their

relative contribution to deficits in CFS. It does, however, show that cognitive deficits can occur independently of anxiety, depression and CFS symptoms.

A limitation of this study was that the sample was not large for the number of variables investigated; however extensive contact with CFS researchers and practitioners in Adelaide – a city of approximately one million people - failed to identify any additional participants. Effect sizes were calculated, which provide a measure of effect independent of sample size, to address this limitation.

Subjective and objective cognitive functioning.

A strength of this study was the matching of self-report and cognitive test measures for memory and attention, with subjective measures obtained in the preceding months and on the day of testing, to identify if variation in the timing of symptom presence differentially related to performance on the day of testing. A systematic evaluation was also undertaken of variables that may influence reporting and performance; specifically depression, anxiety, fatigue and poor sleep. An examination of the relationship between subjective and objective measures in healthy controls revealed that these measures were not related in people with CFS and their healthy peers, suggesting they may be measuring different constructs.

The main limitation of this study is that CFS participants were not impaired on the selected tests of memory and attention, thereby reducing the range of scores and the likelihood of finding a relationship between test scores and self-reported problems. People with CFS were most impaired in information processing speed, and a questionnaire that evaluates this function may find a closer relationship between problems and deficits.

Final Conclusions

Overall, the findings from this thesis suggest that people with CFS are impaired in a number of cognitive domains, including memory and attention; consistent with the problems they frequently report. Many deficits are only minor and affect specific aspects, such as sustained working memory. The greatest impairment for people with CFS, however, was information processing speed; which was not explained by poor test effort, psychological problems or the severity of CFS symptoms (fatigue or poor sleep). People with CFS report experiencing cognitive problems, and although they are not directly related to their performance on cognitive tests, this research suggests that cognitive exertion can cause disabling fatigue for many days afterwards.

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Appendix A: Journal format of paper from Study 1 "Cognitive functioning in chronic fatigue syndrome: a meta-analysis"

The following paper is reprinted with permission.

Cockshell, S. J., & Mathias, J. L. (2010). Cognitive functioning in chronic fatigue syndrome: a meta-analysis. *Psychological Medicine, 40*(8), 1253-1267.

Cockshell, S. J., & Mathias, J. L. (2010). Cognitive functioning in chronic fatigue syndrome: a meta-analysis.
Psychological Medicine, 40(8), 1253-1267.

Appendix B: Journal format of paper from Study 2 (Part 1) "Test effort in persons with Chronic Fatigue Syndrome when assessed using the Validity Indicator Profile"

The following paper is reprinted with permission.

Cockshell, S. J., & Mathias, J. L. (2012). Test effort in persons with Chronic Fatigue Syndrome when assessed using the Validity Indicator Profile. *Journal of Clinical and Experimental Neuropsychology*, *34*(7), 679-687.

Cockshell, S. J., & Mathias, J. L. (2012). Test effort in persons with Chronic Fatigue Syndrome when assessed using the Validity Indicator Profile. *Journal of Clinical and Experimental Neuropsychology, 34*(7), 679-687.

Appendix C: Journal format of paper from Study 2 (Part 2) "Cognitive deficits in Chronic Fatigue Syndrome and their relationship to psychological status, symptomatology and everyday functioning"

The following paper is reprinted with permission.

Cockshell, S. J., & Mathias, J. L. (2013). Cognitive deficits in Chronic Fatigue Syndrome and their relationship to psychological status, symptomatology and everyday functioning. *Neuropsychology, 27*(2), 230-242.

Cockshell, S. J., & Mathias, J. L. (2013). Cognitive deficits in Chronic Fatigue Syndrome and their relationship to psychological status, symptomatology and everyday functioning.
Neuropsychology, *27*(2), 230-242.

Appendix D: Journal format of paper from Study 2 (Part 3) "Cognitive functioning in people with Chronic Fatigue Syndrome: A comparison between subjective and objective measures"

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Cockshell, S. J., & Mathias, J. L. (2014). Cognitive functioning in people with Chronic Fatigue Syndrome: A comparison between subjective and objective measures. *Neuropsychology, 28(3),* 394-405.

Cockshell, S. J., & Mathias, J. L. (2014). Cognitive functioning in people with Chronic Fatigue Syndrome: A comparison between subjective and objective measures.
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