Cognitive Function in Young People with Chronic Fatigue Syndrome

by

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I am the author of the thesis entitled

Cognitive Function in Young People with Chronic Fatigue Syndrome

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# Table of Contents

Acknowledgements ........................................................................................................ IV

Table of Contents ........................................................................................................ V

List of Tables ................................................................................................................ XI

List of Figures ................................................................................................................. XIII

Abstract ......................................................................................................................... 1

Chapter 1 : Historical Perspective of CFS ................................................................. 3

Neurasthenia .................................................................................................................. 3

Epidemic Outbreaks of Fatigue .................................................................................. 5

Postinfectious Fatigue Syndromes ............................................................................. 7

Chronic Fatigue Syndrome ......................................................................................... 10

CFS in Young People ................................................................................................. 15

Chapter Summary ........................................................................................................ 18

Chapter 2 : Epidemiology and Aetiology of CFS in Young People ....................... 20

Methodological Issues ................................................................................................. 20

Epidemiology of CFS ................................................................................................. 21

Prevalence .................................................................................................................... 21

Course ........................................................................................................................... 26

Impact ............................................................................................................................ 29

Educational disturbance ............................................................................................ 29
Chapter Summary ........................................................................................................... 82

Chapter 4 : Factors That Affect Cognitive Function in CFS ......................... 85

Fatigue ....................................................................................................................... 85
Sleep Disturbance ...................................................................................................... 88
Psychological Disturbance ..................................................................................... 95

Chapter Summary .................................................................................................... 99

Chapter 5 : Research Proposal ............................................................................. 101

Study Aims .............................................................................................................. 109
Hypotheses .............................................................................................................. 112

Chapter 6 : Study of Cognitive Function in Young People with CFS .......... 114

Method .................................................................................................................... 114
Participants ............................................................................................................ 114
Diagnosis of CFS ..................................................................................................... 115
Onset and duration of CFS .................................................................................... 116
Illness characteristics ............................................................................................. 117
Materials .................................................................................................................. 119
CFS presentation .................................................................................................... 119
Intellectual functioning ......................................................................................... 119
Perceived cognitive function .................................................................................. 120
Neuropsychological functioning .......................................................................... 121
Academic performance ......................................................................................... 127
Motivation .............................................................................................................. 127
Perfectionism ................................................................. 128
Psychological functioning ............................................... 129
Sleep disturbance .......................................................... 130
Fatigue ................................................................. 131
Procedure ................................................................. 132
Testing protocol ........................................................... 133
Results ................................................................. 135
Presenting symptomatology ........................................... 136
Hypothesis 1: between-group differences in cognitive function. ...... 137
Perceived cognitive function ........................................... 137
Executive function ....................................................... 139
Attention ................................................................. 140
Information processing speed ......................................... 141
Working memory ......................................................... 142
Hypothesis 2: between-group differences in academic achievement. ....... 143
Hypothesis 3: between-group differences in test motivation and
perfectionism ............................................................. 143
Motivation ................................................................. 143
Perfectionism ............................................................. 144
Hypothesis 4: predictive value of motivation and perfectionism. ............ 145
Neuropsychological function ......................................... 146
Academic achievement ................................................ 147
Hypothesis 5: between-group differences in cognitive function when
motivation and perfectionism are accounted for .................... 148
Hypothesis 6: neuropsychological function in adults and young people with CFS. ................................................................. 149

Hypothesis 7: between-group differences in symptoms common to CFS. 150

Sleep disturbance................................................................. 150
Psychological distress. ..................................................... 151
Fatigue.............................................................................. 153

Hypothesis 8: predictive value of symptoms common to CFS .......... 155

Perceived cognitive disturbance........................................... 155
Neuropsychological performance................................. 156
Academic achievement. ................................................... 156

Hypothesis 9: between-group differences in school absenteeism ......... 157

Hypothesis 10: school absenteeism and academic achievement ...... 158

Discussion............................................................................ 159

Participants........................................................................... 160

Hypothesis 1: between-group differences in cognitive function. ......... 161

Perceived cognitive function............................................. 161
Neuropsychological function......................................... 163

Hypothesis 2: between-group differences in academic achievement ...... 176

Hypothesis 3: between-group differences in test motivation and perfectionism................................................................. 179

Motivation............................................................................. 179
Perfectionism..................................................................... 180

Hypothesis 4: predictive value of motivation and perfectionism .......... 181

Neuropsychological function......................................... 182
Academic achievement. ................................................................. 184

Hypothesis 5: between-group differences in cognitive function when
motivation and perfectionism are accounted for. ............................... 187

Hypothesis 6: neuropsychological function in adults and young people with
CFS. ........................................................................................................... 187

Hypothesis 7: between-group differences in symptoms common to CFS. 189

Sleep disturbance. ............................................................................. 189

Psychological distress. ................................................................. 192

Fatigue. ........................................................................................ 194

Considerations for Hypothesis 7. ......................................................... 195

Hypothesis 8: predictive value of symptoms common to CFS................. 195

Hypothesis 9: between-group differences in school absenteeism............. 200

Hypothesis 10: school absenteeism and academic achievement. .......... 201

Limitations and directions for further research ..................................... 201

Conclusion. .......................................................................................... 206

References ........................................................................................... 208

Appendix A

Definition of ME/CFS for Children (Jason et al., 2008) ....................... 272

Appendix B

Plain Language Statements and Consent Forms ................................. 275

Appendix C

Visual Analogue Scale ........................................................................ 282
List of Tables

Table 6.1 Percentage of CFS Participants Meeting Diagnostic Criteria Clusters ................................................................. 115

Table 6.2 Group Means and Standard Deviations for CFS Symptom Cluster Frequencies ................................................................. 136

Table 6.3 Group Means and Standard Deviations for CFS Symptom Cluster Severity ................................................................. 137

Table 6.4 Group Means and Standard Deviations for Perceived Cognitive Disturbance ................................................................. 138

Table 6.5 Group Means and Standard Deviations for Executive Function .......... 139

Table 6.6 Group Means and Standard Deviations for Attention ......................... 140

Table 6.7 Group Means and Standard Deviations for Information Processing Speed ................................................................. 141

Table 6.8 Group Means and Standard Deviations for Working Memory .......... 142

Table 6.9 Group Means and Standard Deviations for Academic Performance . 143

Table 6.10 Group Means and Standard Deviations for Test Motivation ............ 144

Table 6.11 Group Means and Standard Deviations for Test Perfectionism ...... 145

Table 6.12 Group Means and Standard Deviations for Neuropsychological Function ................................................................................ 150

Table 6.13 Group Means and Standard Deviations for Sleep Disturbance ...... 151

Table 6.14 Group Means and Standard Deviations for Psychological Distress 152

Table 6.15 Percentage of Participants Meeting the Criteria for Various Distress Levels From the DASS ................................................................. 153
Table 6.16 Percentage of Participants Meeting the Criteria for Categories of

Depression From the IDS-SR ................................................................. 153

Table 6.17 Group Means and Standard Deviations for Fatigue ...................... 154

Table 6.18 Correlations Between Predictor Variables for the Regression Models

..................................................................................................................... 156

Table 6.19 Multiple Linear Regression Results for Predicting Academic

Achievement From Symptoms Common to CFS ........................................ 157

Table 6.20 Percentage of School Days Missed in School-Aged Participants ..... 158
List of Figures

Figure 1.1. The 1994 CDC Revised Case Criteria for CFS .......................... 11

Figure 1.2. Adapted From the Canadian Clinical Working Case Definition for
CFS ........................................................................................................... 13

Figure 1.3. Paediatric Case Definition for CFS ........................................ 17
Abstract

Chronic fatigue syndrome (CFS) is a common, debilitating condition. Although existing research has largely focused on adult patients, CFS is similarly prevalent in adolescents. The aetiology of the illness remains poorly understood, and treatments typically focus on the alleviation of symptoms rather than cure. One of the most debilitating and frequently reported symptoms of CFS is cognitive impairment. Despite the potentially severe educational, functional, and developmental consequences of cognitive impairment in young people, neuropsychological performance had not been investigated in this population until very recently. In a recent study by some members of the current research team, no differences in cognitive function were found between adolescent CFS patients and healthy controls. Given that these findings were inconsistent previous research and theory, the we hypothesised that motivation or perfectionism might have accounted for the nonsignificant results. The current research group designed a study to investigate cognitive function in adolescents and young adults with CFS. Building on the previous study, we examined the effects of motivation and perfectionism on cognitive performance in young CFS patients. The sample included 23 CFS patients aged between 12 and 21 years, and 23 age and sex matched healthy controls. Participants completed a self-report measure of perceived cognitive impairment as well as a range of cognitively demanding tests on a computerised assessment tool and a written academic achievement test. A measure of intelligence was included to allow for differences in intellectual capacity to be statistically controlled. The participants also completed self-report measures of perfectionism, test motivation, sleep disturbance, fatigue, and psychological adjustment. Compared to controls, the CFS patients reported significantly higher levels of cognitive impairment and
performed less well on measures of executive function, attention, and working memory. However, there were no between-group differences in processing speed, and the CFS patients achieved higher scores on the academic tests than controls. Although test motivation was higher in the CFS group, there were no between-group differences in perfectionism, and motivation and perfectionism were not significant predictors of neuropsychological function or academic achievement. Compared to healthy controls, the young CFS group also reported higher levels of fatigue, sleep disturbance, and psychological distress, however these factors were not significant predictors of perceived cognitive disturbance, neuropsychological performance, or academic achievement. The CFS group reported higher rates of school absenteeism, although no correlation was identified between school absenteeism and academic performance. To investigate whether the cognitive impairment observed in young people with CFS is similar to that found in adult patients, neuropsychological performance was compared between the young participants and adult CFS patients from a concurrent study. The young CFS group achieved higher scores on measures of executive function, but performed similarly on measures of attention and working memory. These findings are discussed with reference to the study limitations and the implications for managing cognitive impairment in young CFS patients.
Chapter 1: Historical Perspective of CFS

To provide a context for understanding Chronic Fatigue Syndrome (CFS), this chapter presents an historical account of the major events that have influenced how the illness is currently conceptualised. The ongoing changes and recent developments in the conceptualisation of CFS have resulted in inconsistent research findings and a poor understanding of the nature of the condition. The beginning of the chapter includes a description of how Neurasthenia briefly came to prominence in the late 19th Century, followed by an investigation of epidemics of fatigue, post-viral syndromes, and chronic infectious illnesses throughout the 20th Century. The rise of CFS as a contemporary diagnosis will then be discussed, along with the development of modern case definitions for adults and paediatric patients.

Neurasthenia

Although CFS is often considered to be a modern condition, fatiguing illnesses were documented centuries ago. Early accounts of illnesses characterised by unexplained debilitating fatigue accompanied by a myriad of somatic symptoms bear a close resemblance to the current conceptualisation of CFS. In 1869, George Miller Beard described and termed one of the earliest known such illness, Neurasthenia (Beard, 1869). He classified the condition as an organic illness defined by a fatigued body and mind associated with a collection of other symptoms, such as malaise, debilitated function, poor appetite, weakness in the back and spine, pain, hysteria, insomnia, hyperchondriases, avoidance of mental effort, nausea, and headache. Beard believed that Neurasthenia was most common in civilised, intellectual communities and was associated with the increasing intellectual and occupational pressures of a modern society. He noted that Neurasthenia appeared to
have a hereditary component and could be provoked by physical or mental stressors (Beard, 1869).

In the same year, Edward Van Deusen (1869) identified a similar illness, also labelling it Neurasthenia. He described the condition as characterised by profound exhaustion, physical sensitivity, neuralgias, depression, irritability, excessive perspiration, sleeplessness, and cognitive and intellectual disturbance (Van Deusen, 1869). Unlike Beard however, he attributed the cause of Neurasthenia to psychological factors, including excessive mental labour, depression, grief, domestic discord, and prolonged anxiety. Van Deusen believed that farmers’ wives were the most commonly affected patients due to excessive isolation and boredom, and he prescribed physical exercise, mental activity, and sufficient sleep and nutrition.

Beard’s (1869) description of Neurasthenia quickly became popular among high social positions of American and Western European society. It was commonly diagnosed and formed the focus of immense public and professional interest until early in the 20th century, when medical professionals and patients lost interest in the condition. This change could be accounted for by a combination of factors, such as inadequate evidence for an organic cause, ineffective medical treatments, and indicators of equally high prevalence rates in lower economic classes (Wessely, Hotopf, & Sharpe, 1998). At this time, psychological explanations for Neurasthenia began to emerge, along with an inevitable social stigma (Demitrack & Abbey, 1996). After the illness was reconceptualised as a psychiatric condition, diagnoses were made less frequently and Neurasthenia was eventually removed from the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (American Psychiatric Association, 1980; Friedberg & Leonard, 1998).
Epidemic Outbreaks of Fatigue

Towards the middle of the 20th century, epidemic outbreaks of CFS-like illnesses were observed in several localised regions around the world. Although these illnesses differ somewhat from the modern characterisation of CFS, the epidemics provide evidence for the existence of a specific medical entity that could be directly related to CFS (Jenkins, 1991). Based on a review of 12 epidemics occurring between 1934 and 1961, common symptoms in these illnesses included myalgia, mood disturbance, memory and concentration impairment, headaches, and muscle weakness (Sabin & Dawson, 1993).

Particular attention has been given to two significant outbreaks that affected the medical staff at hospitals in Los Angeles in 1934 (Lippincott, Williams, & Wilkins, 1937) and London in 1955 (The Medical Staff of the Royal Free Hospital, 1957). In the Los Angeles outbreak, 198 hospital staff members presented with an illness characterised by pain, headaches, muscle tenderness and weakness, fatigue, irritability, emotional lability, depression, sleep disturbance, and impaired memory and concentration. Most sufferers reported significant functional impairment, and staff members missed an average of 13.6 weeks of work during the epidemic (Gilliam, 1938; Wessely, 2001). The outbreak coincided with a poliomyelitis epidemic, and as such, it was initially believed to be a version of poliomyelitis despite clear differences in presentation and course (Smallman-Raynor & Trevelyan, 2006). In the 1955 epidemic, 70 medical staff members at a London hospital were admitted over a two-week period following the rapid onset of an illness characterised by headaches, sore throat, malaise, fatigue, vertigo, and limb pain (Lippincott et al., 1937). In the subsequent months, 292 staff members and 12 hospital patients had developed the illness. Laboratory assessment results were generally unremarkable,
and the illness was particularly prevalent among female resident nursing staff (Compston, 1978; The Medical Staff of the Royal Free Hospital, 1957).

Although such epidemics were rare in young people, children and adolescents were not immune. Following reports of a few isolated poliomyelitis cases in 1948, 488 people in Iceland presented with symptoms of fever, pain, muscle weakness, and irritability. Of these patients, 194 were under 19 years old. Laboratory investigations were predominantly unremarkable. Seven years later, 39 patients were re-examined, and 75% of those who had been severely affected reported residual symptoms (Parish, 1978).

Various explanations for these outbreaks have been proposed. Some argued that hysteria or other emotional disturbances were responsible for the outbreaks. Both the London and Los Angeles outbreaks occurred in the context of intense fear over contracting poliomyelitis, and the selectivity of affected patients along with an absence of physiological markers points towards a psychological explanation in at least some cases (McEvedy & Beard, 1970). In contrast, others suggested that the staff of the Los Angeles hospital were exposed to a modified infection of poliomyelitis (Sabin & Dawson, 1993). Acheson (1959) argued that the consistency of symptoms and illness course among patients from diverse communities is indicative of an infectious illness spread through interpersonal contact. He also suggested that genuine cases of poliomyelitis might have acted as a trigger for hysterical cases among other staff members. To date, the trigger for these epidemics remains unclear, and both an infectious process and a psychological response provide feasible aetiological explanations.

Following an editorial published in the Lancet in 1956, Benign Myalgic Encephalomyelitis became the term used to describe a new clinical entity that might
account for the epidemic outbreaks. The symptom criteria included central nervous system damage, muscle pain, emotional disturbance, normal cerebrospinal fluid, reticuloendothelial system involvement, chronic course, and frequent relapses. The diagnosis allowed for unknown aetiology, and the illness was differentiated from known viral infections and hysteria.

Postinfectious Fatigue Syndromes

An association between infection and chronic fatiguing illnesses has long been recognised. In 1934, Alice Evens argued that many cases of Neurasthenia were actually misdiagnosed brucellosis infections (Evans, 1934). Evans believed that the animal infection could also affect humans, and noted that it is inherently difficult to detect through serum analysis. Although this theory was initially built on anecdote and generalisations from animal studies (Demitrack & Abbey, 1996), Spink (1951) later found that 74 of 120 people with brucellosis continued to exhibit symptoms after one year despite the absence of a clear organic cause or evidence for an infectious illness.

Spink’s (1951) findings sparked interest in the role of psychological factors in cases of prolonged recovery from infectious illnesses. This interest heightened further following a study by Cluff, Trever, Imboden, and Canter (1959) who conducted assessments at several six-month intervals in 24 people who had contracted brucellosis. After one year, 16 patients remained symptomatic, and 10 continued to exhibit symptoms at a two-year follow-up. Laboratory findings revealed no evidence of an active brucella infection or central nervous system damage. Compared to those who recovered quickly, the chronically ill patients scored higher on measures of psychological impairment, were more resistant to
discussing personal issues, and were more likely to attribute their symptoms to organic factors. Biographical assessment also revealed that 11 of the chronically ill patients had experienced traumatic childhood events compared to two of the recovered patients. In addition, 11 of those in the chronic group and none of those in the recovered group reported significant stress in the year preceding the infection. Based on these findings, the authors argued that prolonged postinfectious illnesses were caused by psychological factors (Imboden et al., 1959).

Imboden, Canter, and Cluff (1961) later designed a prospective study to assess whether psychological symptoms exist prior to the development of prolonged postinfectious illnesses. In anticipation of a flu epidemic at a US army base, 600 employees were recruited for psychological assessment. At a three- to six-week follow-up, 12 of the 26 people who contracted the illness reported ongoing symptoms of fatigue, headaches, sleep disturbance, and depressed mood. No differences were observed between the recovered and the symptomatic patients in symptom presentation during the acute phase of the flu and in the laboratory results at onset and at follow-up. However, the symptomatic patients scored higher on measures of morale loss and depression prior to contracting the illness. Imboden et al. (1961) suggested that an infectious illness might trigger a depressive episode in people who are predisposed to psychological disturbances. Following this research, interest in chronic brucellosis rapidly declined in public and medical domains (Wessely et al., 1995). This is perhaps indicative of a bias against illnesses associated with psychological phenomena.

Despite ongoing research efforts, organic explanations for chronic fatiguing illnesses remained unsubstantiated, and accurate diagnosis had become enormously challenging. The clinical symptoms were variable, nonspecific, and common to
many organic and psychological disorders (Henderson, 1994; Holt, 1965; Levine, 1994). To facilitate the development of a unified, operationally defined case definition, a symposium was held at the Royal Society of Medicine in 1978. The group argued that the Los Angeles outbreak was an organic illness primarily characterised by encephalomyelitis and myalgia, and as such, *Myalgic Encephalomyelitis* (ME) was affirmed as the correct diagnostic term (Compston, 1978; Jenkins, 1991). In the absence of epidemic outbreaks in the following two decades, sporadic cases formed the primary focus for research (Wessely et al., 1998). Currently, ME is conceptualised as a noncontagious, chronic, illness with no neurological symptoms that is generally preceded by an infectious illness (Wessely et al., 1998).

Interest in fatiguing illnesses expanded in the 1980’s in response to intense media attention surrounding *Epstein-Barr virus* (EBV) epidemics across North America (Wessely et al., 1999). At this time, three separate reports were published describing patients suffering from persistent symptoms of ME, as well as immunological disturbances and abnormal antibody responses to EBV (Jones et al., 1985; Straus et al., 1985; Tobi et al., 1982). Many patients had also developed the condition following episodes of infectious mononucleosis. These factors led researchers to propose that the persistent illness was caused by chronic EBV (Wessely et al., 1998). Despite subsequent evidence that EBV was often unrelated to this symptom presentation, media focus, public demand, and patient lobbyists suggested that the symptoms and disability associated with EBV were genuine (Wessely et al., 1998). In response, the Centers for Disease Control (CDC) formulated a group of infectious diseases specialists, clinicians, and researchers to
develop a specific case definition for this chronic illness in 1987. This resulted in the birth of the term *Chronic Fatigue Syndrome* (Holmes et al., 1988).

**Chronic Fatigue Syndrome**

The aim of the CDC working group was to develop appropriate nomenclature and form a set of operational criteria without attributing the illness to a specific causative agent. By identifying a homogenous collection of people suffering from the same condition, the group hoped to promote consistent research investigating underlying aetiological processes (Holmes et al., 1988). The working group arrived at the term CFS, describing it as a disabling condition characterised by fatigue lasting at least six months that was accompanied by a range of signs and symptoms. All other physical and psychological explanations for the illness had to be ruled out before a diagnosis was made, and psychiatric illnesses were considered exclusory.

The CDC criteria were largely unsuccessful in promoting research to determine aetiological factors. Fukuda et al. (1994) argued that disagreement among medical professionals and researchers regarding the exclusion of cases with a psychiatric diagnosis and the stringency of the criteria generated inconsistent diagnostic approaches. In 1994, a revision of the case definition was made with the goal of promoting international agreement on a comprehensive and systematic approach to the evaluation, diagnosis, and study of CFS (Fukuda et al., 1994). The new criteria omitted several exclusory psychiatric illnesses, such as somatoform disorders, anxiety disorders, and nonpsychotic or nonmelancholic forms of depression. There was also a reduction in number of somatic symptoms required, and all physical diagnostic signs were removed (Fukuda et al., 1994). The revised criteria are presented in Figure 1.1.
Hickie et al. (2009) measured the construct validity of the 1994 CFS case definition based on 33 studies across 21 countries. The final sample included 2,013
participants with chronic fatigue and 1,958 with CFS. An exploratory factor analysis revealed a five-factor solution for symptoms, including musculoskeletal pain or fatigue, neurocognitive difficulties, inflammation, sleep disturbance or fatigue, and mood disturbance. The solution could distinguish CFS from prolonged fatigue and was remarkably consistent across a wide range of cultures and healthcare settings. However, some argued that although the revised criteria increased the sensitivity of the diagnosis, the specificity was compromised, leading to considerable homogeneity in the presentation of patients with CFS (De Becker, McGregor, & De Meirleir, 2001; Jason et al., 1997). As a result, findings among much of the research are often inconsistent.

Ongoing dissatisfaction with the conceptualisation of CFS led to another collaboration of international experts at the beginning of the 21st century. This effort gave rise to what is now known as the Canadian case definition (Carruthers et al., 2003). Rather than relying on a set of specific criteria, the new diagnostic approach involves a flexible combination of primary and secondary symptoms. This allows for greater scope in identifying individual patients and enables researchers to clearly define their research sample. The aim of the definition was to create a clinically relevant and inclusive diagnostic approach by using criteria that encompassed a range of grouped symptoms (Carruthers et al., 2003; Carruthers, 2007). Figure 1.2 outlines the Canadian Clinical Working Case Definition.

Using a factor-analytic approach, Jason, Corradi, and Torres-Harding, (2007) investigated symptom profiles derived from the Canadian criteria in 114 patients. Four patient groups were identified: patients with infectious symptoms, patients with inflammatory symptoms, patients with prominent cognitive problems, and patients who were less severely impaired. The data suggest that CFS patients may be
Figure 1.2. Adapted From the Canadian Clinical Working Case Definition for CFS

A patient with CFS will meet criteria for symptoms 1-4; have two or more neurological/cognitive manifestations; have one or more symptoms from two of the categories of autonomic, neuroendocrine and immune manifestations; and adhere to item 7. The symptoms must have begun or changed after the onset of this illness. Confirmation of an active disease process that explains most of the major symptoms is grounds for exclusion.

1. **Fatigue:** Significant, new onset, unexplained, persistent, or recurrent physical and mental fatigue that substantially reduces activity level.
2. **Post-Exertional Malaise and/or Fatigue:** An inappropriate loss of stamina (physical and mental), rapid fatiguability (muscular and cognitive), post exertional malaise, fatigue, and/or pain and a tendency for associated symptoms to worsen with fatigue. Recovery is slow (>24 hours).
3. **Sleep Dysfunction:** Unrefreshing sleep, poor sleep quantity, or circadian rhythm disturbance.
4. **Pain:** Significant myalgia, often with headaches.
5. **Neurological/Cognitive:** Two or more of following difficulties: confusion, impaired concentration, short term memory difficulties; disorientation, difficulty with information processing, categorisation and word retrieval, perceptual and sensory disturbances, Ataxia; hypersensitivity to sensory overload.
6. At least one symptom from two of the following:
   - **Autonomic:** Orthostatic intolerance, postural orthostatic tachycardia syndrome, delayed postural hypotension, light-headedness, pallor, nausea and irritable bowel syndrome, urinary frequency, heart palpitations, exertional dyspnea.
   - **Neuroendocrine:** Loss of thermostatic stability, sweating, feverishness and cold extremities, intolerance of temperature extremes, weight change, worsening symptoms with stress.
   - **Immune:** Tender lymph nodes, recurrent sore throat, recurrent flu-like symptoms, general malaise, new sensitivities to food, medications, chemical.
7. **The illness persists for at least six months:** It usually has a distinct onset, although it may be gradual. Preliminary diagnosis may be possible earlier. Three months is appropriate for children.
differentiated according to clinically meaningful subgroups. Preliminary research also suggests that compared to the 1994 criteria, the Canadian case definition is superior in distinguishing CFS from psychiatric illnesses. The new definition also detects cases with a greater level of functional impairment and more symptoms of fatigue or weakness, and neuropsychiatric and neurological symptoms than earlier criteria (Jason, Torres-Harding, Jurgens, & Helgerson, 2004). It is important to recognise however, that like previous case definitions, the Canadian criteria were established through a consensual theoretical approach rather than empirical research. Currently, both the 1994 criteria and the Canadian case definition are commonly used to diagnose CFS.

Due to the heterogeneity of CFS, several authors have attempted to the illness categorise into subtypes. With this aim, Nisenbaum, Reyes, Mawle, and Reeves (1998) conducted telephone surveys with 1,150 people who had suffered from severe fatigue for at least one month. A principal components analysis of symptoms revealed a three-factor structure accounting for intercorrelations among 14 symptoms. The factors included fatigue, mood and cognition, flulike symptoms, and visual impairment. This factor structure only applied for participants who had experienced fatigue for more than six months, and no interpretable factor solution could be identified for those who had suffered severe fatigue for less than six months. Jason, Taylor et al. (2002) also identified subgroups in a community-based telephone study involving 780 CFS patients diagnosed according to the 1994 criteria. A four-factor solution emerged from a factor analysis: lack of energy, physical exertion, cognitive disturbance, and fatigue and rest. Using a cluster analysis approach, several other researchers have also successfully grouped CFS patients into subtypes according to illness severity (Arroll & Senior, 2009; Jason & Taylor, 2002;
Nisenbaum, Reyes, Unger, & Reeves, 2004) and fatigue type (Gielissen, 2007; Jason et al., 2009; Libman et al., 2008; Smets, Garssen, Bonke, & De Haes, 1995).

**CFS in Young People**

In the early 1990s, it became increasingly evident that illnesses characterised by chronic and debilitating fatigue were also common in children and adolescents. However, in the absence of research in paediatric patients, there was considerable uncertainty regarding how to characterise and diagnose young people. Some authors argued that CFS should not be diagnosed in paediatric patients due to insufficient epidemiological and diagnostic research (Harris & Taitz, 1989; Plioplys, 1997). Although several studies indicated that CFS-like illnesses could be identified in young people, many patients did not meet any diagnostic criteria (Bell, 1997; Carter, Edwards, Kronenberger, Michalczyk, & Marshall, 1995; Feder, Dworkin, & Orkin, 1994; Krilov, Fisher, Friedman, Reitman, & Mandel, 1998). Researchers initially attempted to account for this by reducing the stringency of the diagnosis and limiting the symptom duration requirement to three months (Carter et al., 1995; Carter, Kronenberger, Edwards, Michalczyk, & Marshall, 1996; Smith et al., 1991; Vereker, 1992). However, this diagnostic approach was ad hoc and had little basis in empirical research.

The Canadian case definition was the first set of criteria to make an explicit reference to paediatric populations. The criteria specified that three months of fatigue was sufficient for children. The authors also advised that compared to adults, the severity of symptoms may be more variable (Carruthers et al., 2003). Again however, this description was ad hoc and there was a continuing need for an empirical approach to defining CFS in young patients.
In 2006, the first case definition for paediatric CFS was published (Jason et al., 2006). The aim was to arrive at a set of objective criteria that would promote consistent diagnostic approaches in research and practice, provide authenticity to paediatric CFS, and protect children from being perceived as malingering or somatising. The authors took a dimensional approach to the paediatric definition and borrowed symptom categories from the Canadian criteria. Many of the minor symptoms were derived from factor-analytic studies. Figure 1.3 presents the recently revised Paediatric Case Definition for CFS (Jason et al., 2008; see Appendix A for the complete paediatric definition of CFS).

Compared to the adult criteria, fewer secondary symptoms are required for diagnosis in order to emphasise the importance of fatigue and compensate for variations in symptom severity. A preliminary diagnosis can be made following one to two months of fatigue, and CFS is diagnosed if fatigue continues for at least three months. Many premorbid somatic, cognitive, and depressive symptoms are not cited as a basis for exclusion, however a careful assessment is recommended to ensure that an alternative diagnosis does not more accurately account for the symptom presentation. Lifelong fatigue was also removed as a condition for exclusion due to the difficulty in determining reliable premorbid functioning during childhood development. It was noted that fatigue may manifest as irritability, and that compared to adults, children are characteristically more capable of adapting and accommodating to symptom development. Therefore, it was recommended that performance and involvement in educative and recreational activities provides a more reliable indicator of functional impairment in young people. School refusal was identified as an important differential diagnosis (Jason et al., 2006).
Figure 1.3. Paediatric Case Definition for CFS

I. Clinically evaluated, unexplained, persistent or relapsing chronic fatigue over the past three months that
   A. is not the result of ongoing exertion
   B. is not substantially alleviated by rest
   C. results in substantial reduction in previous levels of educational, social and personal activities
   D. must persist or reoccur for at least three months

II. The concurrent occurrence of the following classic ME/CFS symptom clusters, which must have persisted or recurred during the past three months of illness (symptoms may predate that reported onset of fatigue)

A: Post-exertional malaise and/or postexertional fatigue
   • A loss of physical or mental stamina
   • Rapid/sudden muscle or cognitive fatigability
   • Post exertional malaise and/or fatigue
   • A tendency for other associated symptoms to worsen
   • A slow recovery, usually taking longer than 24 hours

B: Unrefreshing sleep or disturbance of sleep quantity or rhythm
   • Prolonged sleep (including frequent naps)
   • Disturbed sleep
   • Day/night reversal

C: Pain or discomfort that is often widespread and migratory in nature. At least one symptom from any of the following;
   • Myofascial and/or joint pain
   • Abdominal and/or head pain

D: Two or more neurocognitive manifestations;
   • Impaired memory
   • Difficulty focusing
   • Difficulty finding the right word
   • Frequently forgetting what wanted to say
   • Absent mindedness
   • Slowness of thought
   • Difficulty recalling information
   • Need to focus on one thing at a time
   • Trouble expressing thought
   • Difficulty comprehending information
   • Frequently losing train of thought
   • New trouble with math or other educational subjects

E: One symptom from two of the following categories;
   1. Autonomic manifestations
   2. Neuroendocrine manifestations
   3. Immune manifestations
Chapter Summary

Examination of the historical context for CFS reveals why the illness remains poorly understood. CFS has undergone several conceptual transitions since the initial reports of similar conditions in the 19th century. Although the conceptualisation of fatiguing illnesses was initially received with great interest, failure to identify a biological cause and the social stigma associated with subsequent psychogenic conceptualisations caused these diagnoses to fall into relative disuse, impeding research progress in this area.

Since the first case definition of CFS in 1988, there has been much disagreement about how the condition should be defined and diagnosed. The Canadian definition enabled CFS to be more reliably distinguished from psychiatric conditions, and recent research classifying CFS patients into subgroups allowed for the heterogeneity of the illness to be integrated into the conceptualisation of CFS. In the last decade, the unique presentation of CFS in children and adolescents was acknowledged through the development of paediatric diagnostic criteria. As a consequence of these ongoing changes and recent developments, research efforts have been inconsistent, and CFS remains poorly understood, particularly in young people.

The historical pattern leading up to our current understanding of CFS has been enormously variable. The only consistent theme is the continuing confusion, debate, and frustration surrounding the conceptualisation of CFS. At present, researchers agree that CFS is an exceedingly important and pertinent illness for study. This is particularly true for young patients, who experience unique and profound impairment and disability at a pivotal life stage. Recent findings regarding
the prevalence of CFS in young people are especially concerning. As such, the following chapter will involve an exploration of the prevalence and impact of CFS in young people.
Chapter 2: Epidemiology and Aetiology of CFS in Young People

This chapter presents an analytic synopsis of the research examining the epidemiology and aetiology of CFS in young people. First, the methodological problems associated with the current research are explored in order to contextualise the discussion of the studies that follow. Research examining the prevalence, course, and impact of CFS in young people is then presented to provide an estimate of the magnitude of the problem that CFS represents for young people. This is followed by a discussion of the major aetiological theories of CFS in order to highlight the need for interventions designed to address key symptoms, such as cognitive impairment. Efforts were made to incorporate research from paediatric populations where possible.

Methodological Issues

The epidemiology of CFS in clinical and community samples is exceptionally difficult to determine. Fatigue is an intangible, vague construct that is resistant to operationalisation and objective measurement (Wessely et al., 1998). The severity and impact of CFS symptomatology is typically determined using self-report measures. Moreover, people with unremitting, severe fatigue present with similar symptom patterns to those with CFS, making the distinction between these patients somewhat arbitrary and difficult to determine (Chester, 1997; Fukuda et al., 1997). Similarly, fatigue is a common core symptom of many physical and psychological conditions, making it difficult to accurately diagnose CFS patients in the absence of a thorough medical assessment (Wessely, 2001). Research has been further impeded by the evolving case criteria and inconsistent diagnostic procedures and nomenclature (Maquet, Demoulin, & Crielaard, 2006). As such, there is immense
heterogeneity between samples, and it is difficult to make reliable comparisons between studies or form generalisations to the entire CFS population (Demitrack, 1998; Jason et al., 2005; Levine, 1997; Wessely et al., 1998).

Research is even more challenging in paediatric populations. Of the few studies investigating the epidemiology of CFS in young people, most involve small, heterogenic samples, and there is little consistency in the diagnostic and assessment approaches used between studies. Further, samples of paediatric patients are largely obtained from tertiary organisations. Given that CFS patients in tertiary health care settings typically report higher levels of impairment and symptom severity than those in the community (Jason, Plioplys, Torres-Harding, & Corradi, 2003), many current findings may be limited to describing patients who are most severely affected by CFS. For these reasons, caution is warranted in forming conclusions regarding the epidemiology of CFS in paediatric patients.

Epidemiology of CFS

Prevalence. Fatigue is a common complaint in clinical and community populations (Chen, 1986). Estimates from worldwide community studies indicate that the prevalence of significantly elevated fatigue is approximately 20-25% (Kroenke & Price, 1993; Lorge, Ekeberg, & Kassa, 1998). Similarly, 21-27% of people in clinical populations report prolonged, high levels of fatigue (Bates et al., 1993; Buchwald, Sullivan, & Komaroff, 1987; Kroenke, Wood, Mangelsdorff, Meier, & Powell, 1988). The incidence of fatigue is consistently higher among females, although the gender ratio varies considerably between studies (Kroenke et al., 1988). Chronic fatigue is also common in nonclinical adolescent populations. Based on semistructured interviews in 8,580 randomly selected households, 14.9%
of those aged between 16 and 24 reported chronic fatigue lasting at least six months (Watanabe, Stewart, Jenkins, Bhugra, & Furukawa, 2008). Similar results were found using a multidimensional questionnaire in 3,467 adolescents aged from 12 to 18. Notable differences were identified between boys and girls, with 20.5% of girls and 6.5% of boys scoring above the clinical cut-off for severe fatigue. Of these participants, 80.0% of the girls and 61.5% of the boys reported severe fatigue for at least one month (ter Wolbeek, van Doornen, Kavelaars, & Heijnen, 2006).

One of the earliest studies to investigate the prevalence of CFS in young people was conducted in Australia (Lloyd, Hickie, Boughton, Spencer, & Wakefield, 1990). General practitioners (GPs) were asked to detect possible cases of CFS in patients presenting at doctors’ clinics. Following GP referral, patients completed a screening questionnaire, participated in interviews conducted by both a physician and a psychiatrist, and underwent a medical examination to exclude alternative diagnoses. Point prevalence rates were estimated at 0.37% in adults, 0.47% in those aged between 10 and 19, and 0.05% in children aged under 10 years. However, compared to similar research in adults, this estimate is moderately low (Cho, Menezes, Hotopf, Bhugra, & Wessely, 2009; Wessely, Chalder, Hirsch, Wallace, Wright, 1997). A possible explanation for this discrepancy is that the probable CFS cases were detected through GPs. Some patients with CFS may not have attended a GP clinic during the data collection period. Further, many GPs are sceptical about the existence of CFS (Bowen, Pheby, Charlett, & McNulty, 2005; Raine, Carter, Sensky, & Black, 2004), and a follow-up of nearly half of the GPs in the original study revealed that 19 possible cases may have been undetected (Lloyd et al., 1990). Therefore, these results may underestimate the prevalence of CFS. Nonetheless, it is interesting to note that the prevalence rates were highest in the adolescent group.
This could be attributable to extraneous factors such as the recruitment method. For example, young people may have been more likely to attend a GP clinic. However, it is also possible that CFS is most common in the adolescent age group.

Due to their scope, community-based screening assessments capture a greater number of people presenting with severe chronic fatigue. Using this approach, a screening of over 12,000 households was conducted in a sample of five- to 17-year-olds. Over 4% of respondents reported significant fatigue, and 2.05% were diagnosed with a CFS-like illness. Higher rates of CFS-like illnesses were observed in adolescents (2.91%) compared to prepubescent children (1.96%), and the rates were similar between males (47.5%) and females (52.5%; Jordan et al., 2000).

However, much lower prevalence estimates have been reported in other studies using the same approach. In a large telephone-based screening of 8,004 households containing 16,970 residents, participants were given a survey followed by a brief interview. Respondents who appeared to meet the 1994 case definition accounted for 0.2% of adult respondents, and a further 1.8% were classified as idiopathic chronic fatigue-like cases. Of the 2,343 residents under the age of 18, 15 (0.77%) reported fatigue lasting more than one month. However, eight (0.34%) of these participants reported fatigue lasting more than six months, of whom three were diagnosed with exclusionary conditions, four (0.17%) had idiopathic chronic fatigue, and one (0.04%) appeared to meet the 1994 criteria (Steele et al., 1998).

Similar results were found in a screening of 10,438 mothers of children aged between five and 15 across the United Kingdom. Chronic fatigue was defined as severe fatigue associated with functional impairment of at least six months' duration, for which rest did not alleviate. CFS was defined according to the 1994 criteria. Although 34.1% of the 4,240 children aged between 11 and 15 endorsed feelings of
fatigue, 0.57% reported chronic fatigue and 0.19% met the criteria for CFS. Moreover, only 0.04% of parents reported that their child had been officially diagnosed with CFS or ME (Chalder, Goodman, Wessely, Hotopf, & Meltzer, 2003). The same research group later conducted a prospective study with 842 adolescents aged between 11 and 15. Incidence rates over a period of four to six months were 1.1% for chronic fatigue, and 0.5% for CFS (Rimes et al., 2007).

A significant limitation of these community-based studies is that the data were derived from self-report questionnaires or basic interviews. In the absence of a medical examination, excusatory conditions cannot be reliably ruled out in accordance with standard diagnostic procedures. This limits diagnostic accuracy, potentially causing inflated prevalence estimates. One group sought to overcome this problem by investigating nationwide prevalence and incidence rates using a similar approach to the study by Lloyd et al. (1990). A representative sample of 354 GPs in the Netherlands completed questionnaires regarding the prevalence of CFS in their patients aged 10 to 18 years. In addition, paediatric hospital departments prospectively reported new cases of CFS in adolescent patients. Prevalence was estimated at 0.11% and incidence was 0.01% (Nijhof et al., 2011). Although this study relied on GP notifications, all Dutch citizens must be registered within a GP clinic, and GP referral is mandatory for patients to access hospital care. Further, GPs are required to make detailed records of patient diagnoses, reducing the likelihood that GPs relied on retrospective recall to report cases.

The prevalence studies discussed above each share the common problem of identifying CFS in young people according to adult case definitions. It is widely recognised that the adult criteria are not equally applicable to paediatric patients, and the criterion that fatigue must be present for at least six months is generally
considered to be excessive for children and adolescents (Carter et al., 1995; Carter et al., 1996; Smith et al., 1991; Jason et al., 2006; Vereker, 1992). As such, it is probable that these studies underestimate the prevalence of CFS in young people (Marshall, 1999).

In seeking to account for this issue, Farmer, Fowler, Scourfield, and Thapar (2004) investigated the prevalence of chronic fatigue and CFS using a range of definitions. The inhabitants of 1,468 households completed initial screening questionnaires, and follow-up telephone interviews were conducted in eight- to 17-year-olds who reported disabling fatigue lasting several days or more. The lifetime prevalence estimate of fatigue lasting more than three months was 2.34%, although this figure dropped to 1.9% when fatigue was accompanied by at least four of the minor criteria from the 1994 case definition. The prevalence of fatigue lasting more than six months accompanied by at least four of the minor symptoms was 1.29%. As expected, this suggests that a paediatric diagnostic approach produces somewhat higher prevalence estimates compared to when young patients are diagnosed according to adult criteria. Note however, that although most other studies include point prevalence rates, these figures provide estimates of lifetime prevalence rates, which are almost certain to be higher.

At present, prevalence estimates of CFS in young people are derived from a small number of studies that are limited by inconsistent diagnostic approaches and samples of patients who did not meet the full criteria for CFS. Future research using the paediatric case definition is needed to gain a more accurate estimate of the prevalence of CFS in young populations. To date, the literature suggests that CFS may be similarly common in adolescents and adults. However, the emerging research suggests that the impact of CFS is unique and perhaps most profound in
younger patients, often resulting in significant disruptions in development and wellbeing throughout life.

**Course.** Although research in younger populations is scarce, preliminary findings suggest that the course of CFS is similar in adult and paediatric patients (Mears, Taylor, Jordan, & Binns, 2004). Like in adults, illness course appears to be somewhat variable in young populations. Some patients experience intermittent patterns of relapse and remittance, while others suffer from persistent, unchanging symptoms (Nisenbaum, Jones, Unger, Reyes, & Reeves, 2003; Smith et al., 1991). The period of illness onset is also variable. For instance, 60% of adolescents in one study reported that onset occurred suddenly following an acute illness (Krilov et al., 1998), while around 75% of adolescents in another study reported that onset was gradual (Patel, Smith, Chalder, & Wessely, 2003). Young CFS patients also commonly report premorbid organic and psychological health problems (Rangel, Garralda, Levin, & Roberts, 2000), and high rates of comorbid psychological disturbances have been identified in both adolescent and adult populations (Hickie, Lloyd, & Wakefield, 1995; Patel et al., 2003; Rangel, Garralda, Hall, & Woodham, 2003).

Although the results are mixed, the prognostic outcome for CFS appears to be more positive for young patients compared to adults. For instance, in a review of studies with varied follow-up durations, 54-94% of children and adolescents with chronic fatigue made substantial improvements or completely recovered, while only 0-6% of adults with CFS returned to their premorbid health status (Joyce, Hotopf, & Wessely, 1997). Importantly however, the children in these studies presented with chronic fatigue, while the adults met the criteria for CFS. Given that the recovery
rates are much higher in those with chronic fatigue compared to CFS (Gill, Dosen, & Ziegler, 2004), the divergent prognostic outcome between adults and young people could be attributable to differences in illness type rather than age.

Other research suggests that a significant portion of young CFS patients remain symptomatic for several years, and complete recovery from paediatric CFS is rare (Dale & Straus, 1992). One group evaluated prognosis over a period of four years in a sample of 42 CFS patients aged between seven and 21 years. At baseline, half the participants had been fatigued for one to six months and the other half had been fatigued for seven to 36 months. After one year, 59% continued to report moderate to severe symptoms, although most patients gradually improved over the following three years. At the final interview, 43% of parents considered their child to be completely recovered, 52% reported that their child had improved but not recovered, and 5% believed that their child had not improved at all (Krilov et al., 1998). Comparable results were found in a 13-year study involving 35 children and adolescents with CFS. At follow-up, 13 participants (37.1%) considered themselves to be completely recovered, 15 (42.9%) reported that they were well but not recovered, four (11.4%) believed that they were chronically ill, and three (8.6%) considered themselves to be more ill than they had been previously (Bell, Jordan, & Robinson, 2001).

However, many patients who report significant improvements continue to suffer debilitating symptoms. For instance, in the 13-year follow-up study, half of those who stated that they were functioning well reported mild symptoms and activity limitations (Bell et al., 2001). Similar results were found in a study of 28 CFS patients aged between seven and 17 who were being treated in a specialist paediatric psychiatric service. Although most young people regarded themselves to
be fully recovered at three-year follow-up, about one third reported ongoing disabling symptoms, and nearly 40% continued to experience fatigue (Sankey, Hill, Brown, Quinn, & Fletcher, 2006). This suggests that even among those patients who identify as recovered or significantly improved, many experience ongoing symptoms and impairment.

One group found that prognosis appears to be considerably worse for young CFS patients compared to fatigued patients who do not meet the criteria for CFS. Following an average of 4.57 years, 25% of 16 adolescents with CFS had made a complete recovery, while 44% continued to meet the 1994 criteria for CFS. In contrast, of the 10 participants who reported fatigue lasting more than six months, 50% reported an almost complete recovery, 10% reported a partial recovery, and 40% reported no improvement. Most remarkably, all of the eight adolescents who had presented with disabling unexplained fatigue of less than six months duration had made a complete recovery (Gill et al., 2004).

In adult patients, the best predictors of poor prognosis include older age, greater illness chronicity, higher incidence of psychological illnesses, and increased somatic attributions to illness cause (Joyce, et al., 1997). Conversely, Gill et al. (2004) found that demographic factors are not reliable predictors of prognosis. Interestingly, secondary school attendance when unwell is an exceptionally strong predictor of positive outcomes in school-aged patients (Bell et al., 2001).

Taken together, these findings suggest that although the course of CFS is variable, many young patients suffer from ongoing symptoms and impairment, and few make a full recovery even after several years. Moreover, it is important to note that young people with lifelong fatigue and patients who were unable to determine the period of illness onset were typically excluded from these studies. As such, the
data may underestimate the long-term morbidity of CFS in young people. The implications for ongoing illness are likely to be considerable when they occur at this vulnerable time of identity formation, academic accomplishment, and general developmental growth.

**Impact.** The unique impact of CFS in young people perhaps represents the greatest distinction between paediatric and adult CFS. For adolescents, CFS can have a particularly substantial negative effect on education, psychological wellbeing, social relationships, and physiological functioning. Due to the critical processes necessary for normal development in young people, CFS is likely to have a distinctive and profoundly damaging impact on this age group.

**Educational disturbance.** Frequent school absenteeism is a characteristic feature of CFS in young patients, and CFS constitutes the leading cause of long-term sickness resulting in absence from school (Colby, 2006). In a longitudinal study of adolescents aged between 12 and 17, all 28 participants reported that CFS had interfered with their education to some degree. At the initial interview, 21% were attending school part time or receiving home tuition, and 43% ceased regular schooling and participated in home education at some stage over a three-year follow-up. Following a period of absence, 64% took up to three months to return to school and 14% took even longer. Further, 54% reported that this process was difficult or very difficult, and 68% felt that their illness had affected their education or career plans significantly (Sankey et al., 2006).

Young CFS patients often miss a significant amount of school over extended periods. This was demonstrated in a 13-year follow-up study involving 35
adolescents with CFS. Over this time, eight participants had missed one to six months of school, three had missed six to 12 months, two had missed one to two years, and eight had missed two years or more (Bell et al., 2001). Another group found that 41 school-aged CFS patients missed 33% of classes over a period of one month. In addition, the 13 adolescents who were not of school age worked 38.7% of a full time job (van Geelen, Bakker, Kuis, & van de Putte, 2010). Comparable results were observed in a larger study involving 211 young patients from a specialist paediatric CFS service. Only 11% attended full-time school, 49% attended 20% or less, 62% attended 40% or less, and 28% did not attend school at all (Crawley & Sterne, 2009).

A comprehensive investigation of school absenteeism was conducted in a cross sectional study of 36 adolescents with CFS. The average rate of school attendance in the week preceding the survey was 29.9%. During that period, 44% had not attended school at all, and only 37.5% attended more than half the full school week. Over two-thirds of the sample expressed worry about returning to school, and 38.9% felt that their school had not supported their educational requirements (Patel et al., 2003). These factors could contribute to the tendency for CFS patients to avoid school and might explain why many do not return to school after their symptoms improve.

It is possible that school absenteeism occurs as a consequence of the difficulties associated with managing school while suffering from a chronic illness. However, research suggests that absenteeism is a unique feature associated with CFS and not other debilitating chronic illnesses. For instance, one group found 39% of 28 CFS patients missed 15-50% of school compared to none of the patients with Juvenile Idiopathic Arthritis (JIA) and 15% of patients with an emotional disorder.
Further, 43% of those with CFS missed at least one school term compared to 3% of the JIA group and 15% of the emotional disorders group (Garralda & Rangel, 2004). Similar results were found in a study comparing young CFS patients with patients suffering from Juvenile Rheumatoid Arthritis (JRA) or Major Depressive Disorder (MDD). In the CFS group, the average number of school days missed since being unwell was 72, and 86% required either half days or home-based education to accommodate for their condition. In contrast, adolescents with MDD and JRA missed 11.4 and 7.5 days per year respectively (Gray, 2001). These results suggest that the frequency of school absenteeism in CFS patients is unlikely to be caused by the general physical or emotional impact of chronic illness. Intriguingly, this indicates that there is something unique to CFS that causes patients to avoid school.

In the context of such severe school absenteeism, it is not surprising to find that CFS is associated with poor academic achievement. Results from a cross-sectional survey in 36 CFS patients revealed that students achieved three out of 10 passes on average over an 18-month period. Of these students, 44% received more than five passes, 25% received one to four passes, and 30.6% failed to receive a single pass grade or even sit their examinations (Patel et al., 2003). In a more recent study, 70% of 21 adolescents with CFS had failed at least one year of study since illness onset. Further, 70% were unable to follow the standard exam schedule, and only 33% of students felt that their grades were in accordance with their capacities (van Hoof, De Becker, Lapp, & De Meirleir, 2009).

Research in this area is impeded by inconsistencies in time parameters, participant sampling, and methods of data collection. This makes it difficult to compare findings across studies and generalise the results to the population of young CFS patients. Nonetheless, these initial findings depict a clear pattern of significant
school absenteeism and educational impairment among young CFS patients. Due to the fundamental importance of the many educational and social functions of schooling (Newman & Newman, 1987), prolonged periods of absence may result in enduring consequences within a range of essential developmental processes. At this stage, it is unclear whether poor academic performance is a consequence of school absenteeism, cognitive impairment, or a combination of both. Determining the unique contributions of these factors may lead to important new insights regarding how to address academic decline in young patients.

**Psychological disturbance.** Young people with CFS often report considerable psychological problems. For instance, in a study of 54 adolescents with CFS, mean self-report scores on measures of mental health and self-esteem were approximately one standard deviation below those of the healthy population (van Geelen et al., 2010). Young CFS patients also tend to report higher levels of psychological distress compared to young people with other chronic illnesses. For example, Garralda and Rangel (2004) found that CFS participants responded to illness-related problems with increased levels of anxiety and depression than those with JRA or an emotional disorder. However, both the CFS and the emotional disorders group reported higher levels of anger than those with JRA. In a similar study, Gray et al. (2001) administered the Minnesota Multiphasic Personality Inventory – Adolescent (MMPI-A) to a small sample of young people with CFS or JRA. Compared to participants with JRA, the CFS patients scored significantly higher on Conversion Hysteria and demonstrated clinical elevations on the Hypochondriasis, Hysteria, and Depression scales (Gray et al., 2001).
Several studies also suggest that diagnosable psychiatric disorders are common in young CFS patients. One group identified psychiatric disorders in approximately half of 50 children and adolescents with a history of CFS. Anxiety and depressive disorders were the most commonly diagnosed conditions (Garralda, Rangel, Levin, Roberts, & Ukoumunne, 1999). The prevalence of comorbid psychiatric disorders also appears to be higher in young CFS patients compared to those with other chronic illnesses. For instance, Rangel et al. (2003) identified psychiatric disorders in 72% of paediatric CFS patients compared to 34% of patients with JIA. The CFS group also reported greater levels of impairment associated with a psychiatric illness. The most common psychiatric complaints included depressive and anxiety disorders, as well as personality disturbances. Another group found that even after controlling for somatic symptoms, adolescents with CFS scored significantly higher on a scale of depression compared to those diagnosed with JRA (Brace, Smith, McCauley, & Sherry (2000). These findings suggest that the high rates of psychopathology in young CFS patients cannot be explained entirely by the presence of a chronic physical illness.

Questions have been raised as to whether psychological disturbances contribute to the development of CFS or if mental health deteriorates following the onset of CFS. One group investigated this subject using a prospective research approach in 301 adolescents diagnosed with glandular fever. Six months following the infection, 39 participants met the criteria for CFS, and a further 39 recovered patients were selected to match the CFS participants. While suffering from glandular fever, both groups reported similar levels of emotional function. However, at a six- and 12-month evaluation, those who had developed CFS reported more difficulty with emotional function than the recovered controls, although these differences were
no longer significant at a 24-month follow-up (Taylor et al., 2010). These results suggest that psychological distress emerges following the development of CFS. However, it is unclear whether CFS acts as a causative agent or whether extraneous factors lead to the development of both CFS and psychological symptoms.

Together, the emerging research provides a clear indication that young people with CFS suffer from significant psychological distress and frequent comorbid psychiatric disorders. The distress and functional impairment associated with psychological disturbances contributes to the already profound impact of CFS in young sufferers. Moreover, patients suffering from these symptoms in adolescence may continue to experience psychological and interpersonal problems throughout life.

**Psychosocial impairment.** Preliminary research suggests that CFS interferes with psychosocial development and function in young people. Rangel et al. (2000) noted that when illness was at its worst, family relationships became strained and the frequency of social contact declined. In a recent study involving 27 CFS patients aged between 12 and 21, approximately half reported that they have had fewer friends since illness onset, and most limited their social outings with friends to once per month. Around half the participants reported conflicts at school associated with CFS, and 56% reported that they had received negative comments from peers when they participated in leisure activities. This was despite indications that 90% had quit their hobby due to their condition and that 93% did not participate in extracurricular activities (van Hoof et al., 2009).

Findings from a prospective study also suggest that CFS patients engage in normal social activity prior to the development of CFS. Specifically, no significant
differences were observed in social activity between patients with glandular fever who either went on to develop CFS or to make a full recovery. However, at a six-, 12-, and 24-month follow-up, those who had developed CFS reported greater limitations to social activity than the fully recovered matched controls (Taylor et al., 2010).

Preliminary research suggests that social impairment is not an inevitable outcome of chronic illness, but rather a unique feature associated with CFS. For instance, Brace et al. (2000) found that compared to young people with JRA, CFS patients perceived themselves to be less socially competent. Another group found that CFS patients participated less frequently in activities at home and with friends than patients with JIA or an emotional disorder. Compared to the JIA group, the CFS participants also reported greater disturbances in social and familial relationships, as well as increased conflict with friends and family. However, those with emotional disorders reported more severe disturbances on these measures and were more likely to withdraw socially than the CFS group (Garralda & Rangel, 2004). These results suggest that disturbances in social functioning are not simply a consequence of chronic illness or physical disability but that CFS is uniquely associated with social impairment. Emotional disturbances, which frequently co-occur with CFS, may also exacerbate the social impact of CFS.

The results from other research investigating the social impact of CFS have been less consistent. One group found that compared to population norms, a group of 36 female adolescents with CFS reported lower perceived competence in romance and less participation in recreational activities. However, perceptions of social acceptance and friendships were within the normal range (van Middenthorp, Geenen, Kuis, Heijnen, & Gerben, 2001). Another group found that young CFS patients
reported greater social limitations and less family activity than healthy controls, although there were no group differences with respect to family cohesion (Kennedy, Underwood, & Belch, 2010).

CFS patients also appear to be particularly susceptible to victimisation. Van Houdenhove et al. (2001) conducted a thorough investigation of victimisation in 95 adults with either CFS or Fibromyalgia. Comparison groups included a chronic illness group comprising of 26 Rheumatoid Arthritis patients and 26 Multiple Sclerosis (MS) patients, and a healthy control group matched for gender, age, civil state, and level of education. Of those with CFS or Fibromyalgia, 64.1% reported victimisation compared to 42.3% of the chronic illness group. The CFS patients also reported significantly greater levels of emotional neglect and abuse than the other control groups. Physical abuse was more common in the CFS group compared to healthy controls but not the chronic illness group. The rates of sexual harassment or abuse were similar between groups. Compared to the other chronically ill patients, victimisation was more likely to be carried out by a family member, occur over a life-long period, and have a greater negative impact in the CFS group (Van Houdenhove et al., 2001).

Taken together, these results suggest that CFS patients suffer profound psychosocial impairment and are subject to significant victimisation and abuse. Given that the formation of interpersonal relationships is considered to be a vital component of adolescent development (Greenberg, Siege, & Leitch, 1983), the psychosocial disturbances associated with CFS are likely to be particularly disruptive for young people. These disturbances may limit lifelong opportunities and impede the negotiation of the social developmental tasks of adolescence.
**Physical impairment.** Physical limitations are another source of considerable impairment for young sufferers of CFS. In many cases, children are unable to perform basic mobility activities. One group found that when illness was at its worst, 57% of 25 adolescents had been bedridden for prolonged periods and several others were confined to a wheelchair (Rangel et al., 2000). In a more recent study, 24 of 28 young CFS patients reported difficulty with mobility and could only walk with support for short distances or not at all (Sankey et al., 2006). However, it is worth noting that the patients in these studies were drawn from tertiary healthcare settings, where the most severely affected patients are likely to present. As a result, these findings may overestimate the prevalence and severity of physiological impairment in CFS patients. Conversely, a substantial portion of patients who were approached for these studies chose not to participate. It is probable that some declined due to the severity of their condition, lowering the prevalence estimates of severe physiological impairment.

Physiological impairment may also cause further limitations to activity. For instance, in a community sample of 25 CFS patients aged from nine to 18, significant role or social limitations were attributable to physical health problems (Kennedy et al., 2010). Similarly, self-report data from a sample of 211 young CFS patients indicated that physical function, and not anxiety, depression, or pain, was positively related to school attendance. Of this sample, 98% reported limitations to mobility or activities of daily living (Crawley & Sterne, 2009). These findings indicate that physical impairment may lead to withdrawal from social and educational activities.

Based on the small number of studies conducted thus far, physiological function appears to be severely limited in a significant portion of young CFS patients, resulting in reduced participation in educational, social, and recreational
activities. Therefore, physiological deterioration could potentially amplify the already profound impairments experienced by young CFS patients.

**Conclusion.** Epidemiological research for CFS in young populations is still in the preliminary stages. To date, findings suggest that the prevalence rates in adolescents approach those observed in adults. Recovery is prolonged for many, and although most young patients improve over time, symptoms often persist for years and many patients fail to recover completely. In addition, CFS causes considerable impairment that uniquely affects young patients, interfering with several vital developmental behaviours and activities at an especially vulnerable age. Given that CFS has such a profound impact on a significant number of young patients over prolonged periods, it is important to build a sound understanding of how young patients are affected. However, even though cognitive impairment is a common symptom that can cause considerable disruption to development and education, little is known about the nature and extent of cognitive dysfunction in young patients. Further research aimed at developing a more complete understanding of how CFS affects young patients will assist in the process of establishing appropriate and effective treatments for this population.

**Aetiology of CFS**

Despite more than two decades of rigorous research, the aetiology of CFS remains largely unknown. Findings from the existing literature are typically ambiguous and contradictory. With the exception of psychiatric theories, paediatric populations have largely been excluded from aetiological research, and current conceptualisations rely on the assumption that children and adults share similar
pathophysiological processes. The following includes a brief examination of the major aetiological theories for CFS.

**Infectious process theories.** Observations of viral infections preceding the development of CFS, along with evidence of shared symptomatology between CFS and infectious illnesses led researchers to theorise that infection was an important causative factor in CFS (Levy, 1994). Initially, researchers gave considerable attention to the role of EBV (Buchwald et al., 1987). Early research suggested that compared to healthy people, patients with a prolonged illness have elevated levels of EBV antibodies (Tobi et al., 1982). Yet further studies revealed that group differences are often mild or not statistically significant, and the majority of people who are infected with EBV do not go on to develop a chronic illness (Buchwald et al., 1987).

However, subsequent research reaffirmed the relationship between CFS and infectious illnesses. In a prospective Australian study, researchers investigated 253 patients infected with EBV, Coxiella Burnetii (Q fever), or Ross River virus. Six months following the initial infection, 11% of patients met the criteria for CFS and a further 1% developed a fatigue syndrome. However, the strongest predictor of enduring fatigue was the severity of the original illness rather than infection type, demographic variables, or psychological factors (Hickie et al., 2006). Using a similar approach, another group found that patients with glandular fever and EBV were no more likely to develop CFS than those who had glandular fever alone (White et al., 1998; White et al., 2001). Recent evidence also suggests that CFS patients have high rates of enteroviral RNA (Chia, 2005; Chia & Chia, 2008; Colby, 2007; Jason et al., 2005).
The infectious illness hypothesis has also been investigated in samples of young patients. One group identified serological evidence of a recent EBV-associated infectious mononucleosis in five of 36 paediatric patients with chronic fatigue (Carter et al., 1995). Laboratory investigations in another sample of 15 adolescents with CFS revealed little evidence of an active infection and no evidence of HHV-6, CMV, Coxsackie virus, EBV, or Toxoplasma (Smith et al., 1991). In a more recent investigation of 58 young people with chronic fatigue, 60% indicated that their fatigue first began during an acute infection. Indicators of previous EBV were detected in 55% of the sample, although only three of these participants demonstrated evidence of an acute infection in the six months preceding assessment for CFS (Krilov et al., 1998).

It is important to note that the infectious process hypothesis is frequently undermined by other research suggesting that CFS often develops following a noninfectious illness or without any apparent preceding condition (Salit, 1997). Even in those studies where infections have been detected, the vast majority of patients exhibit normal laboratory results. As such, it appears likely that the link between CFS and infection is only small or indirect.

**Immunological disturbance theories.** Evidence of a relationship between CFS and infectious diseases generated interest in the role of immunological disturbances in the onset CFS. Immune system dysfunction may be directly responsible for generating some of the common symptoms of CFS. For instance, disturbances in the levels of certain cytokines are associated with fatigue, sleep disturbance, myalgia, and fever (Moldofsky, 1993). Alternatively, immune system abnormalities could have a more indirect association with CFS through the activation
of latent infections or by generating an abnormal response to infection. A range of 
immune system abnormalities have been identified in CFS patients.

Abnormalities in the quantity and activity of natural killer (NK) cells are 
common in CFS patients, although there is little consistency between studies in the 
nature of these abnormalities (Bates et al., 1995; Gold et al., 1990; Klimas, Salvato, 
Morgan, & Fletcher, 1990). Using serological evaluations, one group found that 
CFS patients had elevated numbers and reduced cell cytotoxicity of NK cells 
(Klimas et al., 1990), and another group found that CFS patients with low NK cell 
activity had greater fatigue, sleep disturbance, functional impairment, and cognitive 
deficits compared to those with normal NK cell activity (Siegal et al., 2006). See 
and Tilles (1996) also found that NK cell activity increased in CFS patients 
following treatment with interferon, and this change was associated with 
improvements in quality of life. In contrast, several studies suggest that CFS patients 
have increased NK cell activity (Gold et al., 1990; Peakman, Deale, Field, 
Mahalingam, & Wessely, 1997). Given that stress and depressive symptoms often 
correlate strongly with low NK cell activity (Bonneau, Sheridan, Feng, & Glaser, 
1991), these contradictory findings could be at least partially explained by patient 
differences in psychological distress.

T-cell function has also been investigated in CFS aetiology. T-cells have a 
central role in cell-mediated immunity and belong to the same group of white blood 
cells as NK cells. Researchers have identified lower numbers and reduced function 
of T-cells in CFS patients compared to healthy controls (Lloyd, Wakefield, 
Boughton, & Dwyer, 1989) and depressed patients (Lloyd, Hickie, Hickie, Dwyer, & 
Wakefield, 1992). However, examination of T-cell subtypes reveals that the patterns 
of abnormality are largely inconsistent (Gold et al., 1990; Klimas et al., 1990;
Young CFS patients have been included in a small number of studies investigating immunological disturbances. Ter Wolbeek et al. (2007) recently conducted a longitudinal study involving 61 nonfatigued and 67 severely fatigued adolescent girls, 11 of whom met the criteria for CFS. No differences between groups were observed in mitogen-induced cytokine production or T-cell proliferation. However, despite similar levels of symptom severity between the CFS group and the severely fatigued patients, only those with CFS exhibited increased levels of anti-inflammatory cytokines and reduced levels of proinflammatory cytokines. Rowe (1997) also found that infusions of gammaglobulin, an immunological restoration treatment, were similar to a placebo in generating functional improvements in adolescent CFS patients. Finally, using a prospective study in 14 children who initially presented with nonspecific symptoms, one group found that antinuclear antibodies and the antibody to the 62 kDa protein were significant risk factors for the development of CFS, indicating that autoimmunity may be related to the pathogenesis of childhood CFS (Itoh et al., 1997, 1998).

Researchers have also investigated the role of intracellular immune function in CFS. Several studies suggest that the 2-5A synthetase/RNase L pathway is strongly dysregulated in CFS patients (De Meirleir & Bisbal, 2000; Nijs & De Meirleir, 2005; Suhadolnik et al., 1999; Suhadolnik, Reichenbach, Hitzges, Sobol et al., 1994). Further, studies covering diverse international populations suggest that CFS patients have lower activity levels of 2-5A synthetase, increased concentrations of activated 2-5A synthetase, and elevated RNase L activity compared to healthy controls (Suhadolnik et al., 1999; Suhadolnik, Reichenbach, Hitzges, Adelson et al., 1994).
1994; Suhadolnik, Reichenbach, Hitzges, Sobol et al., 1994). More recently, researchers have identified an association between indicators of intracellular immune dysfunction and CFS severity (Meeus et al., 2008; Snell, Vanness, Strayer, & Stevens, 2002, 2005).

Despite being investigated at length, consistent patterns of immunological disturbances have not been identified. Indeed, one group noted that the collection of research findings is so diverse that almost any conclusion could be drawn about immunological disturbances in CFS (Lyall, Peakman, & Wessely, 2003). Even when disturbances have been identified, they do not provide an adequate or complete explanation for the severity of symptoms and level of impairment observed in CFS patients. The inconsistent and contradictory findings could be partially explained by a range of methodological issues, such as inconsistencies in the application of immunological parameters and laboratory techniques. Moreover, due to the often small and heterogenic samples used, many studies may have failed to account for potentially important differentiating factors such as illness length, inactivity, medication and comorbid psychiatric conditions (Lyall et al., 2003). In consideration of these factors, it seems likely that as a group, CFS patients are affected by a range of subtle immunological abnormalities. However, the diversity of the results suggests that the immune system plays a complex and multifaceted role in CFS aetiology that is far from being well understood.

**Psychological theories.** In the absence of a consistent physiological marker for CFS, many researchers proposed that an underlying psychiatric process could be central to illness aetiology. Evidence for this was initially drawn from consistent findings that CFS patients have high rates of comorbid psychological disturbances
The prevalence of psychiatric disorders in CFS patients ranges between approximately 50-75% for both adults (Matsuda et al., 2009; Nater et al., 2009; Wessely & Powell, 1989) and young people (Garralda et al., 1999; Lines, 2004). Mood and anxiety disorders are consistently identified as the most common conditions. Researchers have suggested that the frequency of psychiatric disorders in CFS patients is caused by the ongoing stress and demands of suffering from a chronic illness. However, this is inconsistent with evidence suggesting that psychiatric illnesses are more common in young CFS patients compared to patients with other chronic illnesses such as JRA (Brace et al., 2000), JIA (Rangel et al., 2003), and MS (Johnson, DeLuca, & Natelson, 1996).

Determining whether psychiatric morbidity exists prior to, or develops following the onset of CFS may afford a valuable insight into the aetiological role of psychiatric disturbances in CFS. In a prospective study, one group found that patients with glandular fever who later developed CFS had similar levels of emotional wellbeing to those who went on to recover. However, the CFS group reported more difficulty with emotional adjustment than the recovered controls at a six- and 12-month evaluation (Taylor et al., 2010). Other prospective research suggests that prolonged fatigue does not predict the development of psychiatric disorders or psychological distress, and psychological factors do not increase the risk of developing fatigue (Hickie, Koschera, & Hadzi-Pavlovi, 1999; van der Linden et al., 1999). These results suggest that although psychiatric disturbances and prolonged fatigue often co-occur, it is unlikely that CFS develops in response to psychiatric morbidity or that CFS causes psychological problems. Nonetheless, psychological wellbeing may decline in some patients following the development of CFS and contribute to the perpetuation of CFS symptoms.
The hypothesis that psychological factors contribute to the maintenance of CFS is supported by a wealth of evidence suggesting that psychological interventions are effective in treating CFS (de Lange et al., 2008; Friedberg & Sohl, 2009; Knoop, Stulemeijer, de Jong, Fiselier, & Bleijenberg 2008; Malouff, Thorsteinsson, Rooke, Bhullar, & Schutte, 2008; Roberts et al., 2009). Moreover, meta-analytic research suggests that Cognitive Behavioural Therapy is similarly effective for people with CFS and those with psychological conditions (Lipsey & Wilson, 1993). However, the effect of psychotherapy is generally moderate, and a significant portion of patients in these studies achieved only minimal improvements or did not respond at all. Nonetheless, these findings suggest that cognitions and behaviours may serve to perpetuate CFS.

Researchers have also given particular attention to the role of personality disturbances in CFS. As with other psychiatric illnesses, personality disorders appear to be remarkably common in CFS patients (Blakely et al., 1991; Buckley et al., 1999; Fiedler et al., 2000; Henderson & Tannock, 2004; Johnson et al., 1996; Schmaling & Jones, 1996). However, given that personality disturbances are sensitive to somatic symptoms and are particularly common in medically ill patients, it is important to contrast CFS patients with other chronically ill patients. Using this approach, researchers have found that personality disturbances are more common in CFS patients compared to those with chronic pain (Blakely et al., 1991), but not those with MS or Rheumatoid Arthritis (Johnson et al., 1996; Wood & Wesseley, 1999). In young patients, personality disturbances have been identified more frequently in CFS patients compared to those with JRA or mood disorders (Gray et al., 2001; Rangel et al., 2003). However, personality disturbances are common in people with psychiatric disorders, and personality problems primarily affect CFS
patients who present with comorbid psychiatric disorders (Fiedler et al., 2000; Johnson et al., 1996; Wood & Wesseley, 1999). As such, the frequency of psychiatric disturbances in CFS patients may account for their high rates of personality disturbances.

A possible explanation for the high rates of psychiatric morbidity in CFS patients could be that these conditions originate from a shared pathology. Factors that increase vulnerability to CFS might also increase the probability of developing a psychiatric condition. Alternatively, the exceptionally high rates of depression in CFS patients could be explained by the diagnostic and conceptual overlap between these conditions. However, evidence of phenomenological differences between these conditions suggests that CFS is unlikely to be a subtype of depression (Carter et al., 1995, 1996; Hickie et al., 1995; Jason et al., 2005; Powell, Dolan, & Wessely, 1990; van Middethorp et al., 2001).

Research investigating the relationship between CFS and psychological disturbances has produced vastly mixed results. Although psychological factors are likely to influence the development and course of CFS, it is immensely difficult to determine the exact nature of the relationship between these factors. At this stage, the importance of psychological factors in the pathogenesis of CFS is not yet established.

**Neuroendocrine theories.** The diversity of physiological and psychological problems associated with CFS is indicative of a centralised physiological disturbance. As such, many researchers have been interested in the role of neuroendocrine function, and in particular, the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is the primary endocrine stress axis. Corticotrophin releasing
hormone (CRH) is released by the hypothalamus in response to stress and synergistically causes it to release adrenocorticotropic hormone (ACTH), which in turn, stimulates the release of cortisteroids (Parker, Wessely, & Cleare, 2001). Control of the HPA axis is also partly achieved through reciprocal interactions with the 5HT (serotonin) system (Chaouloff, 1993).

Findings from a range of studies support the significance of the HPA axis in CFS aetiology. HPA axis dysfunction could potentially account for much of the symptomology and physiological abnormalities observed in CFS patients (Demitrack et al., 1991). After finding evidence of hypocortisolism in CFS patients, Demitrack et al. (1991) suggested that various neuroendocrinological abnormalities are caused by a deficiency in the release of CRH and possibly other secretagogues. The researchers proposed that HPA axis dysfunction might be the common pathway through which several aetiological factors converge to generate the symptom patterns of CFS (Demitrack et al., 1991).

More recently, researchers have found that CFS patients have lower early morning cortisol and ACTH levels than healthy controls (Crofferd et al., 2004; Di Giorgio, Hudon, Jerjes, & Cleare, 2005). Evidence of hypocortisolism in CFS has also been identified by examining the HPA axis response to hormonal infusions. Minimal changes in cortisol and ACTH levels have been observed in CFS patients following the administration of CRH infusions (Cleare et al., 2001; Scott, Medbak, & Dinan, 1999; Van den Eede et al., 2008). Others have found that CFS patients exhibit significantly lower cortisol levels than healthy controls after receiving the corticosteroid, dexamethasone (Gaab et al., 2002; Van den Eede et al., 2008).

Given the high rates of comorbid mood disorders in CFS patients, it is important to acknowledge the relationship between HPA axis dysfunction and
depression. Depressed patients demonstrate elevated levels of cortisol excretion (Gold et al., 1986; Thase et al., 1996), downregulation of the HPA axis (Gold and Chrousos, 2002), and, following infusions of glucocorticoids, blunted ACTH response (Gold et al., 1986). Therefore, the key difference between depressed patients and those with CFS appears to baseline cortisol levels, which are elevated in the former group and reduced in the latter. This hypothesis is supported by studies that include a direct comparison of cortisol excretion levels between CFS and depressed patients (Scott & Dinan, 1998; Strickland, Morriss, Wearden, & Deakin, 1998).

The HPA axis is also implicated in the aetiology of CFS through its role in central nervous system oscillators. The HPA axis forms part of the system that controls circadian rhythm and is involved in adjusting the light-dark and sleep-wake cycles (Crofford et al., 2004; Demitrack & Crofford, 1998). As such, it is possible that impaired HPA axis function disrupts circadian rhythmicity in CFS patients (Williams, Waterhouse, Mugarza, Minors, & Hayden, 2002). In support of this hypothesis, several studies suggest that CFS patients have depressed early morning cortisol levels and a weakened cortisol response to waking (Jerjes, Cleare, Wessely, Wood, & Taylor, 2005; Jerjes, Taylor, Wood, & Cleare, 2007; Nater et al., 2008; Roberts, Wessely, & Chalder, 2004). However, other researchers have found that CFS patients exhibit normal cortisol responses to waking and share similar daytime circadian patterns with nonfatigued peers (Gaab et al., 2002; Jerjes, Taylor, Peters, Wessely, & Cleare, 2006).

Taken together, research suggests that HPA axis dysfunction is common in CFS patients and may be an important factor in illness aetiology. As Demitrack et al. (1991) suggested, HPA axis dysfunction could be the general biological pathway
through which multiple factors collectively generate the symptoms of CFS. The current findings provide evidence of hypocortisolism in many, but by no means all CFS patients. However, variations in the methodological approach and external factors, such as environment, stress, food intake, weight, and natural hormonal cycles can have a particularly profound effect on the results in this area of study. Further, several researchers have found that HPA axis underactivity can occur as a consequence of the factors associated with chronic illness, particularly sleep disturbance, inactivity, and prolonged stress (Demitrack & Crofferd, 1998; Di Giorgio et al., 2005; Gaab et al., 2002; Scott & Dinan, 1999). To date, it remains unclear whether HPA axis dysfunction forms a primary aetiological factor, or develops as a secondary response to the symptoms and behaviours associated with CFS.

**Conclusion.** Extensive research over several decades reveals that CFS is a condition of complex, multifaceted aetiology. Findings across and even within studies are often unclear and contradictory. The infectious process hypothesis attracted moderate support, however it was undermined by contradictory findings and evidence that many patients have not suffered from a recent infection. Although immunological abnormalities are common in CFS patients, many are subtle and not clinically significant. Psychological factors appear to have a significant impact on the development and course of CFS, however the relevance of these factors in the pathogenesis of the condition has not been established. Finally, although the HPA axis theory has considerable explanatory power, it remains unclear whether HPA axis dysfunction develops in response to CFS or forms a primary aetiological factor. The role of each possible factor is complex, and further research is required before
conclusions can be drawn. At this stage, a multidimensional conceptualisation involving both physical and psychological factors provides the most appropriate and functional aetiological.

The ambiguity surrounding the aetiology and epidemiology of CFS has significant implications for determining an effective treatment approach. It is difficult to identify appropriate treatments for all patients given the diversity of symptoms and severity levels between patients, as well as the high rates of comorbid illnesses. Further, unknown aetiology places a great restriction on the process of developing treatments that address the underlying cause of CFS. As such, treatments may be more viable and effective if they are aimed at reducing the impact of CFS by addressing the most debilitating symptoms.

Chapter Summary

The research discussed in this chapter suggests that CFS is most accurately conceptualised as a multidimensional heterogenic illness. In young populations, CFS is a common illness that causes considerable impairment. Symptoms often persist over many years and the impact of CFS interferes with several vital developmental domains. Decades of extensive research suggests that CFS is a condition of complex, multifaceted aetiology. However, it is not yet known whether the biological and psychological disturbances identified in CFS patients play a primary aetiological role or arise as consequence of the illness and associated behaviours. Establishing an effective treatment approach is limited by the exceptionally heterogeneous nature of the condition and poor understanding of the aetiological factors and processes underlying CFS. This highlights the need to withdraw focus from treatments that attempt to cure CFS, and instead centre research on ameliorating
symptoms to enhance quality of life. In taking a symptomatological approach, it is essential to determine which symptoms produce the greatest impairment. Specific investigation in younger populations is required due to the unique impact of CFS in paediatric patients. The discussion in the following chapter focuses on cognitive function, one of the most common and debilitating symptoms in young patients.
Chapter 3: Cognitive Function in CFS

Although research is only just emerging, the significant and unique impact of CFS in young patients is already clear. However, despite rigorous research efforts over several decades, the aetiology of CFS remains unknown and treatments that address illness cause are greatly limited. As such, interventions may be most effective if designed to address the debilitating symptoms and reduce the functional impact of CFS. Impaired cognitive function is one of the most frequently reported and debilitating symptoms in patients with CFS. Research from community populations indicates that cognitive impairment is an essential feature of empirically defined CFS (Nisenbaum et al., 2004), and cognitive dysfunction forms a symptom category in the paediatric case definition (Jason et al., 2006). In young patients, cognitive impairment is likely to generate major difficulties in education and learning, restricting future educational and career opportunities. Increased school absenteeism and delays in education associated with impaired cognitive function may also interfere with social and emotional and development (Newman & Newman, 1987). Despite the potentially severe consequences, there is almost a complete absence of objective research investigating cognitive dysfunction in paediatric CFS patients.

This chapter commences with an exploration of CFS patients’ perceptions of cognitive disturbances through a review of self-report studies and an examination of the discrepancy between these results and those drawn from objective neuropsychological measures. This is followed by an overview of the research investigating neuropsychological performance in CFS patients, including intelligence, academic function, and cognitive processes. A brief discussion of neuroimaging is also presented. This section concludes with a concise overview of
the methodological issues pertaining to the investigation of cognitive function in patients with CFS.

**Subjective Reports of Cognitive Function in CFS**

Cognitive impairment is reported by approximately 85-95% of adults with CFS (Jason, Torres-Harding, Carrico, & Taylor, 2002; Becker, McGregor, & De Meirleir, 2001). Complaints commonly include difficulties with sustained attention, concentration, thinking speed, reaction time, and memory (DeLuca, Johnson, Beldowicz, & Natelson, 1995; Michiels et al., 1996; Michiels, de Gucht, Cludyts, & Fischler, 1999; Ray, Phillips, & Weir, 1993; Smith, Pollock, Thomas, Llewely, & Borysiewicz 1996; Vercoulen et al., 1998).

The level of cognitive impairment reported by adult CFS patients appears to exceed that reported by patients with other chronic illnesses. DeLuca et al. (1995) investigated cognitive impairment in 26 CFS patients, 14 depressed patients, 12 patients with MS, and 20 healthy controls. The CFS group reported greater disturbances in attention, concentration, and anterograde memory compared to the MS and healthy control groups but not the depressed group. The CFS patients also reported significantly greater levels of impairment in attention, prospective memory, and reasoning ability than the other three groups. In addition, only the CFS group reported greater disturbances in retrograde memory than controls. This study suggests that CFS patients perceive themselves to have higher levels of cognitive impairment than those with other chronic illnesses, although further research is required to verify this conclusion.

The emerging research also suggests that young people with CFS frequently report cognitive impairment, although the findings are variable. For instance, one
group found that 33% of 58 young CFS patients reported cognitive difficulties (Krilov et al., 1998), while another found that 60% of 20 young CFS patients reported poor concentration and 20% reported memory difficulties (Lines, 2004). Conversely, no disturbances in attention, thinking, or academic performance were reported by another group of 35 female adolescents with CFS (van Middenthorp et al., 2001). Young CFS patients appear to report similar levels of impairment in attention and information processing compared to patients with other chronic illnesses such as depression and JRA (Carter et al., 1995; Rangel et al., 2003).

It is important to acknowledge that many of these findings were derived from a single question as part of a larger symptom checklist, providing a very limited account of self-perceived cognitive performance. One group recently sought to develop a more detailed understanding of perceived cognitive function in young CFS patients by conducting a qualitative analysis. Parents, teachers, and young people with CFS were asked to describe any memory or concentration difficulties experienced as a consequence of CFS. Using thematic analysis, three cognitive themes were identified: sustained attention, focused attention, and recall. The participants frequently reported that these difficulties were associated with stress. Commonly described problems included attending to external cues, becoming distracted, maintaining mental stamina and interest, concentration span, remembering specific information, recalling learned information, losing things, and retrieving information and relaying it to others (Haig-Ferguson, Tucker, Eaton, Hunt, & Crawley, 2009). However, it is important to note that these participants were recruited from a regional specialised service, and only those patients who reported memory or concentration problems were selected to participate. These factors may
have biased the sample to represent patients with more severe cognitive disturbances than the general population of young CFS patients.

Collectively, these studies suggest that adults and young people with CFS perceive themselves to have significant cognitive impairment. Interestingly however, patients typically report higher levels of impairment than that shown using objective neuropsychological tests. For instance, in a study of 51 CFS patients, no correlation was identified between neuropsychological assessment results and self-reported concentration or memory problems. Moreover, deficits were not detected using neuropsychological assessments in 70% of those who reported concentration problems and 77% of those who reported memory problems (Vercoulen et al., 1998). Another group found that even though a sample of CFS patients reported significantly greater levels of cognitive impairment than healthy controls, neuropsychological assessment results were comparable between groups (Cope, Pernet, Kendall, & David, 1995). In addition, findings from treatment trials in CFS patients suggest that even though perceived cognitive impairment decreases significantly following Cognitive Behavioural Therapy (CBT), neuropsychological test performance remains the same (Prins et al., 2001; Stulemeijer, Jong, Fiselier, Hoogveld, & Bleijenberg, 2005).

The inconsistencies observed between subjective reports and objective assessments of cognitive function could be explained by the differences between controlled laboratory settings and naturalistic environments. Neuropsychological assessments may fail to capture the deficits experienced within everyday settings. Supporting this conjecture, evidence suggests that the correlation between self-reported cognitive function and neuropsychological test performance becomes larger when laboratory tests more closely represent everyday cognitive demands (Bennet-
Levy & Powell, 1980; Sunderland, Watts, Baddeley, & Harris, 1986). Further, neuropsychological assessments conducted in controlled studies often require participants to maintain focus for a limited time with the added social pressure to apply effort and comply with the task demands (Broadbent, 1979; Wearden & Appelby, 1996). In contrast, cognitive function in naturalistic settings requires ongoing mental effort and could also be particularly susceptible to limitations caused by distraction, divided attention, fatigue, sleepiness, or negative beliefs about cognitive capacity (Devolder & Pressley, 1991). Further, although laboratory assessments typically assess isolated cognitive functions under controlled settings, CFS patients generally report problems with complex, everyday tasks that rely on multiple cognitive faculties (Wearden & Appelby, 1996). It is possible that the functions assessed within a laboratory differ from those generally used in naturalistic environments. As such, data drawn from both self-report measures and neuropsychological assessments may provide distinct but similarly important information regarding cognitive impairment in CFS.

**Objective Assessments of Cognitive Function in CFS**

Neuropsychological testing has been employed to provide an objective assessment of various cognitive domains in adult CFS patients. The following presents an overview of the key findings in regards to intellectual functioning, academic ability, executive functioning, working memory, information processing speed, and attention.

**Intellectual functioning.** It is reasonably well established that general intellectual function and higher order cognitive skills remain intact in adult CFS
patients (Tiersky, Johnson, Lange, Natelson, & De Luca, 1997). A large body of evidence suggests that CFS patients match healthy controls on measures that are resistant to brain damage, such as acquired knowledge (DiClementi Schmaling, & Jones, 2001; Johnson, DeLuca, Diamond, & Natelson, 1998; Krupp, Sliwinski, Masur, Friedberg, & Coyle, 1994; Short et al., 2002). Intellectual functions considered more vulnerable to brain-related changes also appear to remain unaffected by CFS. For instance, one group found comparable scores on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) between a group of 20 CFS patients and 17 matched healthy controls (Grafman et al., 1993). Similarly, Cope et al. (1995) found no differences between chronically fatigued patients (most of whom were diagnosed with CFS), matched healthy controls, and depressed patients in performance on the WAIS-R. In a rare twin study, researchers investigated intellectual function in 22 pairs of monozygotic twins. One participant within each pair had been diagnosed with CFS; the other presented without any significant fatigue. Both groups achieved average scores on a seven-subtest version of the WAIS-R, and there were no significant differences between the pairs on any measure (Claypoole et al., 2007). The consistency of these findings provides a reliable indication that global intellectual functioning is not affected by CFS.

**Academic performance.** Relatively few studies have been designed to investigate academic performance in CFS patients despite the potentially severe consequences for young people if disturbances are present. To date, preliminary findings suggest that school performance is significantly diminished among CFS patients. This is reflected in young peoples’ perceptions of how CFS affects their education. For instance, Sankey et al. (2006) found that 68% of 28 school-aged
children felt that their illness had affected their education or career plans significantly, and all participants reported that their education had been affected by CFS to some degree. In contrast, Richards, Chaplin, Starkey, and Turk (2006) found that only two of 21 adolescents believed that their academic performance was impaired as a consequence of CFS.

Academic decline in CFS patients is also evident in grades achieved at school. For instance, data from a cross-sectional study in 36 adolescents with CFS revealed that participants achieved an average of three out of 10 passes over an 18-month period. Only 44% achieved more than four passes, and 30.6% failed to achieve a single pass grade (Patel et al., 2003). However, it is possible that people with poor academic grades are particularly likely to develop CFS or are susceptible to academic decline following illness onset. This question was investigated in a longitudinal follow-up study over a period of four years. Preceding illness onset, 43% of 58 CFS patients averaged A grades, 36% averaged B grades, 18% averaged C grades, and 4% averaged D grades. Following illness onset however, 28% averaged A grades, 38% averaged B grades, 25% averaged C grades, and 9% averaged D grades. Further, 30% reported average or poor academic scores prior to illness onset, compared to 50% at follow-up (Krilov et al., 1998). This suggests that academic performance declines following the development of CFS. However, without a comparison group, is unclear whether these performance changes are attributable to illness-related factors or to extraneous variables such as task difficulty or teacher effects. Although the relationship between CFS and school performance is yet to be thoroughly investigated, the existing findings suggest that CFS is associated with a decline in academic performance.
Executive function. Executive function is a higher order cognitive process that is used in initiating, planning, sequencing, and monitoring goal-directed behaviours (Goldberg & Bougakov, 2005). Although the following section includes an independent examination of executive function in CFS patients, it is worth noting that executive processes are related to, and often depend on other cognitive functions (Rabbitt, 1997).

Set shifting tasks are commonly employed as a measure of cognitive flexibility, a key component of executive function. One such task, The Trail Making Test Part B (Reitan & Davidson, 1974), measures visual task switching ability by requiring participants to quickly connect the dots of consecutive targets, alternating between numbers and letters. According to these tests, cognitive flexibility largely appears to be unaffected by CFS. For instance, although one group identified slower performance among 35 CFS patients compared to 33 matched healthy controls (Michiels et al., 1996), several others found no differences between CFS patients and healthy controls in accuracy or speed (Busichio, Tiersky, DeLuca, & Natelson, 2004; Dobbs, Dobbs, & Kiss, 2001). Moreover, task performance has not been linked to illness length (Santamarina-Perez et al., 2011). Another group found that performance speed and accuracy on a similar task-switching test was comparable between CFS patients and healthy controls before, during, and after receiving a substance that induces flu-like symptoms (Arnold et al., 2002). However, one group found that CFS patients performed similarly to those who had sustained a mild traumatic brain injury (Tiersky, Cicerone, Natelson, & Deluca, 1998). Nonetheless these results largely suggest that cognitive flexibility, as measured by set shifting tasks, remains intact in CFS patients. However, it is worth noting that the Trail Making Test requires input from a range of cognitive faculties, and as such,
performance could be affected by information processing speed, visual tracking, fine motor skill, or attention (Crowe, 1998; Vercoulen et al., 1998).

The Intra-Extra Dimensional Set Shift (IED) task is a sensitive measure of cognitive flexibility that forms part of the test battery on the computerised Cambridge Neuropsychological Test Automated Battery (CANTAB). The IED is a test of rule acquisition and reversal, and it is the computerised analogue of the Wisconsin Card Sorting test. Research using the IED task in CFS patients has drawn mixed results. Joyce et al. (1996) assessed a group of 20 CFS patients and matched controls using the IED task as part of a larger neuropsychological assessment. Up to and including the compound reversal stage, three CFS patients and no controls failed, and three CFS patients and one control failed at the intra-dimensional reversal stage. However, the number of trials needed and errors made on the extra-dimensional shift stage were comparable between groups. In contrast, other researchers found no differences between CFS patients and healthy controls on any part of the IED task (Capuron et al., 2006; Majer et al., 2008; Morriss, Robson, & Deakin, 2002). Although the findings are mixed, the bulk of the research indicates that CFS patients and nonfatigued peers perform with a similar level of accuracy on tasks that require shifting and flexibility of attention. However, the between-group differences evident in some studies may suggest that attentional flexibility is impaired in a subset of patients.

The Rey-Osterrich Figure (Rey-O) recall condition is a common test of executive function that provides a measure of abstract planning. In this task, examinees are required to reproduce a complex, abstract picture from memory (Rey & Osterrieth, 1993). Again, research assessing CFS patients on this task has drawn
mixed results. One group found that CFS patients were more likely to score at least one standard deviation below the healthy mean than controls, however test failure rates were similar between groups (Busichio et al., 2004). In contrast, Tiersky et al. (1998) found no differences between a group of 30 CFS patients and matched healthy controls, and performance on the Rey-O has not been linked to illness length (Santamarina-Perez et al., 2011). Although these results do not provide enough evidence to form conclusions regarding the nature of abstract planning in CFS patients, the data suggest that a subset of CFS patients may experience mild impairment. Further research with a diverse range of measures is needed to provide a greater understanding of how abstract planning is affected by CFS.

The Category Test is measure of problem solving ability that is comprised of several stimulus sets that must be organised according to certain rules. The examinee is required to discover suitable rules and consistently employ those rules on successive trials (DeFilippis & McCampbell, 1979). Researchers have found that CFS patients achieve similar scores on this task compared to healthy controls (Busichio et al., 2004; Tiersky et al., 1998) but also to patients who had sustained a brain injury (Tiersky et al., 1998). Another common measure of planning and problem solving ability is the CANTAB Stockings of Cambridge (SOC) subtest, the computerised version of the Tower of London task. Again however, several studies suggest that CFS patients are able to plan and problem solve on the SOC with a similar level of proficiency as healthy controls (Capuron et al., 2006; Joyce et al., 1996; Majer et al., 2008; Morriss et al., 2002; Santamarina-Perez et al., 2011).

Executive function in CFS patients is still in the preliminary stages of research, and it is not yet clear how or to what degree patients are affected in this area. The limited evidence suggests that at least some CFS patients have deficits in
cognitive flexibility and abstract planning. However, general planning and problem solving ability appears to be unaffected by CFS. Further investigation is required to verify these findings and clarify the inconsistent results. The subtle and often ambiguous nature of the disturbances observed on measures of executive function may be indicative of deficits in related cognitive domains.

Attention. Attention is a complex and multifaceted construct that constitutes a fundamental component of cognitive function. Researchers have investigated the impact of CFS on divided attention, sustained attention, attentional control, and selective attention (Wickens & McCarley, 2008).

The Paced Auditory Serial Addition Task (PASAT) is a popular tool that measures divided attention by requiring examinees to attend simultaneously to several subtasks (Gronwall & Sampson, 1974). In this test, a series of auditory numbers from one to nine is presented, and participants are instructed to sum each new number to the last over several trials of increasing speed (Gronwall, 1977). Much of the research suggests that CFS patients perform poorly the PASAT. For instance, Busichio et al. (2004) found that 36.7% of 141 CFS patients performed one standard deviation below the healthy group mean on the PASAT compared to 15.7% of 76 healthy participants. Tiesky et al. (1998) also found that CFS patients achieved lower scores than healthy controls and performed similarly to those who had suffered from a traumatic brain injury. Another group found that only CFS patients without a comorbid psychiatric condition scored less well than nonfatigued peers (DeLuca, Johnson, Ellis, & Natelson, 1997). In contrast, no significant differences were identified between a group of 25 CFS patients and either matched healthy controls or depressed patients (Constant et al., 2011), and task performance appears to be
uncorrelated with illness length (Santamarina-Perez et al., 2011). Although these studies largely suggest that divided attention is impaired in CFS patients, it is important to note that performance on the PASAT is sensitive to mathematical ability (Chronicle & MacGregor, 1998) and intelligence (Egan, 1988). These factors may act as confounding variables if they are not adequately controlled.

The Stroop Colour Word task (Stroop, 1935) is another popular tool for measuring divided attention. Colour-words are printed in a colour that differs from the word, and examinees are instructed to verbalise the colour while ignoring the word. Research investigating CFS patients using the Stroop has produced mixed results. One group identified significantly lower scores among twins with CFS compared to healthy twins (Claypoole et al., 2007), and DiClementi et al. (2001) found that according to published norms, mean Stroop scores for a group of 21 CFS patients were in the impaired range. Further, CFS patients regularly perform on the Stroop at a slower pace than nonfatigued peers (Mahurin et al., 2004; Michiels, Cluydts, & Fischler, 1998; Ray et al., 1993; Smith, Behan, Bell, Millar, & Bakheit, 1993), suggesting that impaired information processing speed could account for some of the performance deficits on this task. Conversely, other studies indicate that CFS patients and healthy controls complete the Stroop test with similar levels of accuracy and speed (Daly, Komaroff, Bloomingdale, Wilson, & Albert, 2001; Marcel, Komaroff, Fagioli, Komish, & Albert, 1996; Short et al., 2002). Although the results are somewhat varied, research using the PASAT and Stroop largely suggests that many CFS patients have difficulty on tasks that require divided attention.

Researchers have also been interested in how sustained attention is affected by CFS. The Rapid Visual Information Processing (RVIP) task on the CANTAB is a
challenging measure of sustained attention that is capable of detecting subtle performance deficits. In this task, a series of single digits are presented in pseudorandom order at the rate of 100 digits per minute over four minutes, and participants are required to detect three target sequences. In addition to sustained attention, the task places demands on working memory, processing speed, and executive function. Capuron et al. (2006) found that CFS patients with high self-reported mental fatigue achieved lower accuracy scores on RVIP compared to CFS patients without significant mental fatigue and healthy controls. Interestingly, although there were no between-group differences in response latency overall, the mentally fatigued patients became slower in the later stages of the task, suggesting that mental fatigue impairs processing speed for sustained attentional tasks in CFS patients. In contrast, Majer et al. (2008) found no differences between CFS patients and healthy controls in accuracy or response latency on the RVIP task.

Attention can also be measured through movement-based reaction tasks that require participants to respond quickly by attending to particular stimuli. Several studies suggest that CFS participants respond more slowly than controls when performing choice, but not simple reaction tasks (Crowe & Casey, 1999; DeLuca et al., 2004); however others have found no differences between CFS patients and healthy participants on similar tasks (Capuron et al., 2006; Mahurin et al., 2004; Majer et al., 2008).

Finally, researchers have investigated selective attention in CFS patients by measuring how well participants can focus on a particular target while ignoring interfering stimuli. Using the Flanker Test of Selective Attention, Arnold et al. (2002) found that participants with CFS could selectively attend to information as effectively as healthy controls. Similarly, no differences have been found between
CFS patients and healthy controls on the Match to Sample Visual Search task on the CANTAB (Joyce et al., 1996; Morriss et al., 2002). Although the preliminary evidence suggests that selective attention is unaffected by CFS, further research with a wider range of assessment tools is required before conclusions can be drawn.

Taken together, the research suggests that several components of attention may be impaired in CFS patients. However, many findings are contradictory and it is unclear whether the inconsistencies result from variations in sample characteristics, methodological approaches, or other unknown factors. CFS patients often perform poorly on tasks that require divided attention and choice reaction, although a small number of studies suggest that these functions remain intact. Findings from investigations of sustained attention in CFS patients have been less clear; approximately half of all studies suggest that CFS patients are able to maintain attention over time, while the other half suggest that sustained attention is impaired. The limited evidence suggests that selective attention is not affected by CFS, however further research with alternative measurement tools is required to verify these findings. At this stage, the preliminary research suggests that at least a subset of CFS patients suffer from disturbances in several components of attentional function.

**Processing speed.** Processing speed refers to the rate that cognitive tasks can be performed fluently, and includes speed of perceiving, encoding, response selection, and memory retrieval (Wright et al., 2001). Efficient processing speed is required to perform several high level cognitive functions, such as comprehension, working memory, reasoning, planning, and learning (Baddeley, 1986). For this
reason, it is often difficult to distinguish between deficits in processing speed from those of other cognitive functions.

One of the most commonly used tests for assessing processing speed is the Digit Symbol Coding subtest on the WAIS. Several studies suggest that CFS patients perform slowly on this task. For instance, Michiels et al. (1996) found that compared to healthy controls, a group of 35 CFS patients were significantly slower, but not less accurate in correctly matching digits and symbols. Busichio et al. (2004) also found that compared to nonfatigued participants, significantly more CFS patients scored at least one standard deviation below the healthy control mean. Another group identified lower composite scores based on the Digit Span and Digit Symbol Coding tests among a group CFS patients compared to healthy controls and patients with an autoimmune thyroid disease (Dickson, Toft, & O’Carroll, 2009). Neu et al. (2011) also found that CFS patients obtained lower scores on Digit Symbol Coding than healthy participants, but scored higher than patients with sleep apnoea. This suggests that sleep disturbance may contribute to impairments in processing speed.

The Sternberg Memory Scanning Test (Sternberg, 1966) is another common measure of processing speed that assesses speed of searching through memory. Participants are required to encode one to six to digits that are initially presented for 500ms. A target digit then appears for 500ms and participants must determine if the target digit was included in the initial set. One group found that CFS participants detected shorter targets more slowly but not less accurately than healthy controls (Arnold et al., 2002). However, Mahuran et al. (2004) found no performance differences between CFS patients and healthy controls on a similar test.
Processing speed can also be assessed by investigating the extent to which thinking time contributes to performance on other cognitive tasks. Using this procedure, Majer et al. (2008) found that differences between CFS patients and controls on one of two visual memory tests became nonsignificant after controlling for processing speed. Similarly, another group found that CFS patients continued to perform more slowly than healthy participants on a choice reaction task after controlling for movement time, indicating that processing speed rather than movement time accounted for the performance deficits (Vercoulen et al., 1998). Taken collectively, the research provides relatively consistent evidence suggesting that CFS patients have impaired processing speed, and that these deficits may inhibit accuracy and efficiency in other cognitive domains.

Memory. Researchers have given a lot of attention to the function of memory and working memory in CFS patients. Although are several conceptualisation models, it is generally agreed that working memory is a system for temporarily storing and managing the information required to perform complex cognitive tasks (Miyake & Shah, 1999). Baddeley and Hitch (1974) argue that the working memory system is comprised a number of interrelated components, including the phonological loop and the visuospatial sketchpad. the phonological loop, which processes sound or phonological information, and the visuospatial sketchpad, which is involved in the manipulation and storage of spatial and visual information.

Particular attention has been given to verbal memory function in CFS patients. Verbal memory tasks typically involve free recall or recognition of material that is presented immediately or with a delay of approximately 20 minutes. A large
body of evidence suggests that patients with CFS achieve lower scores than healthy controls on measures of verbal free recall (Constant et al., 2011; Daly et al., 2001; Dickson et al., 2009; DeLuca et al., 1997; Marcel et al., 1996; Michiels et al., 1996; Neu et al., 2011; Tiersky et al., 1998; Vercoulen et al., 1998). CFS patients also generally perform these tasks with a similar level of proficiency as other patient groups, such as patients with sleep apnoea (Neu et al., 2011), brain injuries (Tiersky et al., 1998), MS (Daly et al., 2001), and depression (Constant et al., 2011; Daly et al., 2001). One group found that CFS patients without a psychiatric condition achieved lower scores on a short delay verbal recall task compared to CFS patients with a comorbid psychiatric illness (DeLuca et al., 1997). This suggests that verbal memory impairment is not attributable to comorbid psychiatric issues.

Assessment results from tasks that require recognition of verbal material have been more variable. Several studies suggest that CFS patients recognise significantly fewer words than healthy peers (Constant et al., 2011; Lawrie, MacHale, Cavanagh, O’Carroll, & Goodwin, 2000; Smith et al., 1993), while others indicate that CFS patients and healthy controls achieve comparable scores on verbal recognition tests (DeLuca et al., 2004; Mahurin et al., 2004; Michiels et al., 1996; Neu et al., 2011; Vercoulen et al., 1998).

Another method of testing verbal memory is to measure how well examinees can recall meaningful components of a narrative. Preliminary evidence suggests that CFS patients recall fewer narrative details compared to healthy controls (Daly et al., 2001; Dickson et al., 2009) but not to patients with autoimmune thyroid disease (Dickson et al., 2009), MS, or depression (Daly et al., 2001). However, another group found similar scores among CFS patients and healthy controls on a narrative
recall task, and the CFS group recalled more information than participants with a brain injury (Tiersky et al., 1998).

The phonological loop component of working memory is also commonly assessed by measuring immediate recall of numerical data. The Dobbs and Rule Working Memory Task (Dobbs & Rule, 1989) is an established test of immediate auditory memory that requires examinees to recall single digits from randomly ordered digit sets according to a sequence order. One group identified poorer performance on this task among 20 CFS patients compared to matched healthy controls (Dobbs et al., 2001). On a similar task, another group found that CFS patients took longer to respond and made fewer correct responses than healthy controls, but achieved similar scores to participants with depression. A negative correlation was also identified between illness length and median response time and accuracy (Constant et al., 2011).

The Digit Span subtest of the WAIS is common measure of memory that has been used extensively in CFS research. The results largely suggest that CFS patients are able to recall numerical information in forward and reverse order to the same level as healthy controls (Busichio et al., 2004; Daly et al., 2001; Dobbs et al., 2001; Marcel et al., 1996; Tiesky et al., 1998; Vercoulen et al., 1998). However, a small number of studies suggest that CFS patients perform poorly on the Digit Span task. For instance, one group identified poorer performance on Digit Span Forward and Backward in a sample of 35 CFS patients compared to 33 healthy controls (Michiels et al., 1996). DeLuca et al. (1997) also found lower scores among CFS patients on Digit Span Backward but not forward compared to a group of healthy controls and CFS patients with a comorbid psychiatric condition. Other studies suggest that CFS participants are able to perform at least as proficiently as patients with MS,
depression (Daly et al., 2001), brain injury (Tiesky et al., 1998), and sleep apnoea (Neu et al., 2011). Finally, lower scores on Digit Span were identified among CFS patients compared to patients with an autoimmune thyroid disease, and these differences could not be accounted for by self-reported differences in mood (Dickson et al., 2009). The conflicting results could be at least partially attributable to differences in attention, which is an essential function required to complete the Digit Span task.

Researchers have devoted less attention to the visuospatial component of working memory in CFS patients, however current findings reveal similar patterns to those observed for phonological working memory. For instance, several studies suggest that CFS patients achieve lower scores than healthy controls on tasks that require free recall (Attree et al., 2009; Busichio et al., 2004; Capuron et al., 2006; Joyce et al., 1996; Marcel et al., 1996; Michiels et al., 1996), although a minority show no differences between groups (Morriss et al., 2002; Vercoulen et al., 1998). Comparable scores on visuospatial recall tasks have also been identified between CFS patients and those with MS (Daly et al., 2001) and depression (Constant et al., 2011; Daly et al., 2001). Akin to the findings for phonological working memory, tasks that require participants to recognise visual information have drawn mixed results. Some studies suggest that CFS patients perform less well than healthy controls (Capuron et al., 2006; Joyce et al., 1996; Mahuran et al., 2004; Morriss et al., 2002), while others suggest that there are no differences between groups (Constant et al., 2011; Daly et al., 2001; Majer et al., 2008).

Researchers have also employed the recall test phase of the Rey-O to assess visuospatial memory in CFS patients. One group found that scores of one standard deviation below the healthy mean were significantly more common in CFS patients
compared to healthy controls on the Rey-O immediate, but not the delayed condition (Busichio et al., 2004). Tiersky et al. (1998) also found that CFS patients performed more poorly than healthy controls in the immediate recall condition but matched controls on the copy stage, indicating that poor recall was not attributable to impaired planning or motor skill (Tiersky et al., 1998). In contrast, Vercoulen et al. (1998) found that even though patients with CFS were less accurate on the figure copy phase than healthy controls, scores on the recall condition were comparable between groups. DeLuca et al. (1995) also found no significant differences between CFS patients and healthy controls on either the immediate or the delayed condition.

The CANTAB has become an increasingly popular tool for assessing visual memory. An estimate of visuospatial working memory using free recall can be derived from the Spatial Working Memory (SWM) and Spatial Span (SSP) subtests. SWM begins with several coloured boxes positioned in various places on the screen. By touching the boxes and using a process of elimination, the participant must find one blue token in each box over repeated trials of increasing difficulty. For SSP, the participant is presented with several white squares scattered on the screen that briefly change colour in a sequence. The participant is asked to recall the sequence by touching the squares in order (Cambridge Cognition, 2006). Estimates of visual working memory from these subtests in CFS patients have been inconsistent. One group found that, compared to healthy controls, patients with CFS achieved lower scores on SSP and made more errors between, but not within trails on SWM (Joyce et al., 1996). Similarly, another group reported that CFS patients with significant mental fatigue made more between-, but not within-search errors on SWM than healthy controls (Capuron et al., 2006). In contrast, others have found no differences
between CFS patients and healthy controls on SWM or SSP (Majer et al., 2008; Morriss et al., 2002).

The CANTAB also consists of several tests that are designed to assess visual memory through recognition, such as Pattern Recognition Memory (PRM), Spatial Recognition Memory (SRM), and Delayed Matching to Sample (DMS). For PRM, the examinee is presented with a series of 12 abstract patterns followed by 12 sets of two patterns. The examinee must select the pattern within each set that is identical to one of those presented in the first phase. SRM reveals a series of single white squares in different locations on the screen, followed by a series of five pairs of squares. Participants must select the square within each pair that matches the location of those in the presentation phase. The DMS task presents a complex visual pattern followed by four similar patterns after a brief delay. The participant must identify the pattern that matches the original sample (Cambridge Cognition, 2006). Based on these tests, several studies suggest that CFS patients are able to recognise visual information within memory with a similar level of proficiency as healthy controls, albeit often at a slower pace (Capuron et al., 2006; Joyce et al., 1996; Morriss et al., 2002). In contrast, Majer et al. (2008) found that a group of 54 CFS patients made fewer correct responses on SRM, and had longer response latencies on PRM compared to 104 healthy controls.

Despite a growing body of research, working memory function in CFS patients remains poorly understood due to the inconsistent findings between studies. The contradictory results could reflect the complexity of how working memory is affected by CFS. Assessment of working memory is also complicated by confounding factors associated with the function of other cognitive domains (Joyce et al., 1996; Michiels et al., 1998). For example, poor performance on the Digit Span
subset of the WAIS may be caused by an inability to attend to and encode the information rather than a disturbance in working memory. To date, the research suggests that CFS patients often have difficulty completing a range of tasks that require working memory. However, further research designed to clarify the relationships between various cognitive functions will provide a more reliable understanding of working memory capacity in CFS.

**Neuroimaging.** Neuroimaging research may serve to clarify and build on the findings drawn from neuropsychological assessments. This approach provides some insight into how neurological function might account for the cognitive deficits observed in CFS patients. A range of neurological abnormalities have been identified in CFS patients. In an early study, higher quantities of white matter hyperintensities were observed in 78% of 144 CFS patients and only 21% of healthy controls (Buchwald et al., 1992). Natelson, Cohen, Brassloff, and Lee (1993) also found abnormal brain scans in 14 of 52 CFS patients compared to just one in matched controls with a history of headaches or a brain injury. Abnormalities observed in the CFS group included an increased T2 signal in the subcortical region of white matter, or enlarged ventricular or sulcal regions. However, a large portion of the CFS patients in these studies reported depressive symptoms, which may at least partially account for the abnormalities. It is also important to consider that even though abnormal brain scans were significantly more common in the CFS group, most patients presented without any abnormalities despite reports of being considerably unwell.

Adding to the complexity, two similar studies indicated that CFS patients and healthy controls possessed similar numbers of white matter hyperintensities (Cope et
al., 1995; Schwartz et al., 1994). The inconsistent findings could be accounted for by differences in the rates of comorbid psychiatric disorders in CFS patients. Supporting this, Lange et al. (1999) found small subcortical white matter hyperintensities in 66.7% of CFS patients without a comorbid psychiatric condition compared to 22.2% of CFS participants with a comorbid condition. Brain abnormalities were significantly more common in the nonpsychiatric CFS group compared to healthy controls, however, when the two CFS groups were combined, the differences between CFS patients and controls were no longer apparent.

More recently, researchers have explored the relationship between neurological factors and the severity of symptoms associated with CFS. One group found that CFS patients with neurological abnormalities reported significantly greater levels of physical impairment than CFS patients without an identified brain abnormality (Cook, Lange, Deluca, & Natelson, 2001). Another group identified a correlation between gray matter volume in the right prefrontal cortex and self-reported fatigue severity in a group of 16 CFS patients (Okada, Tanaka, Kuratsune, Watanabe, & Sadato, 2004). In contrast, although researchers have found that CFS patients have higher rates of cerebral perfusion than controls (MacHale et al., 2000; Schwartz et al., 1994), others have found no evidence of a relationship between perfusion and fatigue severity in CFS patients (Fischler et al., 1996). Similarly, even though ventricular volumes were found to be larger in a group of CFS patients compared to healthy controls, this irregularity was not associated with illness duration, functional impairment, or psychiatric diagnosis (Lange et al., 2001). Although the findings are variable, this research provides preliminary evidence of an association between cerebral abnormalities and clinically important features associated with CFS.
By monitoring brain activity during performance on neuropsychological assessments, it is possible to determine whether neurological abnormalities are directly related to cognitive function. Using this approach, researchers have found that CFS patients often exhibit unusual cerebral activity while completing neuropsychological tasks. One group recently investigated brain function during verbal and spatial cognitive activity in 61 female CFS patients and 80 healthy controls. The spatial pattern results correctly predicted group classification in 72% of cases, and activity during the verbal task predicted group classification in 83% of cases. The CFS group also exhibited greater brain activity than controls in the left frontal–temporal–parietal regions during all cognitive activity (Flor-Henry, Lind, & Koles, 2010). Similarly, Lange et al. (2000) found that during the completion of a working memory task, CFS patients exhibited bilateral frontal and parietal activity, while healthy controls showed only left-sided activity in the same regions. Cook, O’Connor, Lange, and Steffenerf (2007) argued that abnormal brain function only becomes apparent during tasks that require significant cognitive effort. This group identified a significant relationship between mental fatigue and neuroimaging results during a fatiguing cognitive task but not finger tapping or simple auditory monitoring tasks. Affected brain regions included the cerebella, cingulate cortex, and the temporal, frontal, and left parietal regions.

Preliminary findings also suggest that even when CFS patients and controls receive similar scores on challenging cognitive tasks, participants often exhibit significant differences in cerebral activity. For instance, Lange et al. (2005) found that even though CFS patients and healthy controls processed challenging auditory stimuli with similar levels of proficiency, the CFS group completed the task while using more extensive regions of their verbal working memory system than controls.
This suggests that CFS patients require greater effort than nonfatigued peers to complete the same cognitive activity. Similarly, during the PASAT, patterns of diffuse regional cerebral blood flow were observed in a group of CFS patients compared to patterns of a focal regional cerebral blood flow in healthy controls. However, task performance was not distinguishable between groups, suggesting that CFS patients and nonfatigued peers require different neurological activity to perform similarly on the same task (Schmaling, Lewis, Fiedelak, Mahurin, & Buchwald, 2003). Another group also found that even though CFS patients and healthy controls performed comparably throughout a working memory task, the CFS group demonstrated greater activation in the medial prefrontal regions during the easier task phase. Conversely, throughout the more challenging phase, the CFS patients exhibited reduced activation in the dorsolateral prefrontal and parietal cortices and significant activation of a cluster in the right inferior/medial temporal cortex. Based on these results, the researchers suggested that CFS patients have impairments in the neurological working memory system and that other cerebral systems are employed to compensate for these deficits (Caseras et al., 2006).

This unusual cerebral activity in the absence of cognitive performance deficits in CFS patients could explain why cognitive function appears to be intact even when patients report significant impairments. Cognitive functions are generally assessed in isolation from other activity, enabling patients to compensate for deficits in one area by employing other cognitive faculties. However, mental activity in everyday environments rarely relies on a single cognitive domain, preventing patients from using other cognitive functions to compensate for impairments.

Although neuroimaging research is still in its infancy, the current findings suggest that structural and functional abnormalities are common in CFS patients. In
particular, CFS patients often present with enlarged brain regions and exhibit greater neurological activity while completing cognitive tasks. However, many patients present with no neurological irregularities, and psychological disturbances may account for the atypical findings in some patients. As such, neurological factors are unlikely to provide a complete explanation of the mechanisms underlying cognitive impairment in CFS patients.

Objective Assessments of Cognitive Function in Young People With CFS

In the last few years, research investigating cognitive impairment in young CFS patients has begun to emerge. To date, findings suggest that adults and young patients present with similar cognitive profiles. However, due to the potentially devastating educational and developmental impact of cognitive dysfunction in young people, further research designed to investigate how CFS uniquely affects this population is especially critical.

In the first of major study to investigate neuropsychological function in young CFS patients, 20 participants aged between eight and 16 were recruited from a regional CFS/ME clinical service in England. As part of the inclusion criteria, all participants were required to report current memory or concentration problems. Cognitive assessments included the Behavioural Assessment of the Dysexecutive Syndrome, the Children’s Memory Scale, the Test of Everyday Attention for Children, and the Symbol Search, Digit Span, and Letter-Number Sequencing subsets of the WISC-IV. Participants scored below the normative mean on measures of sustained attention, switching attention, divided attention, auditory learning, and immediate verbal recall. Scores averaging more than one standard deviation below the normative mean were only evident in divided attention. Conversely, scores were
not significantly different from normative data on measures of processing speed, focused attention, spatial learning, immediate and delayed recall, delayed recognition, working memory, and executive function (Haig-Ferguson et al., 2009).

This pioneering study demonstrates that it is feasible to conduct neuropsychological testing in children with CFS, and the results suggest that young CFS patients suffer from cognitive deficits in several domains. However, there are a few important issues to consider. First, all participants were recruited from specialist service, and only those who reported memory or concentration problems were selected to participate. As such, the sample may have represented patients with more severe symptoms and greater cognitive impairment than the general population of young CFS patients. In addition, the participants were required to complete a small number of neuropsychological tests over a period of approximately 30 minutes in order to prevent participants from becoming fatigued (Haig-Ferguson et al., 2009). However, given that many real life circumstances require ongoing cognitive activity, these results may not reveal the severity of typical cognitive function in CFS patients. Finally, the study did not include a comparison group, instead relying on normative data collected by different researchers, under different conditions, and at a different time period. Therefore, the results may be attributable factors associated with the nature of this particular study. In consideration of these factors, the findings in this study need to be substantiated by further research with a larger and more variable sampling pool before conclusions can be drawn.

Cognitive function in young CFS patients was also assessed in a recent unpublished study by some of the members of the current research team (Younis, 2009). A group of 27 adolescents with CFS and 27 age and sex matched healthy controls completed a comprehensive neuropsychological test battery from the
CANTAB. Subsets included IED, SOC, RVIP, RTI, SWM, SSP, and Verbal Recognition Memory (VRM). Participants also completed the Wide Range Achievement Test, third edition, (WRAT-III) and the Vocabulary and Matrix Reasoning subsets of the Wechsler Abbreviated Scale of Intelligence (WASI). Consistent with the research in adults, both groups achieved similar scores on the intelligence assessment. However, there were no differences between groups on any neuropsychological or academic task. This was particularly surprising given that the CFS group reported significantly greater cognitive impairment, school absenteeism, sleep disturbance, fatigue, and psychological distress than the controls. Based on observations of the participants during the assessments, the researchers proposed that the CFS patients may have had higher levels of motivation or perfectionism than controls, and that these differences may have accounted for the nonsignificant results. It is also worth noting that some of the cognitive tasks were given in the early stages of the assessment and the participants were provided with rest breaks if they became fatigued. Therefore, the CFS patients may not have been given sufficient opportunity to reach a level of fatigue that would normally affect cognitive performance in everyday settings. This study is discussed in more detail in Chapter 5.

Evidence of cognitive impairment in young CFS patients was identified in a recently published treatment trial. Participants included 19 adolescents aged between 13 and 15, diagnosed according to the paediatric criteria for CFS (Jason et al., 2006). An age and sex matched healthy control group of 25 adolescents was also included. Before and after receiving CBT and antidepressant medication, the CFS patients completed the Modified Advanced Trail Making Test and the Japanese Kana Pick-Out Test. Prior to treatment, differences in reaction time from the three outcome
measures for the Trail Making Test, including motor skill, selective and alternative attention, and spatial working memory, could differentiate CFS patients from 25 age and sex matched healthy controls with 70.5% accuracy. However, reaction time on Task E (alternative attention) was the only component to contribute significantly to the analysis. The overall and comprehension scores on the Kana Pick-Out Test were not distinguishable between groups, indicating that short-term memory, allocation, and information processing were not affected by CFS. Alternative attention on Task E scores were not related to IQ, depressive symptoms, feeling too unwell to attend school, or short-term memory and information processing on the Kana Pick-Out Test. Reaction time and difference in reaction time on task on alternative attention (Task E) improved significantly from baseline to follow-up. Performance on the other components of the Trail Making Test, including selective attention and spatial working memory did not change from baseline to follow-up. A negative correlation was observed between mental fatigue and difference in reaction time on task on Task E (alternative attention) from baseline to follow-up. No other cognitive indicators were related to changes in physical or mental fatigue following the intervention (Kawatani et al., 2011).

In an earlier study by the same group, cognitive function in 414 young CFS patients was evaluated using event-related potentials and the Kana Pick-Out Test. Compared to 190 healthy controls, the CFS achieved lower scores on measures of information processing, sustained attention, and divided attention (Tomoda, et al., 2007).

Further evidence of cognitive impairment in young CFS patients has been found using neuroimaging technology. For instance, in a sample of 13 children with CFS, hypoperfusion was observed in the left and right temporal and parietal lobes.
There was also evidence of bilateral orbitofrontal and anterior temporal hypoperfusion, as well as hypoperfusion in the right frontal lobe and dorsal aspects of both frontal lobes and both parietooccipital lobes (Goldberg, Mena, & Darcourt, 1997). However, this study lacked a comparison group and the sample size was very limited. In a more recent case report study, regional cerebral blood flow and brain metabolic levels were assessed in three CFS patients aged 11, 12 and, 13. The results were compared to healthy data drawn from another study. Blood flow in the left temporal and occipital lobes was markedly lower than healthy controls in cases two and three. In case one however, blood flow in the left basal ganglia and thalamus was significantly higher than controls. A considerable elevation of the choline/creatine ratio was also observed in all CFS patients. There was no evidence of any focal structural abnormalities (Tomoda et al. 2000).

Although significant advances in the quality and quantity of research are required, preliminary findings suggest that young CFS patients experience significant cognitive impairment, particularly in terms of attention and working memory.

**Methodological Considerations**

There are a number of methodological issues to be considered when interpreting research investigating cognitive function in CFS patients. Firstly, many of the neuropsychological tests used in this research are designed to detect impairment in patient groups with substantial impairment (Gronwall, 1977; Rey & Osterrieth, 1993), and these tests may lack adequate sensitivity for identifying abnormalities in CFS patients who experience mild cognitive deficits in everyday function (Wearden & Appelby, 1996). Moreover, neuropsychological testing performed within a laboratory setting may be inappropriate for detecting deficits that
occur in naturalistic settings (Tiersky et al., 1997; Wearden & Appelby, 1996). In a laboratory, patients are less affected by noise interference, distraction, fatigue, drowsiness, or a willingness to give up. Further, there is often a social obligation to please the researcher and to perform at a high standard. These factors may serve to conceal or compensate for the cognitive deficits that are normally present in CFS patients.

Cognitive assessments and findings are routinely categorised into various domains, such as executive function, attention, and processing speed. However, these faculties are theoretically derived operational constructs that fail to represent the true complexities of cognitive processes. A test designed to assess a single cognitive domain almost always requires the use of one or more other functions. Determining the precise cognitive function that accounts for poor performance can be exceedingly difficult. Conversely, cognitive deficits may be concealed by the superior performance of other cognitive domains.

In light of these issues, caution is recommended when interpreting findings from studies in cognitive function. In future research, some of these issues could be addressed by including measures of both perceived cognitive function and neuropsychological test performance in several cognitive domains. This would contribute to a greater understanding of how CFS affects various cognitive functions in a range of settings.

**Chapter Summary**

In summary, current research suggests that adults and young people with CFS perceive themselves to have a range of cognitive impairments, and many patients perform poorly on academic and neuropsychological tests. Some adults with CFS
experience deficits in executive function, particularly on tasks that involve cognitive flexibility and abstract planning. However, general planning and problem solving ability appears to remain intact. CFS patients also tend to perform poorly on tasks that require divided attention, choice reaction, and sustained attention, but not selective attention. There is considerable evidence suggesting that processing speed is impaired in many CFS patients, and that these deficits decrease the precision and efficiency of other cognitive functions. Finally, performance deficits are often observed on challenging working memory tasks that require free recall of phonological or visuospatial information. CFS patients often have structural and functional neurological abnormalities, and many patients employ different cognitive strategies or require greater neurological effort to complete the same cognitive tasks as nonfatigued peers. However, many patients present with no neurological irregularities at all. In the few studies in young patients, there is evidence of deficits in attention, working memory, and learning.

Nonetheless, the nature of cognitive dysfunction in CFS patients is still far from being well understood, and findings in this area are perhaps best described as inconsistent. This could be caused by methodological variability or inconsistencies in external factors such as environment and time, or internal factors such as symptom severity. It is also possible that these results reflect the true complexities of cognitive function or the heterogeneity of symptom profiles in CFS patients. Until further research becomes available, the nature of cognitive function in CFS patients is largely speculative.

Even less is known about cognitive function in young patients due to the near absence of research in paediatric populations. It cannot be assumed that adults and young people present with similar cognitive symptoms, particularly given that
neurological development continues into young adulthood (De Luca et al., 2003). This research gap is particularly remarkable given the significant implications for young people if cognitive impairments are present. If CFS affects cognitive function at such critical stages of development, cognitive dysfunction could become lifelong, and performance at school may be severely impaired. These factors could cause limitations to educational and occupational opportunities throughout life (Fröjd et al., 2008; Kovacs & Goldston, 1991), and may generate secondary problems in identity formation (Flum, & Kaplan, 2012; Vågan, 2011), social development (Honn & Bornstein, 2002; Kovacs & Goldston, 1991), and psychological adjustment (Austin et al., 2010). In the absence on curative treatments, it is essential to develop targeted interventions that address the most disturbing symptoms of CFS. For young patients, one of these symptoms is likely to be cognitive dysfunction.

Further research is critical to forming an accurate conceptualisation of how CFS affects cognitive function in young people, with the expectation that this will promote additional investigation into treatment or compensatory approaches for cognitive disturbances. Due to the potentially devastating consequences of cognitive impairment in this population, research designed to understand and treat cognition may lead to considerable improvements in the quality of life of young CFS patients.
Chapter 4: Factors That Affect Cognitive Function in CFS

The research discussed in the previous chapter demonstrates that people with CFS commonly experience impairment in several cognitive faculties. However, these deficits might be amplified by the severity of several symptoms common in CFS, including fatigue, sleep disturbance, and psychological distress. The following chapter includes a brief overview of the literature regarding how these factors influence cognitive function in CFS patients.

Fatigue

Fatigue is an enormously complex phenomenon that is greatly influenced by several interrelated psychosocial and behavioural processes (Zwarts, Bleijenberg, & van Engelen, 2008). Even outside clinical populations, fatigue is strongly associated with significant morbidity (Shen, Barbera, & Shapiro, 2006). Constituting the key symptom of CFS, chronic fatigue is responsible for considerable disability and functional impairment in these patients. Considerable efforts have been made to understand the relationship between fatigue and cognitive performance in people with CFS.

Research investigating how cognitive function is affected by fatigue in CFS patients has drawn mixed results. One group found a negative correlation between fatigue and performance on tasks requiring spatial memory and verbal fluency in 20 CFS patients. However, no correlations were identified between fatigue and performance on six other measures of cognitive function (Joyce et al., 1996). Michiels et al. (1999) also found that increased fatigue was associated with poor performance on tasks of attention but not memory in a group of 29 CFS patients. Several other studies suggest that self-reported fatigue is unrelated to performance on
tasks of executive function, working memory, attention, information processing speed, and visual memory (Mahurin et al., 2004; Michiels et al., 1998; Short et al., 2002; Vercoulen et al., 1998).

When mental fatigue is evaluated independently from physical fatigue, the association between fatigue and cognitive performance is generally stronger. For instance, in a study of 43 CFS patients, lower scores on CANTAB tasks of working memory, visual memory, and attention were identified among those who reported significant mental fatigue compared to patients without mental fatigue and healthy controls. However, there were no between-group differences on measures of executive function, choice reaction time, and other visual memory tasks (Capuron et al., 2006). In a combined sample of CFS patients and matched controls, another group identified an association between increased mental fatigue and slower response times on two CANTAB tests. However, no significant correlations were observed between fatigue and other tests of visual memory, executive function, working memory, and attention. In addition, only physical fatigue was correlated with slower movement times, and general fatigue was associated with poor performance on a visual memory task (Majer et al., 2008). However, because these findings refer to CFS patients and controls as a group, the unique impact of fatigue in CFS patients in this study is unclear.

One group investigated the impact of mental fatigue in young CFS patients. Researchers monitored the relationship between fatigue and reaction time on a trail-making test throughout a treatment trial in a group of 19 adolescents with CFS. From baseline to follow-up, patient reports of decreased mental and total fatigue were associated with faster reaction times on task E, but not tasks A-C. Changes in physical fatigue were unrelated to reaction time (Kawatani et al., 2011). These
results suggest that, in young CFS patients, reaction time may improve in response to decreases in mental fatigue.

The relationship between mental fatigue and cognitive impairment was also demonstrated in a neuroimaging study. Nine CFS patients and 11 nonfatigued controls completed the PASAT and several nonfatiguing cognitive and motor tasks. Mental fatigue was associated with brain activity in the cerebella, temporal, cingulate frontal, and left posterior parietal cortex regions while participants completed the PASAT only. In addition, the CFS patients exhibited significantly greater cortical and subcortical activity than controls while completing the PASAT. There were no differences in brain activity between groups on the nonfatiguing tasks. Group differences in neurological activity remained significant when anxiety, depression, and task performance were accounted for. However, the differences became nonsignificant when mental fatigue was controlled for (Cook et al., 2007). These results suggest that mental fatigue affects neurological function during demanding cognitive activity.

Another group found that CFS patients are also particularly susceptible to the effects of acute fatigue. Compared to 126 matched controls, 67 CFS patients achieved lower scores on a test of sustained attention, and the group differences became larger as acute fatigue increased throughout the assessment (Smith et al., 1999).

The impact of fatigue appears to be distinct from sleepiness. This was demonstrated in a study involving 15 CFS patients without sleep disorders or clinically significant sleepiness, 15 sleep apnoea patients without significant fatigue, and 16 healthy participants. Cognitive tests included the Auditory Verbal Learning Test and the Digit Span and Digit Symbol subsets from the WAIS. Both patient
groups achieved lower scores than healthy controls on all tests other than Digit Span. Impairment on the Digit Span and Digit Symbol tests was most severe in the sleep apnoea patients. Although the patients with sleep apnoea scored lower than both groups on the verbal memory task, only the CFS patients failed to increase the number of correctly recalled words over successive trials (Neu et al., 2011). This suggests that fatigue and sleepiness are associated with distinct, but significant cognitive impairment.

Together, the research suggests that fatigue is positively correlated with cognitive impairment in CFS patients. However, the findings are highly variable. Greater clarity is gained by distinguishing mental fatigue from general or physical fatigue, with results suggesting that mental fatigue is associated with impairment on tasks that require working memory, visual memory, attention, and reaction time. Although an association between fatigue and poor reaction time was observed in one adolescent study, considerably more research is required before the relationship between fatigue and cognitive performance can be established in young CFS patients.

Sleep Disturbance

The adverse impact of sleep disturbance on cognitive function has been well documented in both adult and paediatric CFS samples. Sleep disturbance is reported by around 81-95% of CFS patients (Becker et al., 2001; Sharpley, Clements, Hawton, & Sharpe, 1997; Unger et al., 2004), and disturbed sleep is known to generate many symptoms associated with CFS (Horne, 1988; Samkoff & Jacques, 1991). As such, some have suggested that cognitive impairment in CFS patients is caused by disturbances in sleep (Huller & Moser, 1990).
Although sleep disturbances are exceptionally common in CFS patients, primary sleep disorders are considered exclusionary in the CFS case definition (Fukuda et al., 1994). Nonetheless, high incidences of undiagnosed sleep disorders have been identified in CFS patients. Depending on the study, the prevalence of undiagnosed primary sleep disorders in CFS patients ranges anywhere between 0% and 81%. Commonly diagnosed disorders include sleep apnoea, narcolepsy, restless leg syndrome/periodic limb movements, and insomnia or hypersomnia (Buchwald, Pasculay, Bombardier, & Kith, 1994; Fossey et al., 2004; Krupp, Jandorf, Coyle, & Mendelson, 1993; Le Bon et al., 2000; Manu et al., 1994; Morriss et al., 1993; Sharpley et al., 1997; Stores, Fry, & Crawford, 1998). It is probable that the inconsistent findings are caused by differences in research settings, selection criteria, case definitions, and methods of excluding primary sleep disorders (Unger et al., 2004).

Objective assessment techniques provide considerable insight into the nature of sleep disturbance in CFS. Using polysomnograph testing, one group found that compared to healthy controls, 20 CFS patients spent significantly longer in bed, slept less efficiently, and were awake for longer following sleep onset. However, there were no significant between-group differences in total nocturnal sleep time. Abnormal polysomnographs were observed in seven CFS patients and one healthy control (Sharpley et al., 1997). Another group identified abnormal polysomnograph results in 41% of 59 participants with chronic fatigue over a day-night sleep assessment (Buchwald et al., 1994). Other common sleep quality problems identified in CFS patients include poor sleep efficiency, reduced sleep time, interrupted sleep, prolonged sleep latency, and reduced slow wave sleep (Sharpley et al., 1997; Togo et al., 2008; van Hoof, de Becker, Lapp, Cluydts, & De Meirleir,
2007). These abnormalities remain evident when sleep and psychiatric disorders have been accounted for (Sharpley et al., 1997; Togo et al., 2008). With the development of more advanced polysomnograph assessments, one group found that compared to matched healthy controls, 22 female CFS patients transitioned from REM to non-REM sleep less frequently. However, the biological determinants of sleep duration in each stage were normal (Kishi, Struzik, Natelson, Togo, & Yamamoto, 2008). Collectively, findings drawn from polysomnograph assessments suggest that patients with CFS experience significant disturbances in sleep quality.

Researchers have given considerably less attention to the nature of sleep disturbance in young people with CFS. In one of the few studies, actigraph assessments were used to monitor nighttime activity in 12 CFS patients aged between 12 and 16 and matched controls. Compared to controls, the CFS group slept for considerably longer and were more likely to engage in long, uninterrupted sleep exceeding 10 hours (Ohinata et al., 2008). However, because actigraphs detect sleep based on movement, it is possible that these results reflect differences in stillness rather than sleep. In contrast, polysomnograph assessments revealed no differences in time spent asleep between 18 adolescents with CFS and matched healthy controls. However, the CFS patients slept less efficiently and had more frequent and longer sleep disruptions than controls (Stores et al., 1998).

Disturbances in circadian rhythm function have also been identified in young CFS patients. Using a saliva analysis, one group identified significantly higher melatonin levels in 13 adolescents with CFS compared to 15 age-matched controls when sleeping between midnight and 3:00am. All CFS patients and only one control reported unrefreshing sleep (Knook, Kavelaars, Sinnema, Kuis, & Heijnen, 2000). Another group found that young CFS patients lacked a clear rhythm in circadian
variation of core body temperature. In addition, compared to healthy controls, the CFS patients were delayed in reaching their lowest core body temperature and exhibited a lower amplitude of circadian core body temperature changes (Akemi, Takako, & Teruhisa, 2001). These studies suggest that circadian rhythm desynchronisation might be closely related to sleep disturbance in young people with CFS.

It is also important to note that even normal adolescent development is typically characterised by considerable changes in the timing and quantity of sleep and wakefulness. In adolescence, normal changes in circadian rhythm frequently cause young people to experience ongoing phase delay, which is characterised by late sleep times and late awakenings (Carskadon, Acebo, & Jenni, 2004). Adolescents also typically experience a decline in slow wave sleep (Williams, Karacan, & Hursch, 1974; Williams, Karacan, Hursch, & Davis, 1972) and changes in wave frequency during non-REM sleep (Jenni, Achermann, & Carskadon, 2003). Moreover, psychosocial and life-style changes, such as increased autonomy, academic obligations, and late-night social events often interfere with behavioural sleep regulation (Carskadon et al., 2004).

In summary, the research suggests that a significant portion of CFS patients experience disturbed sleep characterised by abnormal sleep architecture, poor sleep efficiency, interrupted sleep, unrefreshing sleep, reduced sleep time, prolonged sleep latency, and circadian rhythm disturbances. Although research in paediatric populations is limited, adults and young people with CFS appear to experience similar levels of sleep disturbance. Furthermore, there is clear evidence suggesting that disturbed sleep is common even among healthy adolescents. As the following section will demonstrate, sleep disturbance can have a significant impact on
cognitive function and may even account for some of the cognitive deficits observed in CFS patients.

To the authors’ knowledge, the relationship between sleep disturbance and cognitive function has only been assessed in CFS patients by one research group. The 67 CFS patients in this study were grouped according to the presence or absence of self-reported sleep disturbance. Compared to healthy controls, the CFS patients who reported sleep disturbances achieved lower scores on tests of attention, free recall, and cognitive vigilance. These differences could not be accounted for by fatigue, illness severity, illness duration, or anxiety. However, no differences were observed between the CFS patients without sleep disturbances and healthy controls on any measure (Smith et al., 1996). This study suggests that sleep disturbance may account for the cognitive deficits observed in CFS patients.

Although the association between circadian rhythm function and cognitive performance is yet to be examined in CFS patients, circadian rhythm disruption is common in CFS patients (van Heukelom, Prins, Smits, & Bleijenberg, 2006; Williams et al., 2002), and research in healthy populations suggests that circadian desynchronicity is related to neuropsychological impairment. In an experimental design, neuropsychological performance was examined in two groups of healthy participants while living in a laboratory for over one month. The relationship between sleep-wakefulness and internal circadian time was intentionally disrupted in one group and maintained in the other. In the desynchronised group, total sleep time, sleep latency, and rapid eye movement latency were shortened, and wakefulness following sleep onset increased. Compared to the synchronised group, learning impairment was significantly greater in participants with disrupted sleep (Wright, Hull, Hughes, Ronda, & Czeisler, 2006). Similarly, another group found that
participants who endure experimentally disturbed sleep-wake cycles exhibit impairments in concentration, learning capacity, and learning efficiency (Harrison, Jones, & Waterhouse, 2007). These results suggest that a disrupted alignment between sleep-wakefulness and internal circadian rhythm is associated with impaired cognitive performance.

If sleep disturbance affects cognitive function, it would be reasonable to expect that treatment for disturbed sleep would reduce the severity of cognitive impairment. This hypothesis was tested in 59 cognitively impaired CFS patients who exhibited disturbed sleep on objective assessments. Following treatment for sleep disorders, 90% of patients reported improvements in cognitive functioning. Note however, that this study relied on subjective measures of cognitive function, and the researchers failed to detail the nature of the treatment or the outcome measures for the reported improvements (Buchwald et al., 1994).

Cognitive deficits are likely to be a particular problem for young people with CFS given the high rates of sleep disturbances in healthy populations. Based on correlational studies in healthy children, researchers have identified an association between inadequate sleep and deficits in attention, visual memory, visual scanning, and working memory (Dahl, 1996; Sadeh, Gruber, Raviv, 2002; Steenari et al., 2003). Many of these findings are also supported by experimental studies. In a randomised controlled trial, 16 children aged between 10 and 14 were assigned to have 11 or five hours in bed over one night in a sleep laboratory. Those with restricted sleep achieved lower scores on abstract learning and verbal creativity tasks than participants with extended sleep. Less complex tasks involving memory, learning, and figural creativity were not affected by sleep restriction (Randazzo, Muehlbach, Schweitzer, & Walsh, 1998). Similar results were found in a study of 77
children who were asked to reduce or increase their sleep by one hour over three consecutive nights. Only the sleep-restricted group received lower scores on the Digit Forward test and a test of sustained attention compared to baseline. However, there were no changes in either group on a test of visual scanning memory and another working memory task (Sadeh, Gruber, & Raviv, 2003).

There is also evidence suggesting that sleep disturbance is associated with impaired academic performance. For instance, results from a comprehensive survey completed by 3,120 adolescents revealed that on average, participants who were achieving a C grade or below were receiving approximately 25 minutes less sleep and went to bed 40 minutes later on school nights than students achieving B grades or above (Wolfson & Carskadon, 1998). Similarly, in a community sample of 972 primary school students, problems with school achievement were significantly more common among those with sleep difficulties, and 21% of poor sleepers had failed at least one year of school (Kahn et al., 1989). Although the research is correlational, these results provide some indication that a disruption in regular sleep may interfere with academic performance. As such, sleep disturbance may compound the issues associated with school absenteeism and cognitive impairment in young people with CFS.

In summary, the research suggests that sleep disturbance is common in CFS patients and healthy adolescents. Disturbed sleep and circadian rhythm desynchronisation may cause neuropsychological performance deficits, particularly on tests of attention, free recall, and cognitive vigilance. In adolescents, sleep disturbances may also cause cognitive impairment on tasks involving abstract learning, verbal creativity, working memory, and sustained attention. Moreover, correlational studies indicate that disturbed sleep is associated with poor performance
in academic settings. However, these findings are based on preliminary research or studies in healthy populations, and it is unclear whether sleep disturbance contributes to academic decline in CFS patients. Determining how sleep is related to cognitive dysfunction in young CFS patients may inform the process of developing treatments that target this debilitating symptom in CFS.

**Psychological Disturbance**

High rates of psychological distress have been consistently documented in CFS populations, with depression and anxiety among the most common complaints (see the Psychological Disturbance section in Chapter 2 for a discussion of the prevalence of psychological disturbances in CFS). This has considerable implications for cognitive function in CFS patients, as there is a well-established relationship between psychological distress and neuropsychological performance.

In healthy populations, the correlation between psychological adjustment and cognitive function has been summarised in several meta-analyses. In a major review of 14 studies with participants who met the criteria for MDD, significant negative correlations were identified between symptom severity and neuropsychological performance on measures of episodic memory, executive function, and processing speed, but not semantic or visuospatial memory. However, the effect sizes explained no more than approximately 10% of the variance (McDermott & Ebmeier, 2009). In another meta-analysis of studies in young adults, clear deficits were observed in depressed patients on measures of executive function, attention, short-term and working memory, and psychomotor function. There was also some evidence of disturbances in verbal memory and learning, although several other studies suggested that performance on these measures was unaffected. In patients with anxiety
disorders, impairments were evident on measures of verbal episodic memory and executive function, and people with Panic Disorder were impaired on measures of divided attention, verbal memory, and learning, but not selective attention, visual memory, executive function, or concentration. Executive function, attention, and long- and short-term memory were also impaired in participants with Obsessive-Compulsive Disorder and Posttraumatic Stress Disorder (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008).

An association has also been identified between cognitive function and stress. Longitudinal research indicates that prolonged cortisol elevation is associated with cognitive dysfunction on measures of learning and selective attention but not memory or divided attention (Lupien, Lecours, Lussier, & Schwartz, 1994; Seeman, 1997). Researchers have also identified a relationship between stress-induced elevations in cortisol and impaired declarative memory (Kirschbaum, Wolf, May, & Wippich, 1996; Lupien, 1997).

Psychological disturbances also appear to affect academic performance. For instance, in a large study involving 400 Iranian students aged between 15 and 19, a negative correlation was observed between Grade Point Average (GPA) and self-reported depression (Yousefi, Redzuan, Mansor, Talib, & Juhari, 2009). Similarly, in a sample of 164 participants, Deroma (2009) found that those with moderate depressive symptoms had significantly lower GPAs than those with normal or minimal depressive symptoms. Another group found that 13 children with comorbid depression and epilepsy achieved lower scores on teacher grade reports than 38 controls with epilepsy alone. In addition, report scores improved in the depressed group following treatment for depression (Tosun et al., 2008). In contrast, several others have found no relationship between achievement outcomes and indicators of
psychological adjustment (Abell, Zwick, & Wheeler, 2007; Vaidya & Mulgaonkar, 2007; Yeh et al., 2007).

Although these studies suggest that psychological disturbances affect cognitive performance, it is important to note that the findings are largely based on correlational relationships from cross-sectional research. It is difficult to know whether the observed cognitive disturbances were caused by psychological distress or some other factor that is common to people who are suffering from psychiatric disturbances. The data may also be confounded by the presence of unassessed comorbid psychological disorders.

The relationship between psychological distress and cognitive impairment has also been investigated in CFS populations. Wearden and Appleby (1997) divided 50 CFS patients into two groups based on the presence or absence of depression. Only the depressed CFS group reported significantly greater levels of cognitive impairment than a group of healthy controls, and the depressed patients recalled significantly fewer items than the nondepressed patients on a free recall and cued verbal memory task. Researchers have also found that once depressive symptoms have been partialled out, cognitive deficits in CFS patients are no longer significant. For instance, Metzger and Denney (2002) found that group differences between CFS patients and controls on the Stroop task became nonsignificant when depression had been statistically accounted for. Another group found that compared to healthy participants, patients with CFS achieved significantly lower scores on measures of immediate memory, delayed memory, and visuo-constructional tasks. In addition, scores on measures of attention were significantly lower in the CFS group compared to patients with autoimmune thyroid disease. However, when the effects
of depression were controlled for, all group differences, with the exception of attention, were no longer significant (Dickson et al., 2009).

Findings from similar studies have been more ambiguous. For instance, one group identified a significant relationship between both depression and anxiety and performance on the Digit Span Backward task, but not on measures of working memory, executive function, or reaction time (Michiels et al., 1998). Similarly, Crowe and Casey (1999) found that depression severity was negatively correlated with scores on the PASAT but was unrelated to performance on tasks involving working memory, executive function, or attention. Adding to the complexity, several studies show no evidence of a relationship between psychological disturbances and cognitive function in CFS patients (Claypoole et al., 2007; Dobbs et al., 2001; Joyce et al., 1996; Mahurin et al., 2004; Michiels et al., 1996; Michiels et al., 1999; Short et al., 2002; Vercoulen et al., 1998).

The conflicting results could be partially accounted for by differences in the severity of depressive symptomatology between studies. While some researchers excluded participants who met the diagnostic criteria for depression, others sought to recruit the most severely depressed patients. For instance, Crowe and Casey (1999) intentionally included CFS patients with high symptom severity, chronicity, and impairment, and 65% of the Metzger and Denney (2002) sample scored above the clinical cut-off score for severe depression. Conversely, in most studies suggesting that depressive symptoms and cognitive performance were unrelated, participants with comorbid depression were excluded and few participants reported severe depressive symptomatology (Claypoole et al., 2007; Joyce et al., 1996; Michiels et al., 1996; Michiels et al., 1999). This suggests that in CFS patients, cognitive
impairment is associated with severe depressive symptoms or a diagnosable depressive disorder.

Taken together, the research suggests that psychological disturbances are related to cognitive dysfunction. In healthy populations, associations have been found between psychological distress and deficits on tests of executive function, attention, long-term memory, working memory, processing speed, learning, and academic achievement. Similar relationships have been identified in CFS patients, although the research is limited and the results are variable. The severity of psychological symptoms appears to be an important factor in determining the level of cognitive impairment, however this has not been investigated directly. Although the research is largely correlational, it suggests that psychological symptoms have the potential to contribute to, or perhaps exacerbate cognitive dysfunction in patients suffering from CFS.

**Chapter Summary**

The research discussed in Chapter 3 suggests that CFS patients have deficits in several cognitive faculties. To explore this further, the present chapter included an investigation of several symptoms common to CFS that have the potential to affect cognitive impairment. In summary, although the research suggests that fatigue impedes cognitive performance in CFS patients, only one study included a paediatric sample, and the exact nature and extent of the relationship between fatigue and cognitive performance remains unclear due to the inconsistent findings between studies. Disturbed sleep may increase or even account for the deficits observed in adult patients, and an association has been identified between sleep disturbance and impaired neuropsychological and academic performance in healthy adolescents.
Finally, although psychological distress may contribute to a decline in cognitive performance, this finding is less well established in CFS patients and is yet to be investigated in young patients.

Investigating the range of factors contributing to cognitive impairment in CFS patients is made complex by several issues. In particular, it is difficult to distinguish between the effects of the individual symptoms, and few studies have explored the unique contributions of each major variable. Moreover, it is unclear whether cognitive decline is caused by the combination of these symptoms or by some unique feature of CFS. In addition, given that most of the research is correlational, it is not clear whether these variables have a causal role in cognitive dysfunction. Nonetheless, the cumulative evidence from research in healthy and clinical samples provides a persuasive argument for the importance of considering fatigue, sleep disturbance, and psychological distress in the study of cognitive function in CFS patients. By inflating cognitive impairment, these symptoms all have the potential to magnify the negative impact of CFS in young populations.
Chapter 5: Research Proposal

Despite rigorous research over several decades, CFS remains poorly understood. An overview of the historical context from which CFS emerged reveals a multitude of conceptual transitions. As such, research efforts and findings have been inconsistent, and little is known about the nature of CFS, particularly in young people. Learning more about paediatric CFS is particularly important given that the prevalence rates are significant and course is prolonged for many young people. In addition, CFS causes considerable impairment that uniquely affects young patients, interfering with several vital developmental domains at an especially vulnerable age.

Establishing an effective treatment approach is limited by the exceptionally heterogeneous nature of CFS and poor understanding of the underlying aetiological factors. As such, interventions may be most effective if designed to ameliorate the debilitating symptoms and reduce the functional impact of CFS. One of the most prominent and destructive symptoms experienced by CFS patients is cognitive impairment. Adults and young people with CFS perceive themselves to have a range of cognitive deficits, and many adult patients perform poorly on neuropsychological tests, including tests of executive function, attention, processing speed, and working memory. If present in young patients, these deficits could cause a severe decline in academic performance and may lead to lifelong cognitive impairment. Cognitive decline may also generate secondary problems, such as school absenteeism, learning difficulties, psychological distress, and disturbed social and emotional development. These factors may limit future educational attainment and career opportunities, and prevent patients from participating in regular activities that are important for adolescent development. The overall affliction of CFS in young people is immeasurable.
Remarkably, almost no research has been designed to investigate objective cognitive function in young patients. Further research is critical to forming an accurate conceptualisation of how CFS affects cognitive function in young people. Improved knowledge in this area could promote additional investigation into treatment or compensatory approaches for cognitive disturbances. Due to the potentially devastating consequences of cognitive impairment in this population, research designed to understand and treat cognition may lead to considerable improvements in the quality of life of young CFS patients.

Furthermore, it is important to account for other symptoms common in CFS that may affect performance on cognitive tasks. Fatigue, sleep disturbance, and psychological distress all have the potential to inflate cognitive impairment, significantly magnifying the negative impact of CFS in young populations. Determining the nature of the relationship between these symptoms and cognitive impairment may lead to new insights regarding how to improve cognitive function in CFS patients. If this is successful, this could reduce the impact of CFS in young populations considerably.

The current research team recently investigated cognitive impairment in a group of 27 adolescents with CFS and 27 healthy controls. All patients had their diagnosis confirmed by a paediatric specialist and were considered to have moderate to severe symptoms. Participants completed comprehensive neuropsychological tests of executive function, attention, processing speed, and working memory from the CANTAB. The WRAT-III was also included to provide a measure of academic achievement. Although the CFS patients reported significantly higher levels of fatigue, sleep disturbance, psychological distress, school absenteeism, and cognitive
impairment, no differences were observed between patients and controls on any neuropsychological or academic test (Younis, 2009).

These findings were considered unusual for a number of reasons. First, much of the research in adults suggests that CFS patients perform poorly on these measures. Although the results vary, studies that include sensitive measures of cognitive function rarely show a complete absence of impairment. Second, the patients themselves reported significantly elevated levels of cognitive impairment. Third, the CFS group reported high levels of sleep disturbance, psychological distress, fatigue, and medication use. Even in healthy populations, these factors are often sufficient to produce significant cognitive impairment. There were no between-group differences in IQ, and the unexpected findings were unlikely to be caused by inaccurate diagnosis, low symptom severity, and insufficient breadth and sensitivity of the neuropsychological assessments.

The unusual findings could be explained by differences in motivation between groups. Throughout the assessment, the researchers observed that the CFS patients appeared to have higher levels of test motivation than the healthy controls. Specifically, the CFS group appeared to have more concern for their performance results, greater task focus, and greater interest in the research and assessment procedure. If these subtle observations were representative of true differences between groups, it is possible that test motivation accounted for the comparable neuropsychological test scores between groups.

Theoretically defined models of test-taking motivation support the hypothesis that motivation affects performance on cognitive tasks (Thelk, Sundre, Horst, & Finney, 2009; Wise & DeMars 2005; Wolf & Smith 1995). Eklöf (2010) recently theorised that there are two central components that are important for motivated
action. The expectancy component is the individuals’ belief in their ability to complete the task, and the task-value component refers to how personally valuable the task is to the individual. This second component is comprised of four factors, including attainment value (importance of doing well), intrinsic value (interest in the task), utility value (usefulness of the task), and cost perceptions (amount of effort required). These perceptions are hypothesised to influence performance by determining the examinees’ level of motivation, effort, and persistence.

This theoretical model is supported by a wealth of research. An association has been identified between academic performance and test motivation in school children (Brown & Walberg, 1993; Fortier, Vallerand, & Guay, 1995; Howse, Lange, Farran, & Boyles, 2003; Logan, Medford, & Hughes, 2010; Nishimura, Kawamura, & Sakurai, 2011; Preckel, Holling, & Vock, 2006; Schultz, 1993; Tavani & Losh, 2003; Verkuyten, Thijs, & Canatan, 2001) and in young adults studying at tertiary institutions (Goodman et al., 2011; Hirschfeld, Lawson, & Mossholder, 2004; Hoyt, 2001; Smith & Smith, 2002; Sundre & Kitsantas, 2004; Wise, Wise, & Bhola, 2006; Wolf & Smith, 1995). High test-taking motivation is also associated with superior performance on a range of neuropsychological tests (Binder, Kelly, Villanueva, & Winslow, 2003; Brunstein, & Schmitt, 2004; Lindem, 2000; Mizuno, Tanaka, Fukuda, Imai-Matsumura, & Watanabe, 2011). Importantly, the influence of test motivation appears to be highest in people with lower cognitive ability (Duckworth, Quinn, Lynam, Loeber, & Stouthamer-Loeber, 2011; Logan et al., 2010). As such, the performance enhancing effects of motivation may be stronger in cognitively impaired CFS patients compared to healthy peers.

According to Eklöf’s (2010) theory of test motivation, examinees will possess greater motivation if they believe that it is important to perform well, have greater
interest in the task, and find the task more useful. In the study by Younis (2009), it is probable that these factors were stronger in the CFS group. Participants with CFS had a vested interest in the research, as the study was designed to investigate their illness and was relevant to their symptom presentation. It is likely that many patients were feeling desperate to find ways of managing their condition and believed that active involvement in the research could contribute to finding solutions. In contrast, the controls were likely to have had little personal interest in the aims of the study, and the research had no personal consequences for them. In consideration of this motivational theory and the cumulative results from research investigating the relationship between test motivation and cognitive performance, it is possible that the CFS group had higher levels of motivation that served to compensate for their cognitive deficits.

Alternatively, the differences in motivation observed between CFS patients and controls in the Younis (2009) study could be attributable to stronger perfectionistic tendencies in the CFS group. Among clinical professionals, researchers, and the general community, CFS patients are commonly perceived to be perfectionistic, conscientious people who maintain high personal standards by incessantly pushing themselves beyond their limits (Lewis, Cooper, & Bennett, 1994; Surawy, Hackmann, Hawton, & Sharpe, 1995).

Perfectionism is generally considered to be a personality trait that encompasses adaptive and maladaptive components (Burns, 1980; Frost, Marten, Lahart, & Rosenblate, 1990; Gilman, Ashby, Sverko, Florell, & Varjas, 2005; Slaney, Rice, Mobley, Trippi, & Ashby, 2001). Adaptive perfectionism is characterised by high personal standards (Frost et al., 1990), perfectionistic strivings for excellence (Rice & Slaney, 2002), and self-oriented perfectionism (Hewitt &
Flett, 1991; Stoeber & Kersting, 2007). Conversely, maladaptive perfectionism is associated with concern over mistakes (Frost et al., 1990; Rice & Slaney, 2002), discrepancies between expectations and results (Slaney et al., 2001), socially-prescribed perfectionism, and other-oriented perfectionism (Chang, 2006; Hewitt & Flett, 1991).

Several studies suggest that CFS patients often present with high levels of adaptive and maladaptive perfectionistic traits. One group found that, compared to controls, CFS patients reported higher levels of adaptive and maladaptive perfectionistic traits prior to and after developing CFS (Luyten, Van Houdenhove, Cosyns, & Van den Broeck, 2006). An Australian group of researchers also found that compared to matched healthy controls, CFS patients scored higher on scales of maladaptive perfectionism, including doubts about actions, and concern over mistakes (White & Schweitzer, 2000). Others have found that CFS patients report high levels of maladaptive but not adaptive perfectionism (Deary & Chalder, 2010), and a positive correlation has been identified between fatigue and maladaptive but not adaptive perfectionism in CFS patients (Kempke et al., 2011). In contrast, Wood and Wessely (1999) found no differences between CFS patients and patients with rheumatoid arthritis on measures of maladaptive or adaptive perfectionism. Another group found similar scores among CFS patients and healthy controls on all scales of perfectionism other than maladaptive perfectionism, which were lower in the CFS group (Blenkiron, Edwards, & Lynch, 1999). Although the results are mixed, the preliminary evidence suggests that at least a subgroup of CFS patients present with high levels of perfectionism.

A clear pattern emerging from the research indicates that adolescents and tertiary students who report high perfectionistic strivings and low perfectionistic
concerns achieve significantly higher academic scores than those who report the opposite pattern and those without perfectionism (Accordino, Accordino, & Slaney, 2000; Bieling, Israeli, Smith, & Antony, 2003; Brown et al., 1999; Cox, Enns, & Clara, 2002; Enns, Cox, Sareen, & Freeman, 2001; Grzegorek, Slaney, Franze, & Rice, 2004; Nounopoulos, Ashby, & Gilman, 2006). Researchers have also found that academic performance is positively correlated with self-oriented perfectionism (Blankstein & Winkworth, 2004; Dykstra, 2007) and negatively correlated with socially prescribed perfectionism (Dykstra, 2007; Flett, Blankstein, & Hewitt, 2009; Witcher, Alexander, Onwuegbuzie, Collins, & Witcher, 2007). However, contrary to theory, a positive correlation has been identified between other-oriented perfectionism and tertiary academic performance (Flett et al., 2009; Witcher et al., 2007). In addition, others have found academic outcomes are unrelated to discrepancy (Accordino, et al., 2000), self-oriented perfectionism, and socially prescribed perfectionism (Chang, 2006; Flett, Blankstein, & Hewitt, 2009).

A handful of studies also suggest that perfectionism is associated with performance on neuropsychological assessments. Researchers have identified positive correlations between perfectionistic strivings and test performance on tasks of reasoning, work performance, information processing speed, and simple letter-detection (Stoeber, Chesterman, & Tarn, 2010; Stoeber & Kersting, 2007). Slade, Coppel, and Townes (2009) also found that performance on measures of executive function, attention, and working memory was positively correlated with adaptive perfectionism and negatively correlated with maladaptive perfectionism.

Although further research is required, current findings suggest that at least a subset of CFS patients have perfectionistic traits, and there is relatively consistent evidence suggesting that adaptive perfectionism is associated with improved
performance on academic and neuropsychological tests. Maladaptive perfectionism is less clearly understood, although the limited findings suggest that maladaptive traits are negatively correlated with academic and neuropsychological test performance. As such, it is possible that, in the Younis (2009) study, the CFS group had higher levels of adaptive perfectionism than the controls and that this served to compensate for their deficits in cognitive function.

An alternate explanation for the comparable scores between groups is that the CFS patients were not given sufficient opportunity to become mentally fatigued throughout the assessment. Some cognitive tests were administered approximately 20 minutes from the beginning of the session, and the entire assessment was typically completed within two hours. Questionnaires were also administered between the cognitive tasks, and rest breaks were offered to provide participants with an opportunity to recover from mental effort and fatigue. The CFS patients may have been able to compensate for cognitive decline associated with fatigue through these regular mental breaks. These factors may have protected participants from reaching the level of fatigue that could generate cognitive impairment in everyday settings.

One final possibility for the unexpected findings is that adolescents might be invulnerable to the cognitive impact of CFS. Although there is a large body of evidence suggesting that cognitive dysfunction is common in adults with CFS, it is not yet clear whether young sufferers experience such impairment. It is possible that cognitive function remains intact in young people with CFS.

In consideration of the present literature, a study was designed to investigate neuropsychological function and academic achievement in young people with CFS. In view of the findings from Younis’s (2009) study, the effects of test motivation and perfectionism on cognitive performance will also be considered.
Study Aims

The study will involve a cross sectional, between groups comparison of young CFS patients and healthy controls. The CFS group will consist of 12 to 21 year-olds diagnosed according to the paediatric case definition (Appendix A). An age and sex matched healthy control group will be included to provide a means of comparison.

Until recently, paediatric CFS patients were diagnosed according to diagnostic criteria developed for adults. However, this approach fails account for the unique presentation and developmental consequences of CFS in younger populations. In order to compensate for this, several researchers used an adapted version of the adult definition, and it was not until recently that a specific paediatric case definition was developed. Consequently, research has drawn inconsistent findings, and little is known about the unique implications of CFS in younger populations. Research investigating the symptoms and impact of CFS in young patients using the paediatric case definition is urgently required to clarify these inconsistencies and build a unique understanding of paediatric CFS. To contribute to the emerging research in young CFS patients, the following study includes a self-report questionnaire that provides detailed information about illness onset, course, impact, and symptom frequency and severity.

A large body of evidence suggests that adults with CFS report considerable cognitive impairment, however, little is known about how young patients perceive their cognitive ability. CFS patients may be able to describe aspects of their cognitive function that are not directly assessable with neuropsychological tests. As such, participants in the current study will complete questionnaires about the severity
and frequency of cognitive symptoms. Neuropsychological measures provide a more objective method of assessing cognitive function, and research in adults suggests that CFS patients perform poorly on measures of executive function, attention, processing speed, and working memory. However, few studies have included measures of neuropsychological function in young CFS patients. As such, the following study will include a thorough assessment of cognitive performance using the CANTAB. A brief measure of intelligence will also be administered to allow group differences in intelligence to be statistically controlled when assessing neuropsychological performance.

If cognitive impairment is present among young CFS patients, learning and academic performance are also likely to be affected. A small number of studies suggest that adolescents with CFS perform poorly at school, however academic performance has not been directly assessed in young patients under laboratory conditions. As such, a measure of academic achievement involving reading and arithmetic will be administered to patients and controls.

Based on observations by researchers in the Younis (2009) study, young people with CFS may have higher levels of test motivation than nonfatigued peers. Increased motivation may enhance cognitive performance, negating the effects of cognitive impairment. As such, a self-report measure of test motivation will be included in order to investigate and control for the impact of motivation on cognitive performance. Similarly, emerging research suggests that perfectionism is common among CFS patients and that perfectionism affects performance on cognitive tasks. To investigate this, the present study will include a brief self-report measure of adaptive and maladaptive perfectionism. Any group differences on this measure will
be statistically controlled for when cognitive performance is compared between groups.

Although it is clear that adults with CFS suffer from a number of cognitive disturbances, it is possible that young patients are less vulnerable to cognitive decline. This supposition is supported by the findings from the Younis (2009) study. To assess whether adults and young people suffer from similar disturbances in cognitive function, the present study will include a comparison group of adult CFS patients drawn from a concurrent research project.

The current literature suggests that young patients experience a range of debilitating symptoms such as fatigue, sleep disturbance, and psychological distress. However, the unique impact of these symptoms in young CFS patients is not well understood. Given that these symptoms have the potential to affect cognitive performance, the current study will include self-report measures of fatigue, sleep disturbance, and psychological distress. Researchers will conduct a statistical exploration of how these symptoms affect performance on neuropsychological and academic tests. Fatigue will also be monitored throughout the assessment procedure to assess the extent to which participants become fatigued in response to ongoing cognitive activity. Although this aspect of the study is exploratory, it is hoped that the findings will provide a starting point for future research.

Frequent school absenteeism is exceptionally common in young CFS patients. Long periods of absence from school may significantly affect academic achievement and psychosocial development. As part of investigating the functional impact of CFS, participants in this study will be asked to report their recent school attendance.
Hypotheses

The study will test the following hypotheses:

1. young people with CFS will report higher levels of cognitive disturbance and perform significantly worse on neuropsychological tests that assess executive function, attention, information processing speed, and working memory than healthy controls;

2. young people with CFS will perform significantly worse on tests of academic achievement than healthy controls;

3. young people with CFS will rate themselves higher on a measures of test motivation and adaptive and maladaptive perfectionism than healthy controls

4. in young people with CFS, high levels of self-reported motivation and adaptive perfectionism will predict greater performance, and high levels of self-reported maladaptive perfectionism will predict poorer performance on tests of neuropsychological function and academic achievement;

5. when the variance from motivation and adaptive perfectionism is accounted for, the differences between CFS patients and controls on neuropsychological and academic tests will become larger, and when the variance from maladaptive perfectionism is accounted for, the differences between CFS patients and controls on neuropsychological and academic tests will become smaller;

6. adults and young people with CFS will perform similarly on measures of neuropsychological tests that assess executive function, attention, and working memory;

7. young people with CFS will report higher rates of symptoms common to CFS, including sleep disturbance, psychological distress, and fatigue than healthy controls;
8. in young people with CFS, high ratings of sleep disturbance, psychological distress, and fatigue will predict poorer perceived cognitive disturbance and lower scores on tests of neuropsychological function and academic achievement;

9. young people with CFS will report higher rates of school absenteeism than healthy controls;

10. in young people with CFS, school absenteeism will be associated with lower scores on tests of academic achievement.
Chapter 6: Study of Cognitive Function in Young People with CFS

Method

Participants. The study included three participant groups: young people with CFS, young people without significant fatigue, and adults with CFS. Eligible participants for the young CFS group included 13 to 21 year-olds diagnosed according to the Paediatric Case Definition (Jason et al., 2006; Appendix A). Patients meeting these criteria were invited to participate by their treating physician at a tertiary paediatric medical centre. Of the 30 who were invited, five declined due to concern that the assessments would be overly fatiguing, and two declined without providing a reason. The 23 participants who agreed were aged between 12 and 21, with a mean age of 17.3 (SD = 2.54) years. Females dominated the group, accounting for 74% of the sample.

Young people without CFS were recruited through advertisement and word of mouth. A group of 23 healthy young people aged between 12 and 21 agreed to participate, although two of these participants failed to return the take-home surveys. The mean age was 17.4 (SD = 2.75), and females again accounted for 74% of the sample. These participants were matched to the CFS group for age and sex.

The adult CFS data was obtained from a concurrent study at the same tertiary institution. The 37 adults were recruited via an established database of patients who had expressed an interest in research participation. Females in this group accounted for 75.7% of the sample.

All participants gave written informed consent, and written parental consent was obtained for participants under the age of 18 (Appendix B).
**Diagnosis of CFS.** All young CFS participants met the 1994 Fukuda criteria (Fukuda et al., 1994) as well as the paediatric definition (Jason et al., 2006). A leading paediatrician who is internationally recognised as an expert in adolescent CFS confirmed the diagnosis. According to the Canadian definition, patients can be assigned to one of three illness categories. Severe CFS is assigned if the criteria for all six symptom clusters are met; Moderate CFS is diagnosed if the criteria for five clusters are met, plus one of three symptoms from cluster six; and Atypical CFS is assigned if the criteria for four or less symptom clusters are met. Appendix A includes a complete synopsis of the paediatric case definition.

Seventeen young CFS participants (73.9%) met the criteria for Severe CFS, five (21.7%) met the criteria for Moderate CFS, and one (4.3%) met the criteria for Atypical CFS. No participants in the healthy control group met the criteria for any diagnostic category. The percentage of CFS patients who met the criteria for each symptom cluster is presented in Table 6.1.

<table>
<thead>
<tr>
<th>Symptom cluster</th>
<th>%</th>
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<tbody>
<tr>
<td><strong>Cluster I:</strong> Fatigue</td>
<td>100%</td>
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<tr>
<td><strong>Cluster II:</strong> Post-exertional malaise</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Cluster III:</strong> Sleep</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Cluster IV:</strong> Pain</td>
<td>95.7%</td>
</tr>
<tr>
<td><strong>Cluster V:</strong> Neurocognition</td>
<td>95.7%</td>
</tr>
<tr>
<td><strong>Cluster VI:</strong> Immune</td>
<td>73.9%</td>
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**Onset and duration of CFS.** Twenty CFS participants (87.0%) reported that an infectious illness precipitated their condition, and the remaining three (13.0%) identified severe stress as an illness trigger. There was considerable variation between participants in the period of illness onset. Some reported rapid onset over a period of 24 hours (4.3%) or approximately one week (13%), and a large proportion of patients reported a moderate onset period of around one month (43.5%) or between two and six months (30.4%). Although no participants believed that their illness developed over a period of six to 24 months, 8.7% reported that onset occurred over a time spanning longer than two years. No participants reported lifelong fatigue.

The young CFS participants predominantly reported prolonged illness duration. Illness length had spanned for more than four years in 34.8% patients, and another 30.4% believed that they had been ill for three to four years. Those reporting an illness duration of one to two years accounted for 13.0% of the sample, and 21.7% claimed that they received their diagnoses within the preceding 12 months. The average illness length for the group was 39.3 months ($SD = 26.25$). No CFS participant believed that their illness was becoming worse, although 34.8% reported that it was unchanging. CFS was described as fluctuating by 47.8% of participants, and a further 4.3% believed that their illness was characterised by periods of remission and relapse. In contrast, 13% felt that they were improving.
Three healthy controls reported fatigue. These participants attributed their fatigue to inadequate sleep, anxiety, or work. The average duration of fatigue was nine months ($SD = 5.20$) and none believed that it had lasted for more than 12 months. One participant reported that onset occurred within one month, and the other two believed that onset occurred over a period of one to two years. All three stated that there was no change in the course of their fatigue.

**Illness characteristics.** Of the young CFS participants, 52.2% stated that they feel worse in response to physical activity, 34.8% reported that they feel worse before feeling better, and 13% stated that they initially feel better before feeling worse. No participants believed that they exclusively feel better following activity. In response to a period of rest, 52.2% reported that their fatigue partially improves, and the remaining 47.8% reported that it does not improve at all. To achieve a partial improvement, 39.1% reported that one day of rest is required, and 13.0% require one to three days. All believed that their fatigue would return if they recommence activity, and 91.3% reported that they deliberately limit activity in order to avoid fatigue.

Of the three fatigued healthy participants, one reported that they feel better following physical activity, another reported that they feel worse before feeling better, and the other believed that activity had no effect. Two believed that rest generated a partial improvement in fatigue, and the other reported a complete improvement. All three reported that one day of rest was required for their symptoms to improve and that fatigue would not reappear after returning to activity. Only one control claimed to limit activity regularly in order to avoid fatigue.
The CFS group were asked to record their three worst symptoms at illness onset and at the time of the assessment. At onset, all participants reported that fatigue was one of their three worst symptoms. The second most frequently reported symptom was headaches (56.5%), followed memory or concentration difficulties (39.1%) and pain (34.8%). Less common symptoms included muscle soreness, cold and flu symptoms, low energy, sore or swollen throat, vomiting or nausea, and hyperactivity. Symptoms reported at the time of the assessment were similar to those at onset, indicating that symptom presentation is consistent over time. Again, the most common symptoms included fatigue (95.7%), followed by headaches (56.5%) and memory or concentration difficulties, pain, and dizziness (34.8% each). One or two participants also reported muscle soreness, low motivation, cold and flu symptoms, sore or swollen throat, joint pain, irritability, and hyperactivity. Most participants (87.0%) reported that their symptoms fluctuated over time.

Of the CFS respondents, 73.9% believed that they typically contract illnesses more easily than their peers, and 82.6% felt that they take longer to recover from being ill. In contrast, only 20% of the healthy control group felt that they catch illnesses more easily, and 15% believed that they take longer to recover than their peers.

In both young groups, 73.91% were of secondary school age. However, four CFS patients (20%) had ceased regular education and commenced home schooling due to the severity of their illness. One control had received a lifelong home school education. School absenteeism was considerable among the CFS participants. Over a six month period, 61.1% had missed at least 15% of school, 33.3% missed 40-50%, and 22.2% missed more than 70%. The average number of days missed was 35.65.
In contrast, only one healthy control had missed more than 15% of school and the average number of days missed by this group was just 4.81.

**Materials.**

*CFS presentation.* All young participants completed the Pediatric Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Questionnaire (PMCQ). This tool was recently developed based on the paediatric case definition of CFS (Jason et al., 2006). It was selected to provide detailed information about illness onset, course, impact, and symptom frequency and severity. The questionnaire covers a range of symptom clusters, including fatigue, sleep, pain, and cognitive and atypical symptoms. Experts in childhood CFS recommend the PMCQ for gathering symptom data for paediatric CFS (Jason et al., 2008).

*Intellectual functioning.* An estimate of intellectual capacity was obtained using the Wechsler Abbreviated Scale of Intelligence (WASI). This is a norm-referenced test that provides an estimate of current and premorbid intellectual functioning (Psychological Corporation, 1999). The WASI can be administered to individuals aged from six to 89 years (Psychological Corporation, 1999). For children, the reliability coefficients for each subset range from .81 to .97 (Psychological Corporation, 1999). Due to time constraints, only the 15-20 minute short version of the test was administered. This is in accordance with recommendations by Kaufman and Lichtenberger (2006), who note that under research conditions, this approach yields a reliable and valid estimate of intellectual function.
The short version of the WASI includes the Vocabulary and Matrix Reasoning subtests. For Vocabulary, participants are asked to verbally define several words of increasing difficulty. This provides a measure of expressive language, word-recognition, and general knowledge. The Matrix Reasoning task requires participants to evaluate a series of increasingly difficult patterns that contain a missing component, and then from a choice of five, select the component that belongs in the pattern. This subtest provides a measure of abstract nonverbal reasoning (Psychological Corporation, 1999). Schoenberg, Lange, Brickell, and Saklofske, (2007) argue that together, these subtests provide an adequate measure of premorbid intellectual functioning in children.

**Perceived cognitive function.** Perceived cognitive function was assessed using the Cognitive Functions subscale of the Modified Fatigue Impact Scale (MFIS), which is based on the original Fatigue Impact Scale (Fisk et al., 1994). The cognitive subscale is a structured, self-report questionnaire consisting of 10 items rated on a five-point scale from *never* to *almost always*.

The MFIS has a Cronbach's alpha of .80 and it has a history of successful use among patients with CFS (Jones, Gray, Frith, & Newton, 2011; Newton, Sheth, Shin, Pairman, Wilton, Burt, & Jones, 2009; Surawy, Roberts, & Silver, 2005). It can also be used to discriminate between the effects of fatigue in CFS patients compared to patients with other fatigue-related disorders such as MS and essential hypertension (Fisk et al., 1994). Although the MFIS has not been psychometrically validated in young populations, the questions are very easy to understand and the test has high face validity.
Neuropsychological functioning. Neuropsychological function was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB), a touch-screen computerised assessment tool (Cambridge Cognition, 2006). Participants were administered 11 individual subtests designed to measure executive function, attention information processing speed, and working memory. All tasks are nonverbal and presented as simple geometric designs or shapes. Language proficiency is only required to understand the verbal instructions provided by the administrator. This battery can be completed in approximately 50 minutes.

The CANTAB is a well validated instrument that has been successfully employed as a measure of cognitive function in individuals aged between four and 90 years (Cambridge Cognition, 2006). Independent studies also demonstrate that the CANTAB can be used effectively in CFS populations (Capuron et al., 2006; Joyce et al., 1996; Lawrie et al., 2000). The following section presents a description of each subtest and the associated outcome measures included in the study.

Motor Screening (MOT). The MOT was administered at the beginning of the assessment to serve as an introduction to the touch screen system. It takes approximately three minutes to complete. Participants are required to touch a flashing cross as it appears in different locations on the screen. Those unable to complete this task would be considered unsuitable to complete the remaining cognitive tests. These results were not included in the evaluation of neuropsychological function.

Stockings of Cambridge (SOC). SOC measures frontal lobe function and provides an assessment of executive function, including spatial planning and problem
solving ability. In the copy phase, participants are shown two displays that each contain three coloured balls. By moving one ball at a time in the lower display, participants must copy the pattern shown in the upper display. In the follow phase, participants are required to follow the computer’s movements of the balls in the upper display one at a time. This phase provides a baseline measure of movement time.

The outcome measure, *SOC Problems Solved in Minimum Moves* records the number of occasions that the examinee successfully completes a problem within the minimum number of possible moves. This provides a succinct measure of planning capacity. *SOC Initial Thinking Time (Five Moves)* represents the difference between the copy and follow conditions in time (milliseconds) taken to select the first ball. This provides a measure of planning time without variance from movement time. *SOC Subsequent Thinking Time (Four Moves)* measures time to complete the problem after the initial move has been made. Again, this provides a measure of thinking time without variance from movement time. The two measures of thinking time provide an estimate of information processing speed (Cambridge Cognition, 2006).

*Big/little Circle (BLC).* In accordance with test recommendations (Cambridge Cognition, 2006), the BLC was administered as a training test of rule acquisition and reversal prior to completing the IED test. For the first 20 trials, participants must touch the smaller of two circles displayed on the screen. They are then asked to touch the larger circle for a further 20 trials. These results were not included in the evaluation of neuropsychological function.
Intra-Extra Dimensional Set Shift (IED). Following BLC, participants completed the IED, a complex test of rule acquisition and reversal. Successful completion of the test requires visual discrimination as well as attentional maintenance, shifting, and flexibility. The test involves two artificial dimensions: colour-filled shapes and white lines. At the beginning, two colour-filled shapes and two white lines are presented and the participant must learn which one is correct by touching it and observing the computer’s feedback. After six correct responses, the stimuli and/or rules are changed. These changes are initially intra-dimensional, where the colour filled shapes remain the only relevant dimension, and later the shift becomes extra-dimensional, where the white lines become the only relevant dimension. If the participant fails to learn a new rule after 50 trials, the test terminates (Cambridge Cognition, 2006).

The outcome measure, IED Total Errors Adjusted represents overall task competence. The score is based on the number of errors made throughout the entire task, adjusted to account for missed opportunities to make errors when participants fail to complete the task. Lower scores represent a greater ability to respond effectively to rule changes by discriminating between visual stimuli and maintaining or shifting attention. IED Block 6 Errors records the number of errors made before successfully completing an intra-dimensional shift: the shift of attention to a novel exemplar within a previously relevant perceptual dimension. IED Block 8 Errors records the number of errors made to successfully complete an extra-dimensional shift: the shift of attention to a novel exemplar of a previously irrelevant perceptual dimension. These measures provide a good indication of attentional flexibility. IED Stages Completed represents the total number of successfully completed stages. This score provides a measure of reversal learning and attentional flexibility.
**Spatial Span (SSP).** SSP was administered to provide a primary test of working memory capacity. In this task, examinees are presented with a pattern of white squares that briefly change colour in a variable sequence. Participants must recall the sequence by touching the boxes in the correct order. The number of boxes in a sequence increases from two to nine throughout the test. **SSP Span Length** represents the longest sequence successfully recalled by the participant, and **SSP Total Errors** measures the number of times the participant selected an incorrect box out of a possible 97. Both measures provide an indication of the participant’s ability to recall spatial information.

**Spatial Working Memory (SWM).** The SWM task requires participants to manipulate spatial information in working memory. In being a self-ordered test, SWM also provides a measure of heuristic strategy. The test begins with several coloured boxes displayed on the screen. By touching the boxes and using a process of elimination, participants must find one blue token inside each box. The number of boxes gradually increases from three to eight throughout the test, and the colour and position of the boxes are varied between trials to discourage stereotyped search strategies (Cambridge Cognition, 2006).

**SWM Total Errors** records the number of times a box is selected that is certain not to contain a blue token. This represents the participants’ ability to manipulate and recall information within working memory. **SWM Strategy** provides an estimate of the participants’ ability to employ an efficient search strategy by following a sequence. This score represents the number of times a participant begins a new search with a different box for the six and eight box problems. A low score is
indicative of superior executive function. *SWM Mean Time to Last Response* is a measure of processing speed that represents the average search time from the beginning of the trial to the final screen touch. Scores for this outcome measure are derived from the second hardest task stage in order to minimise missing data caused by participants failing to reach the final stage.

*Pattern Recognition Memory (PRM).* PRM assesses visual pattern recognition memory in a two-choice forced discrimination paradigm. Participants are presented with a series of 12 abstract patterns followed by 12 sets of two patterns. The examinee must select the pattern within each set that is identical to one of those presented in the initial phase. The test patterns are presented in the reverse order to the original presentation. This procedure is then repeated with 12 new patterns. *PRM Percent Correct* records the percentage of correct responses and, providing a good indicator of visual short-term memory.

*Spatial Recognition Memory (SRM).* SRM assesses visual spatial recognition memory in a two-choice forced discrimination paradigm. The participant is presented with a white square that appears in a sequence of five different locations on the screen. In the recognition phase, five pairs of squares are displayed sequentially and the participant is required to select one square in each pair that matches the location of those in the presentation phase. The recognition locations are presented in the reverse order of the original display. This sequence is repeated three more times, each time with five new locations. *SRM Percent Correct* records the percentage of correct responses achieved by participants, providing an indication of visual-spatial short-term recognition memory.
**Rapid Visual Information Processing (RVIP).** Sustained processing and attention was assessed using the RVIP subtest. This measure is sensitive to dysfunction in the parietal and frontal lobes of the brain and is a reliable measure of general performance. During this task, digits from two to nine appear in a pseudorandom order at the rate of 100 digits per minute. Participants are required to detect three predetermined sequences of three digits (2-4-6, 3-5-7, and 4-6-8) and register their responses using a press pad. Target sequences occur at a rate of 16 every two minutes.

**RVIP A’ Target Sensitivity** measures efficiency of detecting the predetermined sequences while accounting for response tendency. Higher scores within the range of 0.00-1.00 represent greater accuracy in detecting sequences while avoiding false alarms (responding in the absence of a target sequence). This provides a sensitive estimate sustained attention. **RVIP Mean Latency** records the mean time taken to respond to a target sequence in milliseconds, providing a good indication of sustained attention and processing speed. The scores for both outcome measures are calculated from the final three task stages.

**Reaction Time (RTI).** RTI measures attention and speed of response to visual stimuli. The task is divided into five stages that require increasingly complex chains of responses. In each stage, the participant must respond to a suddenly appearing yellow dot by using a press-pad, touching the screen, or both. **Five-Choice Reaction Time** provides an indication of attention by recording the speed that the participant releases the press pad in response to a stimulus appearing in one of five locations. Performance on this measure is also dependant on processing speed.
**Academic performance.** The Wide Range Achievement Test, 4\textsuperscript{th} Edition (WRAT-4; Wilkinson & Robertson, 2006) is a norm-referenced, individually administered measure of academic skills. Adequate validity and reliability has been established using a stratified sample of more than 3,000 individuals aged between five and 94 years. Immediate retest reliability coefficients range from .78 to .89 for an age-based sample, and it has been validated against a variety of achievement and cognitive ability tests (Wilkinson & Robertson, 2006). Standardised assessment scores are available to allow researchers to compare their results to same-age peers. In the present study, participants completed the Word Reading and Math Computation subtests, which together take approximately 20 minutes to administer. The Word Reading task requires respondents to read aloud an increasingly difficult list of words, providing a measure of word recognition and decoding ability. Math Computation comprises of 40 increasingly difficult written mathematic questions that cover a wide spectrum of problem types.

**Motivation.** In the final stage of the assessment procedure, participants were asked to rate their level of test motivation using the Student Opinion Scale (SOS; Sundre & Moore, 2002). This instrument produces two factors, Effort and Importance, each comprising of five test items that are rated on a five-point likert scale. The Effort scale assesses the level of effort and persistence exerted during task completion, and the Importance scale measures the personal relevance or importance of the tasks. This component structure is consistent with current motivational theories (Pintrich & De Groot, 1990), which suggest that willingness to produce
effort is dependent upon perceived task importance and a disposition to perform the work required for task completion.

There is strong evidence for the reliability and validity of the SOS. It has been administered to over 15,000 students in a range of assessment contexts, consistently producing reliability estimates in the .80s for the Total score and component scales (Sundre & Moore, 2002). In addition, positive correlations have been found between the SOS and test performance scores, and SOS scores are reliable in distinguishing between consequential and nonconsequential test conditions (Sundre & Moore, 2002). Although it was originally designed and validated for use in tertiary students, the SOS is appropriate for use in adolescents due to its simplicity and high face validity.

**Perfectionism.** Perfectionistic traits were assessed using the Almost Perfect Scale-Revised (APS-R; Slaney et al., 2001). Participants were asked to rate how they perceive themselves using a five-point Likert scale on a series of 23 questions. The APS-R comprises of two adaptive perfectionism scales: Standards and Order, and one scale of maladaptive perfectionism: Discrepancy.

The APS-R has satisfactory convergent validity, with item structure coefficients ranging from .49 to .83. Strong internal consistency has been identified for Order (.86), Standards (.85), and Discrepancy (.92; Slaney et al., 2001). Correlations have also been identified between the APS-R Standards scale and the Personal Standards scale on the Multidimensional Perfectionism Scale (MPS-1), as well as between APS-R Order and the MPS-1 Organization scale. In addition, a correlation has been found between the Discrepancy scale and the MPS-1 scale of Concern over Mistakes and Doubts about Actions (Frost et al., 1990).
Initially, the APS-R was psychometrically validated in adolescents and adults aged upwards from 17 years (Slaney et al., 2001), however psychometric data has since been produced for younger individuals. In a study of 376 adolescents in grades six to eight, a two-factor solution for the APS-R was produced, yielding Cronbach's alphas of .75 for Standards and .87 for Discrepancy. A test-retest reliability assessment involving 150 of these participants revealed significant correlations for Standards ($r = .72$) and Discrepancy ($r = .67$). Convergent and discriminant validity has also been established against the Behavioral Assessment System for Children (Locicero, 2001).

**Psychological functioning.** A measure of psychological adjustment was obtained using the Depression Anxiety Stress Scale (DASS; Lovibond & Lovibond, 1995). This instrument is a self-report measure consisting of 14 items for three related negative affective states, producing a total of 42 questions. The Depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest or involvement, anhedonia, and inertia. The Anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. The Stress scale is sensitive to levels of chronic nonspecific arousal, including difficulty relaxing, nervous arousal, and being easily upset or agitated, irritable or overreactive, and impatient. Using a four-point scale, participants are asked to rate the extent to which they have experienced each state within the past week.

Based on a sample of 2,914 participants, alpha coefficients for the three scales were identified as .91 for Depression, .84 for Anxiety, and .90 for Stress. The Depression and Anxiety subscales also show good convergent validity with other
measures designed to discriminate between these factors (Lovibond & Lovibond, 1995). High validity and reliability scores for the DASS have been identified in adolescent populations (Tully, Zajac, & Venning, 2009), and these scores are consistent with earlier research in adult populations (Antony, Bieling, Cox, Enns, & Swinson, 1998).

Participants were also administered the Inventory of Depressive Symptomatology–Self-Report (Australian version; IDS-SR; Rush, Carmody, & Reimitz, 2000; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996). This is a 30-item self-report questionnaire designed to assess the severity of depressive symptomatology according to the diagnostic criteria for a Major Depressive Episode (American Psychiatric Association, 2000). Using a four-point scale, respondents are required to record their experience of depressive symptoms over the past seven days. The IDS-SR has good internal reliability (coefficient alpha = .85) and is correlated with both the Hamilton Rating Scale for Depression ($r = .67$) and the Beck Depression Inventory ($r = .78$).

**Sleep disturbance.** The Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) was employed to provide an estimate of disturbance. This self-rated questionnaire produces seven component scores, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication, and daytime dysfunction. These scores can be summed to yield a global PSQI score. The seven components represent standardised measures of factors routinely assessed in patients with sleep disturbances. Completion requires approximately five to 10 minutes. The test
developers suggest that the PSQI is best used as a screening tool for distinguishing between cases and controls (Buysse et al., 1989).

Internal consistency was demonstrated in a sample of healthy participants and individuals with sleep disorders or depression. The global score produced a Cronbach’s alpha of .83, and correlations between the global score and component scales ranged between .35 and .76. The global score correctly identified 88.5% of all patients and controls, and the component scales significantly differentiated between diagnostic groups. Test-retest reliability was .85 for the global score and .65–.84 for the component scales (Buysse et al., 1989).

The International CFS Study Group recommends the PSIQ as a measure of sleep disturbance in CFS patients (Reeves et al., 2003), and the International Association of CFS Paediatric Case Definition Working Group recommends it for use in paediatric populations (Jason et al., 2006). Although there is no published psychometric data for adolescent populations, the PSIQ has been used effectively in research with young people (Cheung & Wong, 2011; Mesquita & Reimão, 2007, 2010). It is also a reasonably straightforward questionnaire with high face validity.

**Fatigue.** The severity of physical and mental fatigue was assessed using the Chalder Fatigue Scale (Chalder et al., 1993). This self-report instrument includes 14 questions rated on a four-point scale. It produces a total fatigue score and two component scores representing physical and mental fatigue. The scale was validated in a sample of 274 patients at a primary care clinic. The split-half reliability was .86 for physical fatigue and .85 for mental fatigue, and the Cronbach’s alpha for individual items ranged from .88 to .90 (Chalder et al., 1993). The reliability and
validity of the Chalder Fatigue Scale has also been demonstrated in CFS populations (Jason et al., 1997; Morriss, Wearden, & Mullis, 1998).

Although it has not been psychometrically validated in paediatric populations, several researchers have used the Chalder Fatigue Scale effectively in adolescents and young adults (Fukuda et al., 2010; Taylor, Lee, Kramer, Shirashi, & Kielhofner, 2011). It is also recommended as a measure of fatigue in young CFS populations by researchers with considerable experience in paediatric CFS (Gledhill & Garralda, 2006).

In the present study, changes in fatigue severity were monitored at five intervals throughout the assessment using a Visual Analogue Scale (VAS; Appendix C). Participants were asked to draw a mark on a blank line to indicate how they were presently feeling from \textit{no fatigue} to \textit{worst possible fatigue}. The VAS has good reliability and validity (Brunier, & Graydon, 1996; Kos, Nagels, D'Hooghe, Duportail, & Kerckhofs, 2006; Kwok & Pope, 2010; Wolfe, 2004), and has been used effectively in paediatric populations (Dudzic, Szymusiak, McCormick, & Miller, 2011; Huguet, Stinson, & McGrath, 2010; Staes, Stappaerts, Vertommen, & Nuyen, 2000).

\textbf{Procedure.} Participants eligible to join the CFS group were provided with plain language statements by their treating paediatrician (Appendix B). These statements included information about the nature and purpose of the study, as well as the possible risks and benefits of participating. The adolescents or their parents then contacted the researcher to schedule an assessment time. Young people without CFS were recruited through advertisement and word of mouth. Basic information statements were posted in public areas, including universities, public transport areas,
and medical centres. Eligible participants were also informed of the study through people associated with the university and research team. Following this, the young person or their parent contacted the researcher, who provided them with the plain language statement and invited them to arrange an assessment time.

Assessments were largely completed within a University laboratory, although some were conducted at the participants’ home due to transportation issues. The testing procedure was conducted over two to three hours, depending on the participant’s performance and fatigue levels. A second set of questionnaires that require approximately one hour were given to participants to complete in their own time. After returning the final questionnaires, participants received a small reimbursement for their time and travel expenses. The study was approved by the relevant Human Ethics Committees, and all data were de-identified and stored on a secure server at Deakin University.

**Testing protocol.** Before the assessment commenced, the test administrator discussed the plain language statements with the participants and their parents (for those under the age of 18) to ensure that all parties understood what was required for participation. Participants were then asked to sign the consent form (Appendix B).

Participants were required to rate their current fatigue levels at the beginning of the assessment, at three equal intervals throughout the procedure, and again at the end. Initially, participants completed a standardised measure of intelligence followed by a series of questionnaires designed to assess current psychological adjustment and perceived cognitive function. The intelligence test was administered first in order to prevent poor performance due to state fatigue in the CFS group. The questionnaires administered next as a means of inciting fatigue in response to mild
mental effort. Participants were encouraged to ask questions if they did not understand any of the material. A brief measure of academic ability was then administered, followed by series of neuropsychological tasks delivered via a touch screen tablet computer. The order of the neuropsychological tests was rotated to control for the effects of fatigue. Finally, participants completed a detailed assessment of present fatigue levels and test motivation. In the weeks following the assessment, participants completed questionnaires concerning symptom severity, sleep disturbance, and perfectionism.
Results

All assessments were conducted between January 2010 and October 2011. Data missing at random accounted for less than 1% of the dataset and there were only three instances of data not missing at random (all associated with symptom severity). Due to the limited sample size and the scarcity of missing data, maximum likelihood estimators were used to estimate all missing data.

Using the recommendations made by Tabanick and Fidell (2001), all data were screened and treated for outliers and violations of normality, linearity, and homoscedasticity. Significant outliers were rescored to one unit more extreme than the next most extreme figure. Square root transformations were performed on DASS Stress total, Global PSQI, IDS total, CANTAB RVIP A’ Target Sensitivity (reflected), CANTAB SOC Problems Solved in Minimum Moves, (reflected), CANTAB SSP Total Errors, APS-R Standards total (reflected), APS-R Order total, and VAS Time 5 (reflected). Log transformations were performed on PMCQ Frequency of Fatigue Symptoms, PMCQ Severity of Other Symptoms, DASS Anxiety Total, DASS Depression Total, CANTAB IED Block 8 Errors, CANTAB IED Total Errors Adjusted, CANTAB SOC Initial Thinking Time, and CANTAB SRM Percent Correct (reflected). An inverse transformation was also performed on PMCQ Frequency of Pain Symptoms.

Two healthy control participants did not return the surveys that were to be completed following the on site assessment procedure. These cases were thus excluded from analyses conducted on CFS symptoms, sleep disturbance, or perfectionism.
To avoid repetition, note that all MANOVA analyses in this study were assessed with group (CFS versus healthy controls) as the independent variable (IV) and were tested according to Pillai’s Trace.

**Presenting symptomatology.** The results of the PMCQ were evaluated to explore the differences between CFS patients and healthy controls in the frequency and severity of CFS symptoms. The descriptive statistics presented in Table 6.2 and Table 6.3 depict clear patterns indicating that, as would be expected, the young CFS group reported more frequent and severe symptoms than the controls on all clusters.

<table>
<thead>
<tr>
<th>Symptom cluster</th>
<th>Controls ($n = 21$)</th>
<th>CFS ($n = 23$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M$</td>
<td>$SD$</td>
</tr>
<tr>
<td>Sleep</td>
<td>0.26</td>
<td>0.60</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.47</td>
<td>0.77</td>
</tr>
<tr>
<td>Pain</td>
<td>0.14</td>
<td>0.26</td>
</tr>
<tr>
<td>Cognitive</td>
<td>0.11</td>
<td>0.26</td>
</tr>
<tr>
<td>Other Symptoms</td>
<td>0.07</td>
<td>0.13</td>
</tr>
</tbody>
</table>

With the five clusters entered as dependent variables (DVs), a significant main effect of group was detected for symptom frequency using a MANOVA, $F(5,38) = 52.97$, $p < .001$. Evaluation of univariate ANOVAs revealed significant effects for all symptom clusters: Sleep, $F(1,42) = 279.28$, $p < .001$; Fatigue, $F(1,42) = 33.75$, $p < .001$; Pain, $F(1,42) = 48.78$, $p < .001$; Cognitive Dysfunction, $F(1,42) = 57.44$, $p < .001$; Other Symptoms, $F(1,42) = 38.29$, $p < .001$. 
Table 6.3
*Group Means and Standard Deviations for CFS Symptom Cluster Severity*

<table>
<thead>
<tr>
<th>Symptom cluster</th>
<th>Controls (n = 21)</th>
<th>CFS (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Sleep</td>
<td>0.43</td>
<td>0.99</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.98</td>
<td>1.73</td>
</tr>
<tr>
<td>Pain</td>
<td>0.39</td>
<td>0.74</td>
</tr>
<tr>
<td>Cognitive</td>
<td>0.22</td>
<td>0.56</td>
</tr>
<tr>
<td>Other Symptoms</td>
<td>0.17</td>
<td>0.33</td>
</tr>
</tbody>
</table>

A second MANOVA revealed that young people with CFS reported significantly higher CFS symptom severity than healthy controls, $F(5,38) = 68.76$, $p<.001$. Follow-up univariate ANOVAs indicated that the CFS patients reported significantly higher severity levels for Sleep, $F(1,42) = 358.84$, $p<.001$; Fatigue, $F(1,42) = 26.66$, $p<.001$; Pain, $F(1,42) = 32.77$, $p<.001$; Cognitive Dysfunction, $F(1,42) = 54.54$, $p<.001$; and Other Symptoms, $F(1,42) = 61.02$, $p<.001$.

**Hypothesis 1: between-group differences in cognitive function.**

*Perceived cognitive function.* The results from the MFIS were compared between groups to test the hypothesis that young people with CFS would perceive themselves to be more cognitively impaired than the healthy controls. The descriptive statistics indicate that the CFS group rated themselves higher than the healthy controls on all items (Table 6.4).
Table 6.4
Group Means and Standard Deviations for Perceived Cognitive Disturbance

<table>
<thead>
<tr>
<th>Test item</th>
<th>Controls (n = 23)</th>
<th>CFS (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>MFIS Total</td>
<td>7.76</td>
<td>10.65</td>
</tr>
<tr>
<td>Less Alert</td>
<td>0.96</td>
<td>0.88</td>
</tr>
<tr>
<td>Difficulty Paying Attention for Long Periods</td>
<td>1.35</td>
<td>1.03</td>
</tr>
<tr>
<td>Unable to Think Clearly</td>
<td>1.00</td>
<td>0.90</td>
</tr>
<tr>
<td>Forgetful</td>
<td>1.35</td>
<td>1.03</td>
</tr>
<tr>
<td>Difficulty Making Decisions</td>
<td>1.43</td>
<td>1.24</td>
</tr>
<tr>
<td>Less Motivated to do Thinking Activities</td>
<td>0.91</td>
<td>0.90</td>
</tr>
<tr>
<td>Difficulty Finishing Thinking Related Tasks</td>
<td>0.96</td>
<td>1.07</td>
</tr>
<tr>
<td>Difficulty Organising Thoughts</td>
<td>1.00</td>
<td>1.04</td>
</tr>
<tr>
<td>Slowed Thinking</td>
<td>0.61</td>
<td>0.89</td>
</tr>
<tr>
<td>Difficulty Concentrating</td>
<td>1.09</td>
<td>0.85</td>
</tr>
</tbody>
</table>

*Note. Figures represent raw scores from a likert scale. MFIS= Modified Fatigue Impact Scale.

Using a MANOVA, a significant multivariate effect of group was detected for the 10 MFIS items, $F(10,35) = 7.90$, $p<.001$. Follow-up univariate ANOVAs revealed significant effects for all 10 items: Less Alert, $F(1,44) = 32.34$, $p<.001$; Difficulty Paying Attention for Long Periods, $F(1,44) = 42.51$, $p<.001$; Unable to Think Clearly, $F(1,44) = 40.85$, $p<.001$; Forgetful, $F(1,44) = 16.71$, $p<.001$; Difficulty Making Decisions, $F(1,44) = 8.69$, $p = .005$; Less Motivated to do Thinking Activities, $F(1,44) = 33.30$, $p<.001$; Difficulty Finishing Thinking Related Tasks, $F(1,44) = 30.36$, $p<.001$; Difficulty Organising Thoughts, $F(1,44) = 36.38$, $p<.001$; Slowed Thinking, $F(1,44) = 39.72$, $p<.001$; and Difficulty Concentrating, $F(1,44) = 91.06$, $p<.001$. As predicted, the CFS group perceived themselves to have significantly greater levels of cognitive impairment compared to the controls.
Executive function. It was hypothesised that young people with CFS would achieve lower scores than healthy controls on tests of executive function. This prediction was assessed using the CANTAB outcome measures for executive function on the IED, SOC, and SWM subtests. The descriptive statistics in Table 6.5 indicate that compared to controls, the CFS participants made more errors and performed less well on all measures of executive function excluding SWM strategy.

<table>
<thead>
<tr>
<th>CANTAB outcome measure</th>
<th>Controls (n = 23)</th>
<th>CFS (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>IED Block 6 Errors</td>
<td>0.17</td>
<td>0.39</td>
</tr>
<tr>
<td>IED Block 8 Errors</td>
<td>6.61</td>
<td>9.29</td>
</tr>
<tr>
<td>IED Total Errors Adjusted</td>
<td>17.17</td>
<td>17.42</td>
</tr>
<tr>
<td>IED Stages Completed</td>
<td>8.83</td>
<td>0.58</td>
</tr>
<tr>
<td>SOC Problems Solved in Minimum Moves</td>
<td>9.22</td>
<td>1.59</td>
</tr>
<tr>
<td>SWM Strategy</td>
<td>28.83</td>
<td>6.73</td>
</tr>
</tbody>
</table>

Note. IED= Intra-Extra Dimensional Set Shift; SOC= Stockings of Cambridge; SWM= Spatial Working Memory.

Using a MANOVA, a significant main effect of group was detected, $F(6,39) = 2.48$, $p = .040$, and follow-up ANOVAs revealed significant effects for IED Block 6 Errors, $F(1,44) = 7.01$, $p = .011$; IED Total Errors Adjusted, $F(1,44) = 6.60$, $p = .014$; and IED Stages Completed, $F(1,44) = 6.21$, $p = .017$. No between-group differences were detected for IED Block 8 Errors, $F(1,44) = 1.32$, $p = .256$; SOC Problems Solved in Minimum Moves, $F(1,44) = 0.34$, $p = .562$; and SWM Strategy $F(1,44) = 1.91$, $p = .174$. Consistent with the hypothesis, the data indicate that,
compared to the healthy controls, the CFS group performed less well on executive function overall. However, the CFS and healthy control groups performed similarly on three of the six individual outcome measures for executive function.

Attention. The hypothesis that CFS participants would perform more poorly than controls on neuropsychological measures of attention was assessed through investigation of the CANTAB outcome measures for RTI and RVIP. The descriptive statistics in Table 6.6 indicate that compared to controls, the CFS group reacted more slowly in response to visual stimuli on RTI, but faster on RVIP. The CFS patients were also less proficient in detecting target sequences and avoiding false alarms on RVIP.

Table 6.6  
*Group Means and Standard Deviations for Attention*

<table>
<thead>
<tr>
<th>CANTAB outcome measure</th>
<th>Controls (n = 23)</th>
<th>CFS (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td><em>a</em> RTI 5-Choice Reaction Time</td>
<td>308.09</td>
<td>55.97</td>
</tr>
<tr>
<td>RVIP A’ Target Sensitivity</td>
<td>0.92</td>
<td>0.04</td>
</tr>
<tr>
<td><em>a</em> RVIP Mean Latency</td>
<td>440.26</td>
<td>104.41</td>
</tr>
</tbody>
</table>

*Note. RTI= Reaction Time; RVIP= Rapid Visual Information Processing.  
*a* Scores are in msec

A significant overall between-group difference for attention was detected using a MANOVA, $F(3,41) = 3.75, p = .018$. Evaluation of univariate ANOVAs revealed significant effects for RTI 5-Choice Reaction Time, $F(1,44) = 5.10, p = .029$, and RVIP A’ Target Sensitivity, $F(1,41) = 4.25, p = .045$. However there were no group differences for RVIP Mean Latency $F(1,41) = 0.68, p = .415$. Consistent with the hypothesis, the data indicate that, compared to the healthy controls, the CFS
group demonstrated poorer overall attention. However, both groups achieved similar scores on one of the three outcome measures for attention.

**Information processing speed.** It was predicted that young CFS participants would perform more poorly on measures of information processing speed compared to healthy controls. This hypothesis was evaluated through investigation of the CANTAB results for SOC Initial Thinking Time, SOC Subsequent Thinking Time, and SWM Mean Time to Last Response. The descriptive statistics presented in Table 6.7 reveal mixed results. Compared to the healthy control group, the CFS participants appeared to spend less time thinking prior to starting the SOC task, but more time thinking throughout task completion. The CFS group also appeared to respond more slowly than controls on SWM.

### Table 6.7
**Group Means and Standard Deviations for Information Processing Speed**

<table>
<thead>
<tr>
<th>CANTAB outcome measure</th>
<th>Controls ($n = 23$)</th>
<th>CFS ($n = 23$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Initial Thinking Time</td>
<td>$M$ 10376.54</td>
<td>$M$ 7058.65</td>
</tr>
<tr>
<td></td>
<td>$SD$ 9648.55</td>
<td>$SD$ 6788.99</td>
</tr>
<tr>
<td>SOC Subsequent Thinking Time</td>
<td>$M$ 1510.26</td>
<td>$M$ 1818.98</td>
</tr>
<tr>
<td></td>
<td>$SD$ 2667.29</td>
<td>$SD$ 2960.28</td>
</tr>
<tr>
<td>SWM Mean Time to Last Response</td>
<td>$M$ 21539.73</td>
<td>$M$ 22354.07</td>
</tr>
<tr>
<td></td>
<td>$SD$ 4015.84</td>
<td>$SD$ 3375.75</td>
</tr>
</tbody>
</table>

*Note. Scores are in msec. SOC = Stockings of Cambridge; SWM = Spatial Working Memory.*

However, a significant main effect for group was not detected using a MANOVA $F(3,42) = 0.96, p = .421$. Contrary to the hypothesis, this suggests that CFS participants and healthy controls performed similarly on tasks that assess information processing speed.
**Working memory.** It was predicted that young CFS participants would perform more poorly than healthy controls on measures of working memory. The descriptive statistics presented in Table 6.8 indicate that the CFS participants achieved lower scores on SSP memory span, made more errors on SSP and SWM, and made fewer correct responses on SRM and PRM.

<table>
<thead>
<tr>
<th>CANTAB outcome measure</th>
<th>Controls (n = 23)</th>
<th>CFS (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSP Span Length</td>
<td>7.30</td>
<td>6.57</td>
</tr>
<tr>
<td>SSP Total Errors</td>
<td>14.17</td>
<td>14.83</td>
</tr>
<tr>
<td>SWM Total Errors</td>
<td>16.91</td>
<td>25.83</td>
</tr>
<tr>
<td>SRM Percent Correct</td>
<td>82.17</td>
<td>74.57</td>
</tr>
<tr>
<td>PRM Percent Correct</td>
<td>91.26</td>
<td>80.80</td>
</tr>
</tbody>
</table>

*Note. SSP= Spatial Span; SWM= Spatial Working Memory; SRM Spatial Recognition Memory Pattern Recognition Memory.*

Using a MANOVA, a significant main effect of group was detected $F(5,40) = 3.81$, $p = .006$, indicating that working memory performance was significantly different between groups. Follow-up ANOVAs revealed that the CFS group achieved significantly lower scores than controls on SSP Span Length $F(1,44) = 4.42$, $p = .041$. However, the group differences were not significant for SSP Total Errors $F(1,44) = 0.21$, $p = .649$ and SWM Total Errors $F(1,44) = 2.80$, $p = .101$. Significant group effects were detected for SRM Percent Correct, $F(1,44) = 6.35$, $p = .015$ and PRM Percent Correct, $F(1,44) = 10.21$, $p = .003$. Although these findings are not entirely consistent, together they indicate that the young CFS participants performed less well on working memory tasks than the healthy controls.
Hypothesis 2: between-group differences in academic achievement. The Reading and Math Computation component scores from the WRAT-4 were assessed to test the prediction that young CFS participants would perform less well on academic tests than healthy controls. The descriptive statistics presented in Table 6.9 indicate that the CFS group achieved higher scores on both measures, and this difference was identified as significant using MANOVA, $F(2,43) = 4.84, p = .013$. Evaluation of univariate ANOVAs revealed significant effects for both Reading, $F(1,44) = 7.12, p = .011$ and Math Computation, $F(1,44) = 9.04, p = .004$. Contrary to the hypothesis, these results indicate that the CFS participants achieved higher scores on measures of academic ability than the healthy controls.

<table>
<thead>
<tr>
<th>WRAT-4 measure</th>
<th>Controls ($n = 23$)</th>
<th>CFS ($n = 23$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M$</td>
<td>$SD$</td>
</tr>
<tr>
<td>Reading</td>
<td>97.35</td>
<td>14.75</td>
</tr>
<tr>
<td>Math Computation</td>
<td>86.13</td>
<td>16.17</td>
</tr>
</tbody>
</table>

Note. Scores are standard scores with a mean of 100 and SD of 15.

Hypothesis 3: between-group differences in test motivation and perfectionism.

Motivation. It was hypothesised that, compared to healthy controls, young people with CFS would report higher levels of test motivation. SOS Total provides a composite measure of overall test motivation and encompasses two outcome measures, Importance and Effort. The descriptive statistics presented in Table 6.10
indicate that the CFS participants rated themselves higher than controls on all indicators.

A significant effect of group was identified using a between groups MANOVA, $F(2,43) = 5.39$, $p = .008$. However follow-up ANOVAs revealed a significant group difference for Effort, $F(1,44) = 9.99$, $p < .003$ but not for Importance, $F(1,44) = 3.27$, $p = .077$. Consistent with the hypothesis, the data indicate that compared to controls, the CFS group rated themselves as more motivated in completing the assessments overall. However, both groups rated the importance of the assessments equally.

Table 6.10
Group Means and Standard Deviations for Test Motivation

<table>
<thead>
<tr>
<th>Measure</th>
<th>Controls ($n = 23$)</th>
<th>CFS ($n = 23$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M$</td>
<td>$SD$</td>
</tr>
<tr>
<td>SOS Importance</td>
<td>12.39</td>
<td>2.68</td>
</tr>
<tr>
<td>SOS Effort</td>
<td>14.52</td>
<td>2.17</td>
</tr>
<tr>
<td>SOS Total</td>
<td>26.91</td>
<td>3.78</td>
</tr>
</tbody>
</table>

*Note. Figures represent the summation of likert scale scores. SOS = Student Opinion Scale.*

**Perfectionism.** The results of the APS-R were evaluated to test the hypothesis that young people with CFS would report higher levels of perfectionism than controls. The descriptive statistics in Table 6.11 indicate that the CFS participants rated themselves lower on the adaptive scales of Standards and Order, and higher on the maladaptive scale of Discrepancy.
Table 6.11  
*Group Means and Standard Deviations for Test Perfectionism*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Controls (n = 21)</th>
<th>CFS (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>APS-R Standards</td>
<td>16.57</td>
<td>4.61</td>
</tr>
<tr>
<td>APS-R Order</td>
<td>10.33</td>
<td>3.95</td>
</tr>
<tr>
<td>APS-R Discrepancy</td>
<td>18.29</td>
<td>13.57</td>
</tr>
</tbody>
</table>

*Note.* Figures represent the summation of likert scale scores. APS-R = The Almost Perfect Scale-Revised.

No significant differences were identified between groups on the adaptive scales using a MANOVA, $F(2,41) = 1.33$, $p = .275$. Similarly, an independent samples $t$-test of APS-R Discrepancy indicated that young CFS participants did not differ significantly from healthy controls on self-ratings of maladaptive perfectionism $t(42) = 1.97$, $p = .056$. This indicates that, contrary to the research hypothesis, the CFS patients and healthy controls perceived themselves to have similar levels of perfectionism.

**Hypothesis 4: predictive value of motivation and perfectionism.** In the interests of completeness, and despite the lack of hypothesised differences between groups on perfectionism and motivation, the relationship between these variables and cognitive function was followed through with, in the CFS group only. The rationale for only using CFS participants was based on previous discussions in the literature where CFS patients have been noted to be higher in terms of perfectionism and conscientiousness (Lewis et al., 1994; Suraway et al., 1995). As such, the focus of the analysis changed from being on whether differences in cognitive performance were related to differences in motivation and perfectionism (when there were none)
to examining whether perfectionism and motivation had any relationship to performance in a CFS population.

A series of multiple and simple linear regressions were conducted to determine how well motivation and perfectionism predicted performance on measures of academic achievement and neuropsychological function in CFS patients. For each multiple regression, SOS Total and APS-R Standards and Order were entered as IVs to represent motivation and adaptive perfectionism respectively. The IVs were assessed for multicollinearity. Tolerance was .448 or above for all variables, indicating that multicollinearity is unlikely to be a problem. Not surprisingly, a significant correlation was detected between the Standards and Order perfectionism scales, $r(22) = .523$, $p = .005$. SOS Total was also correlated with Standards, $r(22) = -.596$, $p = .001$ and Order $r(22) = -.690$, $p < .001$. However, the strength of these correlations is not indicative of multicollinearity.

**Neuropsychological function.** A series of eight standard multiple linear regressions were employed to examine how well neuropsychological performance could be predicted by motivation and adaptive perfectionism. A single variable from the CANTAB was entered as the DV in each analysis. These variables were the eight outcome measures that significantly differentiated the CFS and healthy control groups.

The regression analyses were all nonsignificant: IED Block 6 Errors, adjusted $R^2 = -.135, F(3,22) = 0.13, p = .941$; IED Total Errors Adjusted, adjusted $R^2 = -.107, F(3,22) = 0.29, p = .830$; IED Stages Completed, adjusted $R^2 = -.107, F(3,22) = 0.29, p = .831$; RTI 5-Choice Reaction Time, adjusted $R^2 = -.098, F(3,22) = 0.34, p = .795$; RVIP A’ Target Sensitivity, adjusted $R^2 = -.036, F(3,22) = 0.75, p = .537$; SSP Span
Length, adjusted $R^2 = -.108$, $F(3,22) = 0.29, p = .836$; SRM Percent Correct, adjusted $R^2 = .038$, $F(3,22) = 1.29, p = .306$; PRM Percent Correct, adjusted $R^2 = -.008$, $F(3,22) = 0.94, p = .441$. In contrast to the hypothesis, these results indicate that self-rated motivation and adaptive perfectionism did not predict performance on tests of neuropsychological functioning.

A series of eight simple linear regression analyses were employed to examine how well neuropsychological performance could be predicted by maladaptive perfectionism. In each analysis, APS-R Discrepancy was the IV and a single variable from the CANTAB was entered as the DV. Again, these variables were the eight CANTAB outcome measures that significantly differentiated the CFS and healthy control groups.

All analyses were nonsignificant: IED Block 6 Errors, adjusted $R^2 = -.041$, $F(1,22) = 0.12, p = .726$; IED Total Errors Adjusted, adjusted $R^2 = .030$, $F(1,22) = 1.68, p = .209$; IED Stages Completed, adjusted $R^2 = .064$, $F(1,22) = 2.51, p = .128$; RTI 5-Choice Reaction Time, adjusted $R^2 = .025$, $F(1,22) = 1.57, p = .224$; RVIP A’ Target Sensitivity, adjusted $R^2 = -.038$, $F(1,22) = 0.19, p = .665$; SSP Span Length, adjusted $R^2 = .007$, $F(1,22) = 1.15, p = .296$; SRM Percent Correct, adjusted $R^2 = -.040$, $F(1,22) = 0.16, p = .690$; PRM Percent Correct, adjusted $R^2 = .008$, $F(1,22) = 1.17, p = .291$. Contrary to expectations, self-rated maladaptive perfectionism did not predict performance on tests of neuropsychological functioning in the CFS group.

**Academic achievement.** Standard multiple linear regressions were employed to test the hypothesis that higher levels of motivation and adaptive perfectionism would predict better performance on tests of academic achievement. WRAT-4 Reading and Math Computation were entered as single DVs in two respective
analyses. Both were nonsignificant: Reading, adjusted $R^2 = -.072, F(3,22) = 0.51, p = .684$; Math Computation, adjusted $R^2 = -.089, F(3,22) = 0.40, p = .753$. Contrary to expectations, motivation and adaptive perfectionism were not predictors of academic achievement in the CFS group.

Two simple linear regressions were conducted to test the hypothesis that higher levels of maladaptive perfectionism would predict poorer performance on tests of academic achievement. APS-R Discrepancy was the predictor, and WRAT-4 Reading and Math Computation were entered as DVs in each respective analysis. Contrary to expectations, APS-R Discrepancy was not a significant predictor of Reading, adjusted $R^2 = -.024, F(1,22) = 0.00, p = .999$ or Math Computation, adjusted $R^2 = .002, F(1,22) = 1.10, p = .300$.

Hypothesis 5: between-group differences in cognitive function when motivation and perfectionism are accounted for. It was predicted that when the variance from motivation and adaptive perfectionism is accounted for, the differences between CFS patients and controls on the neuropsychological and academic tests would increase. Conversely, it was hypothesised that when the variance from maladaptive perfectionism is accounted for, the differences between CFS patients and controls on the neuropsychological and academic tests would become smaller. However, motivation and perfectionism were not significant predictors of neuropsychological or academic test performance. As such, it was unnecessary to assess group differences in cognitive function while accounting for motivation and perfectionism.
Hypothesis 6: neuropsychological function in adults and young people with CFS. It was predicted that adults and young people with CFS would perform similarly on measures of neuropsychological function. To test this hypothesis, results from the CANTAB were compared between the young CFS patients and a group of adult patients drawn from a concurrent research project. Because this project was addressing a different research question than the current one, not all outcome measures used in the current study were available for the adult patients. The descriptive statistics in Table 6.12 indicate that both groups performed similarly, with a pattern of somewhat superior performance in the young patients on all tasks excluding IED Total Errors Adjusted and SWM Strategy. A between-groups MANOVA revealed a significant effect of group for executive function $F(4, 55) = 3.31, p = .017$, and follow-up univariate ANOVAs indicated that the between-group differences were significant for IED Total Errors, $F(1, 58) = 6.24, p = .015$ but not IED Stages Completed, $F(1,58) = 0.69, p = .410$. The univariate results were also significant for SOC Problems Solved in Minimum Moves, $F(1,58) = 5.97, p = .018$ but not for SWM Strategy, $F(1,58) = 0.13, p = .720$. In contrast, the MANOVA results were not significant for attention, $F(2,55) = 1.66, p = .220$ or working memory $F(2,55) = 0.40, p = .673$. Contrary to expectations, this suggests that the young CFS patients performed significantly better than the adult patients on tests of executive function. Consistent with the hypothesis however, the data indicate that adults and young people with CFS performed similarly on measures of attention and working memory.
Table 6.12  
*Group Means and Standard Deviations for Neuropsychological Function*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Adult CFS (n = 37)</th>
<th>Young CFS (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Executive function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IED Total Errors Adjusted</td>
<td>19.65</td>
<td>10.65</td>
</tr>
<tr>
<td>IED Stages Completed</td>
<td>8.05</td>
<td>1.86</td>
</tr>
<tr>
<td>SOC Problems Solved in Minimum Moves</td>
<td>7.24</td>
<td>2.49</td>
</tr>
<tr>
<td>SWM Strategy</td>
<td>32.30</td>
<td>10.43</td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTI 5-Choice Reaction Time</td>
<td>378.18</td>
<td>66.96</td>
</tr>
<tr>
<td>RVIP A’ Target Sensitivity</td>
<td>0.88</td>
<td>0.17</td>
</tr>
<tr>
<td>Working memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRM Percent Correct</td>
<td>73.24</td>
<td>21.32</td>
</tr>
<tr>
<td>PRM Percent Correct</td>
<td>83.88</td>
<td>17.25</td>
</tr>
</tbody>
</table>

*Note.* IED = Intra-Extra Dimensional Set Shift; SOC = Stockings of Cambridge; SWM = Spatial Working Memory; RTI = Reaction Time; RVIP = Rapid Visual Information Processing; SRM = Spatial Recognition Memory; PRM = Pattern Recognition Memory;

**Hypothesis 7: between-group differences in symptoms common to CFS.**

*Sleep disturbance.* The results of the PSQI were compared between groups to test the prediction that young people with CFS would report higher levels of sleep disturbance than healthy controls. The group means and standard deviations presented in Table 6.13 portray a clear pattern supporting this hypothesis.

A significant multivariate effect of group was detected for the PSQI using a MANOVA, $F(7,36) = 3.38$, $p = .007$. However, only four of the seven univariate ANOVAs for the individual components were significant. No significant between-group differences were observed for Subjective Sleep Quality, $F(1,42) = 3.01$, $p = .090$ and Sleep Latency, $F(1,42) = 0.85$, $p = .361$. However, the groups differed
significantly on Habitual Sleep Efficiency, \( F(1,42) = 7.28, \ p = .010 \); Sleep Disturbance, \( F(1,42) = 8.22, \ p = .006 \); Use of Sleeping Medication, \( F(1,42) = 15.23, \ p< .001 \); and Daytime Dysfunction, \( F(1,42) = 14.07, \ p = .001 \). In contrast, no significant differences were observed for Sleep Duration, \( F(1,42) = 0.05, \ p = .829 \). Although the results were mixed, the data indicate that the CFS group reported greater levels of disturbed sleep than the controls overall.

Table 6.13

<table>
<thead>
<tr>
<th>Sleep measure</th>
<th>Controls ( n = 21 )</th>
<th>CFS ( n = 23 )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( M )</td>
<td>( SD )</td>
</tr>
<tr>
<td>Global PSQI</td>
<td>4.71</td>
<td>2.90</td>
</tr>
<tr>
<td>Subjective Sleep Quality</td>
<td>1.00</td>
<td>0.77</td>
</tr>
<tr>
<td>Sleep Latency</td>
<td>1.24</td>
<td>1.00</td>
</tr>
<tr>
<td>Habitual Sleep Efficiency</td>
<td>0.10</td>
<td>0.30</td>
</tr>
<tr>
<td>Sleep Disturbance</td>
<td>0.71</td>
<td>0.56</td>
</tr>
<tr>
<td>Use of Sleeping Medication</td>
<td>0.05</td>
<td>0.22</td>
</tr>
<tr>
<td>Daytime Dysfunction</td>
<td>0.95</td>
<td>0.86</td>
</tr>
<tr>
<td>Sleep Duration</td>
<td>0.67</td>
<td>1.02</td>
</tr>
</tbody>
</table>

*Note.* PSQI = Pittsburg Sleep Questionnaire.

**Psychological distress.** Between-group comparisons of the DASS and IDS-SR results were conducted to assess the hypothesis that young people with CFS would report higher levels of psychological distress than healthy controls. These descriptive statistics in Table 6.14 suggest that, compared to controls, the CFS group reported greater levels of stress, anxiety, and depression.
Using a MANOVA with the DASS and IDS-SR component scores entered as DVs, a significant difference was identified between groups, \( F(4,41) = 6.23, p < .001 \). Evaluation of univariate ANOVAs indicated that the CFS group rated themselves higher on all measures of psychological distress: DASS Stress, \( F(1,44) = 4.35, p = .043 \); DASS Anxiety, \( F(1,44) = 10.88, p = .002 \); DASS Depression; \( F(1,44) = 9.95, p = .003 \); and IDS-SR, \( F(1,44) = 22.85, p < .001 \). Consistent with the hypothesis, these results indicate that the CFS group scored higher on a measure of psychological distress than the healthy controls.

It is useful to evaluate psychological distress according to clinical standards. Lovibond and Lovibond (1995) provide criteria for categorising the DASS components into mild, moderate, severe, and extreme. The percentage of CFS and control participants who fell within these categories is presented in Table 6.15. Similarly, the percentage of participants falling within different severity categories on the IDS-SR (Rush et al., 1996) is presented in Table 6.16. Compared to controls, the CFS group is represented less frequently in the normal to mild range, and more frequently in the moderate to severe or extreme range of psychological distress. The significance of these differences was assessed with Fisher’s exact test. No

Table 6.14

<table>
<thead>
<tr>
<th>Measure</th>
<th>Controls (n = 23)</th>
<th>CFS (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( M )</td>
<td>( SD )</td>
</tr>
<tr>
<td>DASS Stress</td>
<td>8.96</td>
<td>6.68</td>
</tr>
<tr>
<td>DASS Anxiety</td>
<td>3.96</td>
<td>4.69</td>
</tr>
<tr>
<td>DASS Depression</td>
<td>5.17</td>
<td>8.14</td>
</tr>
<tr>
<td>IDS-SR total</td>
<td>13.39</td>
<td>13.15</td>
</tr>
</tbody>
</table>

*Note. Figures represent the summation of Likert scale scores. DASS = Depression Anxiety Stress Scale; IDS-SR = The Inventory of Depressive Symptomatology-Self Report*
significant differences were identified for DASS Stress ($p = .433$). However, the CFS group rated themselves significantly higher than controls on DASS Anxiety ($p = .033$), DASS Depression ($p = .002$), and IDS-SR Depression ($p < .001$).

Table 6.15
*Percentage of Participants Meeting the Criteria for Various Distress Levels From the DASS*

<table>
<thead>
<tr>
<th>Category</th>
<th>Controls$^a$</th>
<th>CFS$^a$</th>
<th>Controls$^a$</th>
<th>CFS$^a$</th>
<th>Controls$^a$</th>
<th>CFS$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>82.6%</td>
<td>60.9%</td>
<td>87.0%</td>
<td>47.8%</td>
<td>87.0%</td>
<td>43.5%</td>
</tr>
<tr>
<td>Mild</td>
<td>8.7%</td>
<td>13.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>17.4%</td>
</tr>
<tr>
<td>Moderate</td>
<td>4.3%</td>
<td>8.7%</td>
<td>4.3%</td>
<td>21.7%</td>
<td>4.3%</td>
<td>34.8%</td>
</tr>
<tr>
<td>Severe</td>
<td>4.3%</td>
<td>17.4%</td>
<td>8.7%</td>
<td>21.7%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Extreme</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>8.7%</td>
<td>8.7%</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

$^a_n = 23$.

Table 6.16
*Percentage of Participants Meeting the Criteria for Categories of Depression From the IDS-SR*

<table>
<thead>
<tr>
<th>Category</th>
<th>Controls ($n = 23$)</th>
<th>CFS ($n = 23$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>73.9%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Mild</td>
<td>13.0%</td>
<td>30.4%</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.0%</td>
<td>30.4%</td>
</tr>
<tr>
<td>Moderate-Severe</td>
<td>0.0%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Severe</td>
<td>13.0%</td>
<td>17.4%</td>
</tr>
</tbody>
</table>

**Fatigue.** The hypothesis that young people with CFS would report higher levels of fatigue than healthy controls was assessed through investigation of the
Chalder Fatigue Scale and the VAS. The descriptive statistics (Table 6.17) indicate that compared to healthy controls, the CFS patients reported higher levels of fatigue on all outcome measures.

### Table 6.17

<table>
<thead>
<tr>
<th>Measure</th>
<th>Controls (n = 23)</th>
<th>CFS (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Chalder Fatigue Scale Total</td>
<td>15.96</td>
<td>3.55</td>
</tr>
<tr>
<td>Chalder Fatigue Scale- Physical Fatigue</td>
<td>9.39</td>
<td>2.15</td>
</tr>
<tr>
<td>Chalder Fatigue Scale- Mental Fatigue</td>
<td>6.57</td>
<td>2.33</td>
</tr>
<tr>
<td>VAS Time 1</td>
<td>2.78</td>
<td>2.42</td>
</tr>
<tr>
<td>VAS Time 2</td>
<td>3.11</td>
<td>2.26</td>
</tr>
<tr>
<td>VAS Time 3</td>
<td>3.20</td>
<td>2.50</td>
</tr>
<tr>
<td>VAS Time 4</td>
<td>3.72</td>
<td>2.57</td>
</tr>
<tr>
<td>VAS Time 5</td>
<td>4.37</td>
<td>2.96</td>
</tr>
</tbody>
</table>

Note. VAS = Visual Analogue Scale

a Scores are a summation of likert scale scores.
b Scores on a 10cm visual analogue scale

A MANOVA for the Chalder Fatigue Scale revealed a significant group difference in overall fatigue, $F(2,43) = 8.74, p<.001$, and follow-up ANOVAs were significant for Physical Fatigue, $F(1,44) = 13.97, p = .001$ and Mental Fatigue, $F(1,44) = 12.76, p< .001$.

A repeated measures ANOVA was conducted to assess group differences in fatigue throughout the test-taking period. Group was entered as the between-subjects variable, and the five VAS fatigue scores were entered as the within-subjects variables. A significant between-groups effect of fatigue was detected, $F(1,44) = 8.12, p = .007$, indicating that there was an overall difference between CFS patients
and controls on the VAS fatigue scores. The within-groups effect of time was also significant $F(1.65, 72.56) = 28.85, p < .001$, indicating that the fatigue scores changed significantly over time. In addition, the interaction between group and time was significant, $F(1.65, 72.56) = 9.91, p < .001$. In combination with the group means in Table 6.17, this suggests that both groups became more fatigued over time and the group differences became larger throughout the assessment. As predicted, these results indicate that the CFS group rated themselves as more fatigued than the healthy controls throughout the testing procedure.

**Hypothesis 8: predictive value of symptoms common to CFS.** In every multiple linear regression conducted for this hypothesis, the same three IVs were included to represent each symptom domain. The Global PSQI score represented sleep disturbance, IDS total was selected for psychological distress, and VAS Time 5 represented fatigue symptoms. These variables demonstrated the most significant difference between groups for each symptom domain. To assess multicollinearity, the correlations among the predictor variables were examined. Although most correlations are positive and significant (as shown in Table 6.18), none are large enough to suggest that multicollinearity is likely to be a problem. Tolerance was also acceptable, ranging between .497 and .745, indicating that multicollinearity is unlikely among these variables.

**Perceived cognitive disturbance.** A standard multiple linear regression was employed to investigate the hypothesis that perceived cognitive disturbance could be predicted by symptoms common to CFS. MFIS Total was entered as the DV. The analysis was nonsignificant, adjusted $R^2 = .138, F(3, 22) = 2.17, p = .125$. 
Table 6.18

**Correlations Between Predictor Variables for the Regression Models**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Global PSQI</th>
<th>IDS total</th>
<th>VAS Time 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global PSQI</td>
<td>1</td>
<td>.421*</td>
<td>.184</td>
</tr>
<tr>
<td>IDS total</td>
<td>.421*</td>
<td>1</td>
<td>.460*</td>
</tr>
<tr>
<td>VAS Time 5</td>
<td>.184</td>
<td>.460*</td>
<td>1</td>
</tr>
</tbody>
</table>

*Note.* PSQI= Pittsburg Sleep Questionaire; IDS= Inventory of Depressive Symptomatology; VAS= Visual Analogic Scale.

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

**Neuropsychological performance.** Seven standard multiple linear regressions were conducted to examine how well cognitive performance could be predicted by sleep disturbance, psychological distress, and fatigue. In each analysis, a single variable from the CANTAB was entered as the DV. These variables were the eight outcome measures that significantly differentiated the CFS and healthy control groups.

All regression analyses were nonsignificant: IED Block 6 Errors, adjusted $R^2 = .029$, $F(3,22) = 1.21$, $p = .330$; IED Total Errors Adjusted, adjusted $R^2 = .022$, $F(3,22) = 1.17$, $p = .349$; IED Stages Completed, adjusted $R^2 = .082$, $F(3,22) = 1.65$, $p = .211$; RTI 5-Choice Reaction Time, adjusted $R^2 = .043$, $F(3,22) = 1.33$, $p = .295$; RVIP A’ Target Sensitivity, adjusted $R^2 = -.021$, $F(3,22) = 0.85$, $p = .483$; SSP Span Length, adjusted $R^2 = -.064$, $F(3,22) = 0.56$, $p = .650$; SRM Percent Correct, adjusted $R^2 = .034$, $F(3,22) = 1.26$, $p = .318$; PRM Percent Correct, adjusted $R^2 = .075$, $F(3,22) = 1.59$, $p = .225$. Contrary to the hypothesis, symptoms common to CFS were not significant predictors of neuropsychological function.

**Academic achievement.** Two standard multiple linear regressions were employed to examine how well academic achievement could be predicted by sleep
disturbance, psychological distress, and fatigue. The WRAT-4 Reading and Math Computation components were entered as the DV in each respective analysis. Both regression analyses were nonsignificant: Reading, adjusted $R^2 = .031$, $F(3,22) = 1.23$, $p = .325$; Math Computation, adjusted $R^2 = -.127$; $F(3,22) = 0.17$, $p = .912$. Table 6.19 displays the beta weights and corresponding $t$-tests for each analysis. Contrary to the hypothesis, this suggests that symptoms common to CFS did not predict performance on measures of academic achievement.

Table 6.19

<table>
<thead>
<tr>
<th>Symptom measure</th>
<th>$\beta$</th>
<th>df</th>
<th>$t$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>WRAT-4 Reading</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global PSQI</td>
<td>0.33</td>
<td>22</td>
<td>1.46</td>
<td>0.16</td>
</tr>
<tr>
<td>IDS total</td>
<td>-0.35</td>
<td>22</td>
<td>-1.4</td>
<td>0.18</td>
</tr>
<tr>
<td>VAS Time 5</td>
<td>-0.29</td>
<td>22</td>
<td>-1.2</td>
<td>0.24</td>
</tr>
<tr>
<td>WRAT 4-Math Computation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global PSQI</td>
<td>.117</td>
<td>22</td>
<td>0.49</td>
<td>.633</td>
</tr>
<tr>
<td>IDS total</td>
<td>.021</td>
<td>22</td>
<td>0.08</td>
<td>.940</td>
</tr>
<tr>
<td>VAS Time 5</td>
<td>.135</td>
<td>22</td>
<td>0.52</td>
<td>.608</td>
</tr>
</tbody>
</table>

Note. PSQI= Pittsburg Sleep Questionaire; IDS= Inventory of Depressive Symptomatology; VAS= Visual Analog Scale; WRAT-4= Wide Range Achievement Test- 4th Ed.

**Hypothesis 9: between-group differences in school absenteeism.**

It was hypothesised that young participants with CFS would report higher rates of school absenteeism than the healthy control group. An independent samples $t$-test was employed to evaluate group differences in school absenteeism. Six participants in each group (26.09%) were not of school age and were thus excluded from the analysis. A significant between-group difference was detected in the
The number of days absent from school, $t(42) = 5.23, p < .001$. Over a six-month period, the CFS group missed an average of 35.65 days, while the controls missed only 4.81 days. The participants were grouped according to the percentage of days missed (Table 6.20). Using Fisher’s exact test, a significant between-group difference in the percentage of days absent was detected ($p < .001$). Consistent with the hypothesis, this indicates that the rate of school absenteeism was higher in the CFS group compared to healthy controls.

Table 6.20

<p>| Percentage of School Days Missed in School-Aged Participants |
|---------------------------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Days missed</th>
<th>CFS ($n = 17$)</th>
<th>Controls ($n = 16$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>0-19%</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>20-39%</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>40-59%</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>60-80%</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>&gt;80%</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

**Hypothesis 10: school absenteeism and academic achievement.** A Pearson’s correlation coefficient was employed to assess the hypothesis that school absenteeism would be negatively correlated with performance on measures of academic achievement. Contrary to the hypothesis, school absenteeism was not significantly correlated with WRAT-4 Reading, $r = -.263, n = 23, p = .225$, or WRAT-4 Math Computation, $r = .047, n = 23, p = .833$. 
Discussion

This study had three major aims. First, it was designed to assess whether young CFS patients would report greater cognitive impairment and perform more poorly than healthy controls on measures of neuropsychological function and academic achievement. The second aim was to investigate whether test motivation and perfectionism would be higher in young CFS patients compared to controls, and whether these differences would affect neuropsychological and academic test performance. Finally, the study was designed to assess whether young people with CFS would report higher levels of symptoms common to CFS compared to nonfatigued peers and whether these factors would predict perceived cognitive function and neuropsychological and academic test performance. These aims were investigated in a sample of 23 young people with CFS aged from 12 to 21, and 23 healthy controls matched for age and gender.

As expected, the CFS group reported greater levels of cognitive impairment and performed more poorly on a number of neuropsychological tasks compared to controls. However, the CFS group achieved higher scores than controls on the academic tests. Although the CFS patients rated themselves higher on a level of test motivation, both groups reported similar levels of perfectionism, and neither motivation or perfectionism were significant predictors of neuropsychological or academic test performance. Finally, the CFS patients reported higher levels of sleep disturbance, psychological distress, and fatigue than controls, although, surprisingly, these factors were not related to perceptions of cognitive function or performance on neuropsychological or academic tests. Beginning with a description of the participants, the following section contains a detailed discussion of each research
hypothesis, followed by a consideration of the study limitations and directions for future research.

**Participants.** Detailed information about CFS symptoms was derived from the PMCQ. As expected, the CFS patients reported significantly and substantially greater symptom frequency and severity than the controls on each symptom cluster, including Sleep, Fatigue, Pain, Cognitive, and Other Symptoms. Consistent with epidemiological studies in paediatric patients (Krilov et al., 1998; Lines, 2004; Richards et al., 2006; Sankey et al., 2006), the most frequently reported trigger for CFS was an infectious illness, followed by stress. Similar to previous research (Carter et al., 1995; Dougall, Baum, & Jenkins, 1998; Patel et al., 2003), there was considerable variability in illness onset and duration between patients. However, on average, the period of onset and duration was somewhat longer compared to earlier studies (Carter et al., 1995; Rangel et al., 2003; Sankey et al., 2006). The majority of patients reported a moderate onset period spanning between one and six months, and almost two-thirds reported that they had been unwell for more than three years. Consistent with previous research, the participants primarily described their illness as fluctuating, or, characterised by periods of remission and relapse (Krilov et al., 1998; Sankey et al., 2006).

Functional impairment was considerable: most patients reported that CFS caused a significant reduction in activity and school attendance. Consistent with previous research suggesting that paediatric CFS patients typically limit physical activity (Crawley & Sterne, 2009; Kennedy et al., 2010), almost all CFS participants reported feeling worse following physical activity and intentionally limited their activity to avoid fatigue. The majority of participants reported that fatigue was their
worst symptom, followed by headaches and then memory or concentration difficulties. Similarly, Sankey et al. (2006) found that fatigue and headaches were the most commonly reported symptoms in a paediatric CFS sample, although concentration difficulties were less frequently reported than sleep disturbance. Rates of school absenteeism were also comparable to previous research (Garralda & Rangel, 2004; Gray, 2001; Sankey et al., 2006). Most patients missed a substantial quantity of school, and some attended no school altogether. Similar to earlier research (Bell et al., 2001; Crawley & Sterne, 2009; van Geelen et al., 2010), the students in this study missed approximately one-third of school on average over a period of six months. Collectively, the data suggest that the course, presentation, and functional impact of CFS described by patients in the current study are largely comparable to previous research. As such, it is probable that this sample is representative of paediatric CFS patients.

**Hypothesis 1: between-group differences in cognitive function.**

*Perceived cognitive function.* In support of the hypothesis, the CFS patients perceived themselves to be significantly more cognitively impaired than the controls. All CFS patients reported cognitive symptoms on the PMCQ, and compared to controls, the CFS patients reported more frequent and severe symptoms associated with memory, concentration, comprehension, and divided attention. On the MFIS, the CFS patients reported greater impairment than controls on every test item. This is indicative of difficulties with everyday tasks that require sustained attention, concentration, thinking, memory, and processing speed.

The incidence of perceived cognitive impairment in the CFS group is high compared to previous studies in young patients. For instance, one group found that
33% of 58 young CFS patients reported cognitive difficulties (Krilov et al., 1998). Lines, 2004 also found that, of 20 young CFS patients, 60% reported poor concentration and 20% reported memory difficulties. Conversely, no disturbances in attention, thinking, or academic performance were reported by a group of 35 female adolescents with CFS (van Middenthorp et al., 2001). The discrepancy between these findings and the current study could be explained by differences in the nature of the questionnaires used. Specifically, while the present study included detailed questionnaires designed to assess a range of cognitive functions, previous findings were largely derived from a single question within a symptom checklist. As such, the earlier studies may not have captured the range and depth of cognitive disturbances experienced by young CFS patients. Supporting this explanation, results drawn from detailed cognitive questionnaires in adult samples are comparable to the current study (Becker et al., 2001; Jason, Taylor et al., 2002; Smith et al., 1993; Vercoulen et al., 1998).

The nature of cognitive impairment reported by patients in this study is consistent with previous research. For instance, studies in adults suggest that the most common cognitive complaints include problems with sustained attention, concentration, thinking speed, and memory (DeLuca et al., 1995; Michiels et al., 1996; Michiels et al., 1999; Ray, Phillips et al., 1993; Smith et al., 1996; Vercoulen et al., 1998). Similarly, research in paediatric patients suggests that young people often report impairments in focused attention, sustained attention, memory, and concentration (Haig-Ferguson et al., 2009; Lines, 2004).

In support of the hypothesis, the results suggest that adolescents and young adults with CFS perceive themselves to have frequent and severe cognitive impairment in a range of functions. These disturbances may affect performance in
everyday settings, potentially disrupting scholastic activity (Fröjd et al., 2008; Kovacs & Goldston, 1991). However, previous literature suggests that self-report measures of cognitive function may overestimate impairment or detect deficits that are only apparent under specific conditions (Cope et al., 1995; Ray et al., 1993; Short et al., 2002; Vercoulen et al., 1998), and as such, objective neuropsychological tests were employed to gain a more complete understanding of cognitive function in young CFS patients.

**Neuropsychological function.** Consistent with the hypothesis, the CFS group achieved lower scores than controls on measures of executive function, attention, and working memory. However, between-group differences were not observed for all outcome measures, and information processing speed appeared to be unaffected by CFS. Although these results were not entirely consistent with expectations, they are similar to findings from previous research in adults.

As expected, the CFS patients and controls achieved comparable scores on a test of intelligence, performing within the average range. This finding is consistent with previous studies (Claypoole et al., 2007; DiClementi et al., 2001; Grafman et al., 1993; Johnson et al., 1998; Krupp et al., 1994; Lawrie et al., 2000; Majer et al., 2008; Short et al., 2002) and suggests that intellectual functioning remains intact in young CFS patients. As such, there was no need to control for intelligence when assessing group differences in cognitive function.

**Executive function.** Overall, the CFS patients did not perform as well as controls on measures of executive function. The CFS group achieved lower scores on IED Block 6 Errors, IED Total Errors Adjusted, and IED Stages Completed. This
suggests that compared to the healthy controls, the CFS patients had poor attentional flexibility and were less able to shift attention within a previously relevant perceptual dimension. However, there were no group differences on IED Block 8 Errors, suggesting that the CFS patients were able to shift their attention to a previously irrelevant perceptual dimension. In addition, the CFS patients and controls obtained similar scores on SOC Problems Solved in Minimum Moves and SWM Strategy. This suggests that the CFS patients could plan and problem solve as effectively as controls.

The IED results parallel an earlier study involving 20 adult CFS patients and 20 matched healthy controls. Three CFS patients failed the intradimensional reversal stage (IED Block 6 Errors) compared to one control (Joyce et al., 1996), and there were no significant differences between groups in the number of errors made on the extradimensional shift stage (IED Block 8 Errors). In contrast, other studies show no differences between CFS patients and healthy controls in overall performance on IED in paediatric (Younis, 2009) and adult samples (Capuron et al., 2006; Majer et al., 2008; Morriss et al., 2002).

Supporting the present study, many researchers have also discovered that adults and young people with CFS are able to plan and problem solve on the SOC task with a similar level of proficiency as healthy controls (Capuron et al., 2006; Joyce et al., 1996; Majer et al., 2008; Morriss et al., 2002; Santamaria-Perez et al., 2011; Younis, 2009). Similar results have been identified with other measures of planning and problem solving in both adults (Busichio et al., 2004; Tiersky et al., 1998) and paediatric patients (Haig-Ferguson et al., 2009). In contrast, the nonsignificant results for SWM Strategy appear to be anomalous. Several studies suggest that adult CFS patients typically employ a less efficient search strategy on
SWM than nonfatigued peers and CFS patients with low mental fatigue (Capuron et al., 2006; Joyce et al., 1996; Majer et al., 2008). Further, the patients in this study reported significant psychological distress, and there is evidence to suggest that depressed adults achieve low scores on SWM Strategy (Elliott, Sahakian, McKay, & Herrod, 1996; Weiland-Fiedler et al., 2004).

In consideration of the findings from previous research, the results suggest that like adults, young CFS patients have difficulty performing tasks that require attentional flexibility but are able to plan and problem solve as effectively as nonfatigued peers. However, contrary to findings from studies in adults, the CFS patients and controls achieved similar scores on SWM Strategy. Although it is possible that young CFS patients are less susceptible to deficits in their capacity to employ an effective cognitive strategy, firm conclusions should be withheld until further research is conducted.

These findings have some important implications for young people with CFS. Patients with poor cognitive flexibility may have difficulty generating ideas, making decisions, regulating behaviour, and adapting to change (Shouten, Oostrom, Peters, Berloop, & Jennekens-Schinkel, 2007; Stahl & Pry, 2005). Treatments designed to assist young patients to compensate for or overcome these difficulties may reduce the functional impact of CFS by enabling patients to engage flexibly with their environment. Conversely, these results suggest that it may be unnecessary to focus interventions on improving planning and problem solving ability in young CFS patients.

Attention. As expected, the CFS group obtained lower scores than controls on tasks designed to assess attention. Specifically, the CFS patients performed more
poorly on RTI 5-Choice Reaction Time and RVIP A’ Target Sensitivity but not RVIP Mean Latency. This suggests that compared to controls, CFS patients were slower to react when a choice was presented and were less accurate but not slower on a visual continuous performance task. These results indicate that the CFS patients had difficulty maintaining attention.

These findings are largely consistent with previous research in adults with CFS. For instance, researchers have found that CFS patients are slower to respond than healthy controls on choice reaction tasks (Crowe & Casey, 1999; DeLuca et al., 2004). Another group found that CFS patients with high self-reported mental fatigue obtained significantly lower RVIP accuracy scores compared to healthy controls and CFS patients without significant mental fatigue (Capuron et al., 2006). Majer et al. (2008) also found comparable RVIP Mean Latency scores between a group of CFS patients and healthy controls. Furthermore, children and adolescents with CFS have been found to perform more poorly than healthy controls on other measures of sustained, switching, and divided attention (Haig-Ferguson et al., 2009; Kawatani et al., 2011; Tomoda, et al., 2007). One group also found that alternative attention, but not selective attention, improved significantly in children with CFS following a combined CBT/pharmacological intervention (Kawatani et al., 2011). In contrast however, others have identified no differences between adult CFS patients and healthy participants on choice reaction tasks (Capuron et al., 2006; Mahuran et al., 2004; Majer et al., 2008), or RVIP accuracy (Majer et al., 2008).

In view of the hypotheses and findings from previous research, the results suggest that young CFS patients have difficulty maintaining attention. However, they may be able to process information at regular speeds when they attend to the required information. Attention deficits could affect how young people function in
everyday life in a number of ways. CFS patients with poor attention at school may be less able to follow instructions or perform academic tasks over long periods, particularly during an exam. This could affect grades and limit opportunities for further education and career attainment. If it is known that young people with CFS suffer from attentional deficits, compensatory measures could be implemented in educational environments. For example, teachers could provide students with rest breaks, limit task duration, provide instructions in stages, and allow more time for students to respond. Interventions such as these could ease the disadvantage that patients experience at school, reducing the functional impact of CFS in young people.

*Information processing speed.* Contrary to expectations, there were no significant differences between the CFS and healthy control groups on measures of information processing speed. The outcome measures included SOC Initial Thinking Time, SOC Subsequent Thinking Time, and SWM Mean Time to Last Response. This suggests that the CFS patients processed information on tasks of executive function and working memory at regular speeds.

This finding is inconsistent with much of the previous research in adults with CFS. For instance, Morriss et al. (2002) found that CFS patients spent longer periods thinking and planning on SOC compared to healthy controls, and several others have found that adult CFS patients process information within memory more slowly than controls on SWM (Capuron et al., 2006; Majer et al., 2008). Similar results have also been identified using other tests that require rapid processing speed, such as Digit Symbol Coding (Busichio et al., 2004; Dickson et al., 2009; Michiels et al., 1996; Neu et al., 2011), the PASAT (Busichio et al., 2004; DeLuca et al., 1997;
Tiesky et al., 1998), and the Stroop test (Mahurin et al., 2004; Michiels et al., 1998; Ray et al., 1993; Smith et al., 1993). Moreover, this study conflicts with the theory supported by many authors, that CFS patients approach challenging cognitive tasks by reducing speed in order to improve accuracy (DeLuca et al., 2004; Michiels et al., 1998; Ray et al., 1993).

However the results of this study are consistent with a significant portion of the previous research in adults. For instance, several authors found no significant differences between CFS patients and healthy controls in initial or subsequent thinking time on the SOC (Capuron et al., 2006; Joyce et al., 1996; Majer et al., 2008). Many have also found that CFS patients and healthy controls search through memory at similar speeds (Capuron et al., 2006; Joyce et al., 1996; Majer et al., 2008; Morriss et al., 2002). Comparable rates of processing speed between CFS patients and controls have also been identified for the PASAT (Constant et al., 2011) and the Stroop test (Daly et al., 2001; Marcel et al., 1996; Short et al., 2002). Haig-Ferguson et al. (2009) also found that young CFS patients scored within the normal range on the WISC-IV Symbol Search test.

Together with the unexpected findings in this study, the substantial inconsistencies among the previous research make it difficult to form conclusions. The myriad of contradictory results suggest that processing speed is a complex function that may be vulnerable to the effects of other cognitive processes or unmeasured participant variables. It is important to note that although the results did not support the hypothesis, findings from several studies with similar assessment tools suggest that processing speed remains intact in adult CFS patients (Capuron et al., 2006; Joyce et al., 1996; Majer et al., 2008; Morriss et al., 2002). This supports the conclusion that young CFS patients are able to process information as rapidly as
nonfatigued peers. However, further research is required to determine the source of the research inconsistencies before this conclusion can be confirmed.

**Working memory.** As expected, the CFS patients performed more poorly than the healthy controls on tests of working memory. The CFS group achieved lower scores on SSP Span Length, SRM Percent Correct, and PRM Percent Correct. This suggests that CFS group had difficulty recalling information from spatial memory and correctly identifying visual targets from memory. In contrast, no differences between groups were apparent on the number of errors made for SSP and SWM. However, on average, the CFS patients made 25.83 errors on SWM while the healthy controls only made 16.91. The absence of a significant effect despite this substantial difference could be due to the high variability of the scores, particularly in the CFS group. Perhaps only a subgroup of CFS patients had difficulty recalling visuospatial information.

These results are consistent with much of the previous research in adults. For instance, Majer et al. (2008) found that compared to controls, CFS patients were less accurate on SRM and had longer response latencies on PRM, but both groups made a similar number of errors on SWM. Joyce et al. (1996) also found that CFS patients recalled significantly fewer sequences on SSP (Span Length) than matched healthy controls, and Morriss et al. (2002) identified similar error rates between a small group of CFS patients and healthy controls on SWM and SSP. One group also found that children with CFS perform more poorly than healthy peers on measures of spatial working memory but not short-term memory (Kawatani et al., 2011). However, these findings are inconsistent with several other studies. For instance, in the study by Joyce et al. (1996), the CFS group made significantly more between-
but not within-search errors than controls on SWM. This finding was replicated in a more recent study with CFS patients who reported significant mental fatigue (Capuron et al., 2006). Results from some of the same studies also indicate that CFS patients and controls perform equally well on SRM and PRM (Capuron et al., 2006; Joyce et al., 1996; Morriss et al., 2002), and one group found no improvements in spatial working memory following a combined CBT/pharmacological intervention for CFS in young patients. Haig-Ferguson et al. (2009) also found that young CFS patients scored within the normal range on the WISC-IV Digit Span and Letter-Number Sequencing tests.

In consideration of the collective findings from previous research, the results for working memory were not unexpected. However, the inconsistent findings in these studies make it difficult to form conclusions. The present study suggests that young CFS patients have difficulty recalling information from spatial memory and correctly identifying visual targets from memory, although they are able to manipulate visuospatial information in working memory. However, given the inconsistencies among the previous research, these findings must be replicated before such conclusions can be confirmed.

Deficits in working memory may affect young CFS patients in several ways. Poor working memory can have a considerable impact on learning, particularly in academic settings (Curtis & D'Esposito, 2003), limiting students’ capacity to remember instructions and complete learning or assessment activities. Disturbances in working memory may also cause further deficits in attention (Fukuda & Vogel, 2009). These factors could affect performance at school and cause associated problems with motivation and self-esteem. By introducing compensatory measures in schools, such as providing written instructions and allowing more time to
complete activities, students with CFS may be able to overcome the effects of working memory impairment at school. This could reduce the functional impact of CFS in young people considerably.

Further examination of the neuropsychological test results. Although the results are consistent with much of the previous research, a number of findings were unexpected and it is important to explore the various possible explanations. Contrary to the hypotheses, the CFS patients did not demonstrate impairment on any measure of processing speed or on some measures of executive function, attention, and working memory. These findings are inconsistent with the CFS patients’ self-reported indications of deficits in planning, processing speed, attention, and working memory. In addition, other symptoms associated with significant cognitive dysfunction, including psychological distress, fatigue, and sleep disturbance (see Chapter 4: Psychological Disturbance), were all more common in the CFS patients.

Nonsignificant or atypical results in CFS research are sometimes attributable to inadequate diagnostic approaches or a failure to identify CFS subgroups. However, each patient in the current study had their diagnosis confirmed by a specialist CFS paediatrician, and although the patients were not subgrouped according to distinguishing illness characteristics, all were recruited from the same tertiary centre and there was considerable homogeneity in illness course and presentation among the participants. Nonetheless, some patients may have had cognitive deficits that were masked by the performance of the whole group. Alternatively, although the sample appeared to be representative of the young CFS population, the participants may represent an unidentified subgroup that is resistant to or does not present with impairment in certain functions.
Nonsignificant findings in CFS research can sometimes be caused by the nature of the neuropsychological assessment tool. Previous literature suggests that CFS patients often have subtle impairments that can only be detected with an exceptionally sensitive assessment tool. However, the CANTAB is a precise measure of cognitive function that is capable of detecting slight deficits. For example, in a sample of patients with Obsessive-Compulsive Disorder, scores on SWM and SOC were distinguishable between patients based on illness subtype (washers, checkers, obsessonals, and mixed symptom profile; Nedeljkovic et al., 2009). Another group found that performance on IED was sensitive to the effects of short-term treatment for depression with ginkgo biloba (Hartley, Heinze, Elsabagh, & File, 2003). Moreover, all subtests in the current study have been used successfully in previous research to distinguish between adult CFS patients and healthy controls (Capuron et al., 2006; Joyce et al., 1996; Majer et al., 2008; Morriss et al., 2002). As such, it appears doubtful that the CANTAB lacked adequate sensitivity for detecting cognitive impairment.

The inherent variability of CFS may be responsible for some of the unexpected findings. Most CFS patients described their illness as fluctuating or characterised by periods of remission and relapse. It is well established that CFS symptoms vary according to recent activity, including physical or mental exertion (Fuentes, Hunter, Strauss, & Hultsch, 2001), and many patients elected to participate during the school holidays in order to avoid significant interference with school. As such, the participants may have been less affected by severe symptoms and ongoing mental effort at the time of the study than during a regular school term. Therefore, typical levels of cognitive impairment may not have been captured due to the timing of the assessment.
The nonsignificant results may also be attributed to a lack of statistical power relating to the sample size and high variability of scores. These factors may have led to insufficient statistical power for detecting mild impairment. However, significant differences in cognitive function have been detected in adult CFS patients using similar statistical procedures with comparable sample and effect sizes (Joyce et al., 1996; Lawrie et al., 2000). Therefore, it seems unlikely that the nonsignificant findings were caused exclusively by inadequate power.

Akin to the research in adults, this study revealed a discrepancy between self-perceived cognitive function and neuropsychological test performance. The CFS patients reported disturbances on tasks that require planning, processing speed, and working memory despite receiving similar scores to controls on some of the CANTAB items assessing these functions. Although it is possible that CFS patients overestimate or overgeneralise their impairment, there are several alternative explanations for the discrepancies.

The study may not have captured a number of true deficits due to the significant differences between the laboratory setting and naturalistic environments. Supporting this, research suggests that the more a laboratory test represents everyday cognitive tasks, the higher the correlation between self-reported cognitive function and neuropsychological test performance (Bennet-Levy & Powell, 1980; Sunderland et al., 1986). Participants in the current study were asked to describe their usual cognitive function during complex tasks that involve the simultaneous use of multiple cognitive faculties in everyday settings (Wearden & Appelby, 1996). Further, performance within naturalistic environments such as school may be particularly susceptible to the effects of distraction, divided attention, fatigue, sleepiness, low effort, or negative beliefs about cognitive capacity (Devolder &
Pressley, 1991). In addition, educational or work environments are often repetitive and require ongoing cognitive demands and learning over extended periods. In contrast, the assessments in the current study measured isolated cognitive functions using simple-to-follow tasks in a quiet laboratory environment. The assessment setting was also a novel, time-limited environment, and participants were required to maintain focus over short periods. Therefore, deficits normally present in naturalistic settings may not have been apparent in the current laboratory study.

The discrepant findings between the self-report and neuropsychological assessments could also be related to motivational differences between groups. Consistent findings from previous research suggest that test performance is positively correlated with motivation (Brown & Walberg, 1993; Eklöf, 2010; Logan et al., 2010; Nishimura et al., 2011; Preckel et al., 2006), and the influence of test motivation is highest in people with lower cognitive ability (Binder et al., 2003; Duckworth et al., 2011; Logan et al., 2010). In the current study, the CFS group reported greater test-taking effort than controls, although both groups considered the assessments to be similarly important. However, motivation was not a significant predictor of cognitive performance. Nonetheless, test motivation theory suggests that motivation will be higher if examinees believe that it is important to perform well, have greater interest in the task, and find the task more useful (Eklöf, 2010). It is probable that the CFS patients were particularly interested and invested in the research given that it related to their poorly understood health situation. Moreover, CFS patients may be particularly unmotivated to perform well in everyday settings due to the fatigue caused by ongoing mental effort or demoralisation due to the effects of their condition (Wearyn & Appleby, 1996). Conversely, it is reasonable to expect that the controls would perform normally in everyday settings. For the
CFS patients, increased motivation to perform well in the study may have masked cognitive deficits that would usually be present in everyday settings.

It is also important to consider the possible factors that may have increased the differences in neuropsychological performance between patients and controls. One possibility is that the CFS group represented a subgroup of patients with higher levels of illness severity than the total population of young CFS patients. All patients were recruited from a paediatric tertiary care clinic that specialises in CFS. It is likely that these patients or their parents opted to receive tertiary care due to the severity of their condition, and research in adult studies suggests that tertiary patients have higher levels of impairment than those managed in community settings (Jason et al., 2003). Therefore, the sample may have represented patients suffering from more severe symptoms and greater levels of cognitive impairment compared to the wider paediatric CFS population.

In summary, the nonsignificant findings were not likely to be caused by inaccurate diagnoses, inadequate sensitivity of the assessment tool, or insufficient power. However, it is possible that certain impairments were not detected due to the timing of the assessments, differences between the laboratory and naturalistic environments, and motivational factors. Conversely, the deficits found could be exaggerated if the particular participants in this study represented patients with greater illness severity than the general young CFS population. Nevertheless, it is reasonable to propose that young CFS patients suffer from impairments in cognitive flexibility, attention, and working memory, but not planning and problem solving, processing speed, and visuospatial manipulation in working memory.

These findings have considerable implications for young people with CFS. Impaired cognitive flexibility, attention, and working memory may inhibit learning
within academic and nonacademic contexts. Patients may have difficulty generating ideas, making decisions, regulating behaviour, adapting to change, following instructions, and maintaining performance on academic tasks. This could affect performance at school and limit opportunities for further education and career attainment, leading to associated problems with motivation, identity, and self-esteem. If it is known that young people with CFS suffer from cognitive deficits, compensatory measures could be implemented in educational and work environments, and treatments could be specifically designed to improve cognitive function. Interventions such as these could significantly reduce the functional impact of CFS in young people.

Hypothesis 2: between-group differences in academic achievement.
Contrary to the hypothesis, the CFS group obtained higher scores than controls on academic tests of reading and arithmetic. This was particularly surprising given that the CFS group reported substantially higher rates of school absenteeism and performed worse on measures of cognitive function than controls. These results are also inconsistent with previous research. For instance, Patel et al. (2003) found that a group of 36 CFS-affected students received an average of three out of 10 passes at school over an 18-month period. Of these patients, 25% achieved one to four passes and 30.6% failed to receive a single pass grade or sit their examinations. Another group found that 70% of participants with CFS had failed at least one year of study since illness onset and only 33% felt that their grades were in accordance with their capacity (Van Hoof et al., 2009). Sankey et al. (2006) also reported that 19 of 28 young CFS patients felt that their illness had significantly affected their education or career plans.
These inconsistencies could be explained by differences in the methods of data collection used. In previous research, impaired academic performance was identified using self-report measures designed to assess long-term achievement in school settings. In contrast, the participants in this study performed a small set of academic tasks under laboratory conditions. It is possible that CFS patients overestimate their impairment on academic tasks or that academic function is directly related to achievement capacity rather than school absenteeism. As such, the present study may be accurate in suggesting that academic function is unaffected by CFS.

However, there are other possible explanations for the discrepant findings. One possibility is that compared to laboratory conditions, cognitive performance in school settings may be more susceptible to distraction, divided attention, fatigue, sleepiness, and negative self-beliefs about cognitive capacity (Devolder & Pressley, 1991). Given that the CFS patients in the current study were less proficient on tests of attention and reported higher rates of fatigue, sleep symptoms, and psychological distress than the controls, the patient group might be especially vulnerable to cognitive disturbances at school. Such disturbances may not be apparent in a laboratory where these factors exert less influence. Furthermore, the participants in the current study were required to maintain focus for short periods and perform mentally effortful tasks over a few hours rather than an entire school day. There is some evidence to suggest that following prolonged mental effort, CFS patients are more likely to exhibit cognitive impairment than healthy controls (Smith et al., 1999). Therefore, although performance deficits may be normal for the CFS patients in a school environment, their performance within a laboratory test situation might approach their premorbid capacity.
As discussed within the evaluation of Hypothesis 1, the unexpected findings could also be explained by between-group differences in test motivation. Findings from previous research consistently suggest that academic performance is positively correlated with motivation in school settings (Brown & Walberg, 1993; Eklöf, 2010; Logan et al., 2010; Nishimura et al., 2011; Preckel et al., 2006). The CFS group believed that they exerted greater test-taking effort than controls, although both groups described the assessments as similarly important and motivation was not a significant predictor of academic performance. However, compared to controls, there may have been a greater discrepancy in the CFS patients’ motivation to perform well in the study compared to school. Therefore, the study may have failed to detect impairments that are only apparent in the context of motivational deficits in a natural school environment.

It is also worth noting that the CFS patients had very high rates of school absenteeism. It seems reasonable to expect that missing significant quantities of school would limit learning opportunities and lead to poorer academic performance. Although a causal relationship has not been identified, there is evidence to suggest that increased school absenteeism is associated with poor academic performance in clinical populations (Belachew et al., 2011; Breuner, Smith, & Womack, 2004; Krenitsky, 2007). The incongruity between these findings and those of the current study could be explained by the effect of the CFS treatment intervention. All patients involved in the study were treated at a clinic that has a focus on minimising the impact of CFS on education. As part of treatment, the patients often develop achievable educational goals and are given appropriate resources that allow them to continue their education. In addition, psychoeducation, psychotherapy, and medication are generally used to address psychological symptoms and sleep
disturbance in order to minimise functional impairment. These factors may have protected the patients in this study from significant disruptions in education. It is possible that academic decline would be more apparent in young CFS patients who are not involved in such intervention programs.

In consideration of the inconsistent results between this study and findings from previous research, it is difficult to form conclusions regarding how CFS affects academic performance in adolescents. Perhaps this study accurately suggests that academic performance is not affected by CFS in young patients. However, this conclusion may be limited to this particular subgroup of patients due to the nature of their treatment intervention. Alternatively, although academic performance may be affected by CFS in a school environment, true deficits may not have been detected due to the nature of the laboratory environment or motivational factors. Further research conducted in a range of settings with varied populations is required to investigate these alternatives before the impact of CFS on academic achievement can be determined.

**Hypothesis 3: between-group differences in test motivation and perfectionism.**

**Motivation.** As expected, the CFS group perceived themselves to be more motivated in completing the assessments than the healthy controls. However, although the CFS group scored higher on test-taking effort, both groups rated the importance of doing well equally. This is perhaps not surprising given that the Importance scale refers to how interested examinees are in their results, and since the participants were aware that their results would not be revealed, both groups did not rate the importance of doing well highly.
The significant between-group difference in test-taking effort has important implications for interpreting the academic and neuropsychological test results. Theoretical models of test motivation suggest that motivation affects performance on cognitive tasks (Eklöf, 2010; Thelk et al., 2009; Wise & DeMars, 2005; Wolf & Smith, 1995), and these models are supported by a wealth of research on academic performance (Brown & Walberg, 1993; Eklöf, 2010; Goodman et al., 2011; Hirschfeld et al., 2004; Hoyt, 2001; Logan et al., 2010; Nishimura et al., 2011; Preckel et al., 2006; Smith & Smith, 2002; Sundre & Kitsantas, 2004; Wise et al., 2006; Wolf & Smith, 1995) and neuropsychological function (Binder et al., 2003; Brunstein & Schmitt, 2004; Lindem, 2000; Mizuno et al., 2011). Further, the impact of test motivation appears to be strongest in people with low cognitive ability (Duckworth et al., 2011; Logan et al., 2010). The higher rates of test motivation reported by the CFS group in the current study may have enhanced their cognitive performance relative to the controls. Therefore, between-group differences in motivation may need to be accounted for when evaluating the neuropsychological and academic test results (this is considered further in the discussion of Hypothesis 4).

**Perfectionism.** Contrary to the hypothesis, the CFS patients and controls reported similar levels of adaptive and maladaptive perfectionism. This finding is inconsistent with much of the previous research. Several studies suggest that self-reported maladaptive perfectionistic traits are more common in adults with CFS compared to nonfatigued peers (Deary & Chalder, 2010; Luyten et al., 2006; White & Schweitzer, 2000), and a positive relationship has been identified between fatigue severity and maladaptive perfectionism in CFS patients (Kempke et al., 2011).
Conversely, one group found that CFS patients actually reported less maladaptive perfectionism than healthy controls (Blenkiron et al., 1999), and Wood and Wessely (1999) found no differences in self-reported maladaptive perfectionism between CFS patients and patients with rheumatoid arthritis. For adaptive perfectionism, the results were perhaps more consistent with previous research. Although one group found that adaptive perfectionistic traits were more common in CFS patients compared to healthy controls (Luyten et al., 2006), others researchers found no differences between adult CFS patients and nonfatigued peers (Deary & Chalder, 2010; Blenkiron et al., 1999), and one group found that adaptive perfectionism was unrelated to fatigue in CFS patients (Kempke et al., 2011).

Given the paucity of previous research, the results in the present study are difficult to interpret. It is worth noting that the mean Discrepancy scores were 25.86 and 18.29 for the CFS patients and healthy controls respectively, and this difference almost reached significance ($p = .056$). These results might reflect true group differences that were not detected due to insufficient statistical power. Alternatively, this study may be accurate in suggesting that young people with CFS do not have elevated levels of maladaptive perfectionism. Further research is required before either conclusion can be confirmed. The results for adaptive perfectionism are somewhat less unusual. Together with the previous research, this study suggests that young people with CFS do not have higher levels of adaptive perfectionism than nonfatigued peers. Again however, this conclusion needs to be verified through further research.

**Hypothesis 4: predictive value of motivation and perfectionism.**
**Neuropsychological function.** A series of eight standard multiple linear regressions were employed to examine how well neuropsychological performance could be predicted by motivation and adaptive perfectionism. In contrast to the hypothesis, none of the analyses were significant, indicating that self-rated motivation and adaptive perfectionism were not predictors of performance on tests of executive function, attention, or working memory. Similarly, maladaptive perfectionism was not a significant predictor of neuropsychological performance on any measure.

Although research in this area is scarce, previous studies in motivation suggest that these findings are atypical. For instance, positive correlations have been identified between motivation and performance on tasks of attention and working memory in healthy participants (Mizuno et al., 2011; Piedmont, 1988). Further, in a study of patients with a mild head injury, an association was identified between motivation and high scores on measures of executive function and working memory (Binder et al., 2003). Lindem (2000) also found that poor test motivation was correlated with diminished performance on tasks of attention, executive function, and memory in 240 Gulf War veterans. In contrast, the current findings were consistent with other research. For instance, in a study involving 30 depressed patients and matched healthy controls, no relationship was identified between induced motivation and performance on tests of attention and working memory tasks (Richards & Ruff, 1989). Similarly, another group found no differences between motivated and unmotivated participants with a mild brain injury on a range of measures designed to assess executive function and working memory (Orey, Cragar, & Berry, 2000).

A recent study in people suffering from severe burnout may provide a clue to understanding why motivation failed to predict cognitive performance in the young
CFS patients. At baseline, participants with burnout performed more poorly than controls on a challenging attention task. However, after motivation was induced through positive performance feedback and financial incentives for good results, improvements in performance were only observed in the control group (Dam, 2011). This suggests that although increased motivation may enhance cognitive performance among healthy individuals, people suffering from fatigue and effort intolerance, such as CFS patients, may be impervious to motivational interventions.

In contrast to the current study, previous research in healthy populations suggests that adaptive perfectionism is associated with improved neuropsychological function and maladaptive perfectionism is associated with poor neuropsychological function (Slade et al., 2009; Stoeber et al., 2010; Stoeber & Kersting, 2007). However, only two studies known to the author included measures of the cognitive domains assessed in the current study. In one of these, a positive correlation was identified between personal standards and attention using the Stroop test (Kobori & Tanno, 2005). In the second study, researchers found that adaptive perfectionism was positively correlated with attention and negatively correlated with executive function, and maladaptive perfectionism was negatively correlated with attention and executive function. No relationship was identified between either type of perfectionism and working memory (Slade et al., 2009). Findings from the small collection of previous studies do not provide compelling evidence that perfectionism predicts performance on tasks of executive function, working memory, and attention. Therefore, the present study may accurately reflect the relationship between these cognitive domains and perfectionism in young CFS patients. However, much more research is required before this conclusion can be confirmed.
Alternatively, methodological issues may have accounted for the nonsignificant findings for both motivation and adaptive perfectionism. A regression analysis assumes that important unmeasured IVs are not correlated with the measured IVs. If there is a significant negative correlation between a measured and unmeasured IV, the coefficient will be underestimated. In the current study, motivation or perfectionism may have been negatively correlated with unmeasured variables, such as parental expectations or patient resilience, causing the correlation between the predictors and cognitive performance to become small or nonsignificant. In addition, statistical power was limited due to the small size of the sample. Tabanick and Fidell (2001) recommend that, assuming a medium sized relationship between the IVs and the DV ($\beta = .20$ and $\alpha = .05$), the number of cases should be at least 104 plus the number of IVs in the analysis. In the current study, this equation equals 106, substantially more than the actual CFS sample size of 23. As such, power may have been insufficient for detecting a significant result.

In view of the inconsistent findings among the previous research and the possible alternative explanations for the nonsignificant findings in the current study, firm conclusions cannot be made. Although the results suggest that motivation and perfectionism are not predictors of neuropsychological performance in young CFS patients, further research is required before conclusions can be drawn.

**Academic achievement.** Contrary to the hypothesis, self-reported motivation and adaptive perfectionism did not predict performance on the academic assessments. Similarly, maladaptive perfectionism was not a significant predictor of reading or mathematic ability.
In contrast, several previous studies in healthy schoolchildren suggest that there is a positive relationship between motivation and academic performance (Fortier et al., 1995; Howse et al., 2003; Logan et al., 2010; Preckel et al., 2006; Schultz, 1993; Tavani & Losh, 2003; Verkuyten et al., 2001). Researchers have also identified significant positive correlations between test motivation and academic performance in young adults studying at tertiary institutions (Goodman et al., 2011; Hirschfeld et al., 2004; Hoyt, 2001; Smith & Smith, 2002; Sundre & Kitsantas, 2004; Wise et al., 2006; Wolf & Smith, 1995). The measures of motivation and academic performance used in these studies were similar to those in the present study.

Findings from the current study are also inconsistent with earlier research investigating the relationship between perfectionism and academic performance. Several researchers have identified positive correlations between adaptive perfectionism and GPA (Accordino et al., 2000; Nounopoulos et al., 2006). Higher academic scores have also been observed in tertiary students with high perfectionistic strivings and low perfectionistic concerns, compared to those who report the opposite pattern or no perfectionism (Bieling et al., 2003; Brown et al., 1999; Cox et al., 2002; Enns et al., 2001; Grzegorek et al., 2004; Rice & Slaney, 2002). Equally, in a sample of 166 students from grades six to eight, a negative correlation was identified between APS-R Discrepancy and GPA (Nounopoulos et al., 2006). A number of studies also suggest that academic performance and socially prescribed perfectionism are negatively correlated (Dykstra, 2007; Flett et al., 2009; Witcher et al., 2007). However, other researchers have found no relationship between maladaptive perfectionism and academic performance in samples of tertiary (Brown et al., 1999) and secondary students (Accordino et al., 2000).
Although much of the previous research conflicts with the current study, the relationship between perfectionism and academic performance has not yet been investigated in young CFS patients. Therefore, this study may be accurate in suggesting that perfectionism is unrelated to academic performance in young people with CFS. Perhaps the cognitive impact of other illness characteristics masks the effect of perfectionism. It is also worth noting that almost every preceding study supporting the relationship between maladaptive perfectionism and academic performance refers to socially prescribed perfectionism, a fundamentally different construct to the measure in the current study that assesses the perceived discrepancy between personal standards and performance.

It is possible that methodological issues accounted for the nonsignificant findings for both motivation and perfectionism. As noted in the neuropsychological section, there may have been a negative relationship between the measured and unmeasured IVs, causing the regression coefficient to become small or nonsignificant. Further, statistical power may have been insufficient due to the limited sample size. Alternatively, the nonsignificant findings could be explained by homogenous scores on the motivational or perfectionistic scales. Specifically, if the CFS patients all scored similarly on these measures, motivation and perfectionism could not be used to make predictions about other variables. However, the raw data and standard deviations are indicative of considerable heterogeneity between the participants, suggesting that motivation and perfectionism were distinguishable variables within the sample.

In summary, the previous research investigating the relationship between motivation and academic performance almost unanimously conflicts with this study, and the results among the paucity of prior research in perfectionism are largely
inconsistent. As such, it is difficult to form any conclusions. Although the results suggest that there is no relationship between academic ability and motivation or perfectionism in young CFS patients, further research is required to verify these findings.

**Hypothesis 5: between-group differences in cognitive function when motivation and perfectionism are accounted for.** It was predicted that after controlling for the variance from motivation and adaptive perfectionism, the differences between CFS patients and controls on neuropsychological and academic tests would become larger. Conversely, it was predicted that when the variance from maladaptive perfectionism is accounted for, the differences between CFS patients and controls on neuropsychological and academic tests would become smaller. These hypotheses were developed in accordance with previous research and theoretically derived suppositions suggesting that high levels of motivation and perfectionism are common in CFS patients and that these factors affect performance on cognitive tasks.

However, many findings were inconsistent with these original assumptions. In contrast to expectations, no significant differences were observed between groups on either measure of perfectionism. Further, motivation and perfectionism did not predict neuropsychological or academic test performance. In consideration of these findings, it was considered unnecessary to assess group differences in cognitive performance while accounting for motivation and perfectionism.

**Hypothesis 6: neuropsychological function in adults and young people with CFS.** It was predicted that adults and young people with CFS would perform
similarly on neuropsychological measures of executive function, attention, and working memory. Contrary to the hypothesis, the young CFS patients achieved higher scores than the adult group on tests of executive function, including IED Total Errors and SOC Problems Solved in Minimum Moves. However, as expected, no between group differences were detected for IED Stages Completed, SWM Strategy, and measures of attention and working memory. This suggests that compared to the adult patients, the young people with CFS had superior skills in cognitive flexibility and problem solving but were similarly impaired on measures of sustained attention and visual working memory.

Among the published literature, there appears to be no research involving a comparison of neuropsychological performance between adults and young people with CFS. As such, the present results need to be replicated before conclusions can be made. These findings could be attributable to a range of extraneous participant and researcher variables that are specific to this study. Nonetheless, the results raise some interesting questions regarding how CFS might uniquely affect young patients. The superior performance of the younger group on tasks of executive function is inconsistent with findings in the general population. Researchers have established that attentional flexibility and problem solving ability continues to develop throughout adolescence and early adulthood (Asato, Terwilliger, Woo, & Luna, 2010; Huizinga, Burack, & Molen, 2010; Konrad et al., 2005; Kuhn, & Pease, 2006). Furthermore, healthy adults generally perform better than adolescents on measures of executive skill (Ikeda, Okuzumi, Kokubun, & Haishi, 2011; Mäntylä, Carelli, & Forman, 2007; Manzi, Nessler, Czernochowski, & Friedman, 2011; Wendelken, Munakata, Baym, Souza, & Bunge, 2012).
The incongruity between these findings and those of the present study could reflect true differences between CFS patients and the general population. It is possible that young CFS patients are less vulnerable to cognitive decline than adults with CFS. This is supported by a recent study involving a group of healthy participants and children and adolescents/adults with high-functioning autism (HFA). Although executive function improved with age in the healthy group, no differences were observed between the child and adult HFA groups (Kuschner, Bodner, & Minshew, 2009). Similarly, another group found that performance on measures of executive control and cognitive flexibility improved with age in healthy participants but not in participants with Attention Deficit Hyperactivity Disorder (Gualtieri & Johnson, 2006). Furthermore, cerebral plasticity is more pronounced during maturation than in the adult brain (Kolb, 1995), and young people are better at adapting to neurological damage than adults (Müller, Rothermel, Behen, & Chugani). Combined with the previous research, this study raises the possibility that compared to adults, young CFS patients are more resilient to cognitive decline. However, further research is required to determine whether CFS affects cognitive function differently in adult and paediatric patients.

**Hypothesis 7: between-group differences in symptoms common to CFS.**

*Sleep disturbance.* In support of the hypothesis, the CFS group reported significantly higher rates of sleep disturbance than the controls. The average global PSQI score was 8.91 for the CFS group and 4.71 for the controls. This suggests that the CFS patients were suffering from a moderate level of sleep disturbance. Similarly, previous studies in adults with CFS indicate that global PSQI scores typically range from 7.1 to 10.17 (Mariman et al., 2011; Neu et al., 2007; Roberts et
al., 2009) and these scores are approximately double those of nonfatigued peers (Kerr et al., 2008; Roberts et al., 2004).

A greater depth of understanding can be derived through examination of the individual indices on the PSQI. Compared to controls, the CFS participants scored significantly higher on four of the seven outcome measures for sleep disturbance. Firstly, CFS patients reported poorer sleep efficiency. Even though the CFS group spend longer periods in bed than controls, a smaller proportion of that time is spent asleep. Secondly, the CFS group scored higher on the Sleep Disturbance index. High scores on this measure are indicative of symptoms associated with a diagnosable sleep disorder, such as breathing problems, disturbed dreams, pain, and physical discomfort. Thirdly, the CFS group used sleeping medication more often than controls. Almost half of the CFS patients stated that they regularly use pharmacological treatments to manage sleep compared to none of the healthy participants. It is worth noting that sleeping medication may have affected the scores on the other PSQI components. In particular, sleeping medication may reduce the severity of symptoms associated with Habitual Sleep Efficiency, Sleep Latency, and Sleep Duration. Finally, the CFS patients reported greater dysfunction during the day than the controls. High scores on this measure suggest that daytime activity is impeded by sleepiness and poor enthusiasm for getting things done.

Even though the CFS patients scored higher on the Sleep Efficiency and Sleep Disturbance indices, ratings on the Sleep Quality index were similar between groups. Furthermore, self-ratings on the Sleep Latency index were comparable between groups. This suggests that even though the CFS patients were awake for a larger proportion of their time in bed (as indicated by the Habitual Sleep Efficiency index), they did not take longer to get to sleep than controls. Finally, scores on the
Sleep Duration index indicated that the perceived length of time spent asleep was comparable between groups. Given that the CFS patients reported that they spend significantly more time in bed than controls, this suggests that the CFS group are awake for much of their time spent in bed after initially going to sleep. It is not known whether they are attempting to sleep throughout this time or are just aiming to rest.

Many of these findings are consistent with previous research. For instance, poor sleep efficiency among CFS patients has been observed in several adult studies (Morriss et al., 1993; Sharpley et al., 1997; Whelton, Salit, & Moldofsky, 1992), as well as one study in adolescents (Stores et al., 1998). Similarly high rates of perceived sleep disturbance have also been identified in adult CFS patients (Krupp et al., 2003; Unger et al., 2004). In contrast, use of sleeping medication was more common among the patients in this study compared those in previous research, where the incidence of medication use is closer to 20% (Boneva, Lin, Maloney, Jones, & Reeve, 2009; Jones, Nisenbaum, & Reeves, 2003). However, the PSQI does not specify medication type, and similarly high rates of medication use have been observed among adult CFS patients when nontraditional sleeping medications are included in the assessment (Vercoulen, Swanink, Fennis, & Galama, 1996). Like the patients in this study, adults with CFS also report high rates of daytime sleepiness and dysfunction (Creti et al., 2010; Neu et al., 2008; Sharpley et al., 1997). Finally, Sharpley et al. (1997) found that adult CFS patients and healthy controls reported comparable sleep durations.

Contrasting this study, other researchers have found that CFS patients have an extended sleep latency onset (Creti et al., 2010; Fischler et al., 1997; Unger et al., 2004; Whelton et al., 1992) and believe that the quality of their sleep is poor (Neu et
al., 2007; Sharpley et al., 1997). These inconsistencies could be a consequence of differences in question construction. For example, in contrast to the other PSQI indices and questionnaires used in similar studies, the Sleep Quality index is derived from a single question. This highly subjective approach may fail to capture the range of sleep difficulties experienced by young CFS patients. Alternatively, considering that changes in sleep patterns and behaviours are characteristic of adolescent development, the healthy participants may have also felt that they suffer from disturbances in sleep quality and latency. In support of this, the descriptive statistics indicate that both groups scored highly on these measures. Although it is also possible that young CFS patients do not experience problems with sleep quality or latency, further research is required to explore the alternative explanations and clarify the inconsistencies between this study and earlier research.

Together with the findings from previous research, these results suggest that young CFS patients have lower sleep efficiency, sleep disturbance, use of sleeping medication, and daytime dysfunction. These factors could contribute to and indeed exacerbate the debilitating symptoms associated with CFS, such as cognitive impairment, fatigue, lowered mood, postexertional malaise, and school absenteeism. However, these results suggest that like adults, young CFS patients do not sleep for longer periods than nonfatigued peers. This supports the conceptualisation of CFS as a disorder of excessive fatigue rather than sleepiness.

Psychological distress. Consistent with the hypothesis, the young CFS patients reported significantly higher levels of depression, anxiety, and stress than the controls. Group differences in psychological adjustment were also evaluated relative to clinical standards. According to severity criteria for the DASS (Lovibond &
Lovibond, 1995), the CFS patients predominantly scored in the normal or mild range for depression, anxiety, and stress. A further 40% fell in the moderate to extreme range for depression and anxiety, and about one-third reported moderate to severe stress. In contrast, 82-87% of the healthy controls scored in the normal range for each psychological component, and no more than 8.7% were in the severe to extreme range. According to clinical criteria for the IDS-SR (Rush et al., 1996), approximately 60% of all CFS patients scored in the moderate to severe range for depressive symptoms compared to just 13% of controls. However, the scores on the IDS-SR could be inflated in the CFS group due to the higher proportion of questions pertaining to sleep disturbance on this measure. The between-group differences in the proportion of participants meeting the criteria for the clinical severity categories were significant for all measures other than Stress. Elevated levels of depression and anxiety have been consistently observed in both adult (Wessely et al., 1998; Wilson et al., 2001) and paediatric CFS populations (Carter et al., 1995; Garralda & Rangel, 2004; Rangel et al., 2003; Smith et al., 2003; van Geelen et al., 2010), and CFS has been linked with an impaired stress response (Demitrack et al., 1991; Hatcher & House, 2003).

Together with the findings from previous studies, these results suggest that young CFS patients experience elevated levels of depression, anxiety, and stress. This finding has considerable implications for young people with CFS. Further to the suffering experienced as a direct consequence of psychological distress, research suggests that psychological disturbances can cause psychosocial impairment and behavioural problems (McCauley, Katon, Russo, Richardson, & Lozano, 2007; Rossen, 1997). Moreover, poor psychological adjustment has been linked to impaired academic and neuropsychological performance (Castaneda et al., 2008;
Dickson et al., 2009; Lupien et al., 1994; Metzger & Denney, 2002; Rossen, 1997; Wearden & Appleby, 1997). As such, psychological distress may serve to exacerbate functional impairment and amplify any existing cognitive disturbances in young CFS patients.

**Fatigue.** As expected, the CFS patients reported greater levels of fatigue than controls. Following the testing procedure, the CFS patients reported greater levels of physical and mental fatigue on the Chalder Fatigue Scale than the controls. The mean physical fatigue score was 12.61 for the CFS group and 9.39 for the controls, and mental fatigue was 9.26 and 6.57 for the CFS and control groups respectively. These scores are comparable to those found in adult patients (Kerr et al., 2008; Roberts et al., 2004) and suggest that young CFS patients have a larger increase in fatigue following cognitive activity than nonfatigued peers. This finding is supported by the VAS, which was administered several times throughout the testing procedure in order to monitor subjective changes in fatigue. Compared to controls, the CFS patients reported higher levels of fatigue throughout the assessment, and although both groups became more fatigued over time, the magnitude of the change was significantly larger in the CFS group. This suggests that compared to controls, the CFS patients became more fatigued in response to mental effort. The current author is not aware of any studies in CFS patients that included an assessment for monitoring changes in fatigue levels throughout mental activity.

These results suggest that young CFS patients become progressively more fatigued in response to mental effort. This has considerable implications for young patients. Since fatigue is associated with impaired cognitive performance (Capuron
et al., 2006; Cook et al., 2007; Kawatani et al., 2011; Majer et al., 2008), young CFS patients may become increasingly impaired throughout the completion of mental activity. Therefore, acute fatigue could exacerbate the existing cognitive deficits in young CFS patients, causing further disruptions to education and learning. Further, fatigue may amplify other problems associated with CFS, such as low mood, social withdrawal, and school absenteeism.

**Considerations for Hypothesis 7.** In summary, the results suggest that young CFS patients experience high levels of sleep disturbance, psychological distress, and fatigue. These factors could contribute to, and indeed exacerbate the debilitating symptoms associated with CFS, such as postexertional malaise, poor health-related quality of life, and psychosocial impairment. This may serve to worsen functional impairment, particularly in terms of cognitive and educational development. However, these conclusions should be considered with caution. The data were collected using self-report measures, which are subject to common limitations such as response style, social desirability bias, poor self-awareness, and dishonesty. Further, given that the CFS participants were recruited from a tertiary clinic, there is a possibility that the sample represented a subgroup of patients with more severe symptoms than the wider CFS population.

**Hypothesis 8: predictive value of symptoms common to CFS.** A series of regressions were employed to assess how well sleep disturbance, psychological distress, and fatigue predicted perceived cognitive disturbance, neuropsychological function, and academic achievement. For each analysis, three IVs were entered to represent each symptom domain. Global PSQI, IDS total, and VAS Time 5 were
selected to represent sleep disturbance, psychological distress, and fatigue respectively. These variables were selected as they demonstrated the most significant group differences of all measures for each symptom domain. Contrary to the hypothesis, CFS patients with greater sleep disturbance, psychological distress, and fatigue were not more likely to report cognitive impairment or receive lower scores on measures of neuropsychological function or academic achievement.

These results are inconsistent with much of the previous literature. Sleep disturbance is present in almost all CFS patients (Becker et al., 2001; Fukuda et al., 1994; Sharpley et al., 1997; Unger et al., 2004), and a relationship has been identified between neuropsychological performance and sleep disturbance in adult CFS patients (Smith et al., 1996) and healthy paediatric populations (Dahl, 1996; Randazzo et al., 1998; Sadeh et al., 2002; Steenari et al., 2003). Moreover, one group found that, following treatment for sleep disorders, 90% of 59 cognitively impaired CFS patients reported improvements in cognitive functioning (Buchwald et al., 1994). Smith et al. (1996) also found that although CFS patients with disturbed sleep achieved lower scores than healthy controls on assessments of attention and memory, no differences were observed between the controls and CFS patients without sleep disturbances. Attention and working memory are also commonly impaired in healthy people who endure experimentally disturbed sleep (Harrison et al., 2007; Sadeh et al., 2003; Wright et al., 2006). In contrast, Randazzo et al. (1998) found that performance on memory tasks was not affected by experimentally restricted sleep in a sample of healthy children.

Sleep disturbance also appears to be associated with impaired academic performance. In a study involving 3,120 healthy students, Wolfson and Carskadon (1998) found that those who achieved a C grade or below received less sleep and
went to bed later than those who received higher grades. In another large sample of 972 primary school students, 21\% of those considered to be poor sleepers had failed at least one year of school, and academic performance difficulties were significantly more common among the students with disturbed sleep (Kahn et al., 1989).

Psychological distress is also particularly common in young CFS patients (Garralda and Rangel; 2004; Gray et al., 2001; van Geelen et al., 2010), and researchers have found that when the effects of depression are partialled out, differences between CFS patients and controls on measures of memory, executive function, and attention become nonsignificant (Dickson et al., 2009; Krupp et al., 1994; Metzger & Denney, 2002). Moreover, one group found that depressed CFS patients perceived themselves to be more impaired than healthy controls on a range of cognitive tasks, while nondepressed CFS patients and healthy controls reported comparable levels of impairment. The depressed CFS group also achieved lower scores on verbal memory tasks than CFS patients without depression (Wearden & Appleby, 1997). However, consistent with the current research, a number of other studies suggest that psychological distress and cognitive function are unrelated (Claypoole et al., 2007; Dobbs et al., 2001; Joyce et al., 1996; Mahurin et al., 2004; Michiels et al., 1996; Michiels et al., 1999; Short et al., 2002; Vercoulen et al., 1998). One group also found that depressive symptoms were not related to deficits in reaction time on a measure of alternative attention in a group of children and adolescents with CFS (Kawatani et al., 2011).

There is also evidence of an association between psychological adjustment and academic performance. Researchers have identified a relationship between GPA and depression in tertiary (Deroma, 2009) and secondary students (Yousefi et al., 2009). One group also found that depressed students with epilepsy achieved lower
teacher rated scores than students with epilepsy alone, and significant improvements in scores were reported following treatment for depression (Tosun et al., 2008). In contrast, Buddington (2002) found that GPA was negatively correlated with stress, but not self-esteem or depression, and others have found that academic outcomes are unrelated to indicators of psychological adjustment (Abell et al., 2007; Vaidya & Mulgaonkar, 2007; Yeh et al., 2007).

The relationship between fatigue and cognitive impairment in CFS patients is not well established. Several studies suggest that fatigue is unrelated to performance on neuropsychological tests, including tests of executive function, attention, and working memory (Mahurin et al., 2004; Michiels et al., 1998; Short et al., 2002; Vercoulen et al., 1998). Even when a relationship has been observed, only a small number of cognitive functions appear to be affected. For instance, one group found a negative correlation between fatigue and spatial working memory but not other measures of working memory and executive function (Joyce et al., 1996). Similarly, Michiels et al. (1999) identified an association between fatigue and poor performance on tasks of attention but not memory in a group of 29 CFS patients. Capuron et al. (2006) also found that compared to healthy controls and CFS patients without significant mental fatigue, mentally fatigued CFS patients performed less well on CANTAB tests of working memory, visual memory, and attention, but not executive function and other visual memory tasks. In a sample of children and adolescents, one group identified a negative correlation between mental fatigue and reaction time on a test of alternative attention but not selective attention or spatial working memory (Kawatani et al., 2011).

In the context of the inconsistencies among the previous research, it is difficult to interpret the nonsignificant findings in the present study. It is possible
that the data accurately reflect an absence of a relationship between symptoms
associated with CFS and perceived cognitive disturbance, academic achievement,
and neuropsychological function. As discussed, this conclusion is supported by
some of the previous literature. Alternatively, methodological issues might account
for some of the unexpected findings. As mentioned in the discussion of Hypothesis
4, there may have been a negative relationship between measured and unmeasured
IVs, causing the regression coefficient to become small or nonsignificant. Further,
the limited sample size and variability of scores may not have produced sufficient
statistical power for detecting a significant result. Given that most participants in the
CFS group had considerable sleep disturbance, psychological distress, and acute
fatigue, the variability of scores on these measures would have been low, and as
such, a large sample size would be necessary to achieve sufficient statistical power.

It is also important to note that the CFS patients actually scored higher than
the controls on the academic assessments. If the CFS group were not more likely to
perform worse on the academic tasks, it follows that symptoms associated with CFS
would not predict academic performance. Therefore, the possible explanations for
the atypical findings discussed for Hypothesis 2 may also explain why academic
performance was unrelated to CFS symptoms. Specifically, the results could reflect
a true absence of academic impairment that had not been captured by previous
research due to data collection methods. Alternatively, the nonsignificant findings
could be caused by differences between laboratory and environmental settings,
motivational patterns, or the nature of the patients’ treatment intervention that
focused on minimising the impact of CFS on academic achievement.

In summary, the present study suggests that sleep disturbance, psychological
distress, and fatigue do not predict perceived cognitive impairment,
neuropsychological function, or academic achievement in young CFS patients. In consideration of the collective results from previous research, these findings were not entirely unexpected. Although several studies suggest that these symptoms are associated with impaired cognitive performance, a number of other studies indicate that they are unrelated. These inconsistencies make it difficult to form firm conclusions, and further research is required to clarify the contrast between this study and findings from earlier research. If certain symptoms predict cognitive performance, it may be possible to improve cognitive function by ameliorating the symptoms directly. In the absence of curative treatments for CFS, this may be an effective method of reducing illness burden in young patients.

**Hypothesis 9: between-group differences in school absenteeism.** As predicted, the school-aged CFS patients reported significantly higher rates of school absenteeism than the healthy controls. Over a period of six months, the CFS group missed 35.65% of school, while the controls missed 4.81%. Only one healthy control missed more than 20% of school compared to 14 (82.35%) of the CFS patients. These results are consistent with previous research. For instance, van Geelen et al. (2010) found that a group of 41 CFS patients missed 33% of classes over one month. In a larger sample of 211 young CFS patients, 11% attended school full-time, 49% attended 20% or less, 62% attended 40% or less, and 28% did not attend school at all (Crawley & Sterne, 2009). Similarly, Garralda & Rangel (2004) found that 39% of 28 CFS patients missed between 15-50% of school.

Together with the previous research, these results suggest that young CFS patients often miss a considerable amount of school. This may lead to substantial academic and psychosocial disturbances as well as secondary problems in
psychological adjustment and identity formation. The impact of CFS may thus be significantly reduced if patients are provided with appropriate support and resources to promote maximum school attendance.

**Hypothesis 10: school absenteeism and academic achievement.** Contrary to the hypothesis, no relationship was identified between school absenteeism and academic performance on measures of reading and arithmetic. This is inconsistent with findings from research in clinical populations. Several studies suggest that increased school absenteeism is associated with poor academic performance in a range of areas (Belachew et al., 2011; Breuner et al., 2004; Krenitsky-Korn, 2011; Krenitsky, 2007).

There are a few possible explanations for the inconsistent findings. As discussed for Hypothesis 2, most CFS participants were treated in a clinic that had a particular focus on minimising the impact of CFS on academic achievement. This approach may have protected patients in this study from the typical academic consequences of school absenteeism. Alternatively, the current study differs from previous research in that achievement was assessed directly rather than obtaining data from school grades. It is likely that absence from school would have a more profound effect on grades associated with the specific content learned during a school term than on general mathematic or reading ability. Further research with a diverse sample of CFS patients and a range of assessment methods is required to clarify the inconsistencies between these findings and those from previous research.

**Limitations and directions for further research.** There are several study limitations that should be considered carefully when interpreting the findings. First,
a nonprobability sampling method was adopted for both samples. The CFS patients were recruited from a single suburban children’s hospital in Australia, and most patients had been treated by the same paediatrician. This sampling method was selected to avoid one of the largest issues in conducting research with young CFS patients, diagnostic accuracy. The necessity of using medical practitioners to perform diagnostic tests, along with the recent subclassification of CFS for paediatric patients, has meant that previous studies were often restricted to a sample of participants with CFS-like symptoms or young people diagnosed according to adult criteria. The recruitment method in the current study was selected to circumvent this issue.

However, a potential consequence of using a limited sampling pool is that the participants may not accurately represent the diverse population of young CFS patients. Patients receiving treatment at suburban tertiary settings may be different from those treated in the community and those living in regional locations. Therefore, these findings may be less applicable to other patient groups, such as those with less severe symptoms or those from dissimilar cultural or socioeconomic backgrounds. Moreover, the CFS participants were generally receiving treatment with a particular focus on minimising the impact of CFS on education, which may have protected participants from academic decline. In future studies, these issues could be addressed by including patient samples from a range of treatment and nontreatment settings.

Similarly, an availability sampling method was employed to recruit the nonfatigued participants. Candidates were invited to participate via general advertising and direct contact with the research team. This method of data collection was chosen due to the lack of available volunteers. Although efforts were made to
select participants from a range of socioeconomic and cultural backgrounds, this approach may have caused some degree of self-selection or character biases that could have influenced performance and motivation. A major consequence of using nonprobability methods is that the probability of obtaining a representative sample is unknown, and caution is warranted when making inferences about the results to the entire young CFS population.

Due to limitations in time, funding, and participant availability, the study was cross-sectional in design. As such, the results reflect the performance and responses of participants at a single time-point. However, most CFS patients described their illness as fluctuating or characterised by periods of remission and relapse, and illness severity is known to vary according to circumstances and activity. Several CFS patients elected to participate during the school holidays in order to avoid significant interference with school, and it is likely that many others chose to participate when their symptoms were less severe or when they were less affected by other activity. Under these circumstances, the participants’ capacity to perform cognitive tasks may have been uncharacteristically high at the time of the study. Therefore, the data may depict the lower range of symptom severity and cognitive impairment for this particular patient group, reducing the probability of identifying between-group differences. This issue could be addressed in future research by restricting assessment periods or repeating assessments at different times to ensure that participants are tested over a range of symptom fluctuation levels.

The correlational design of the study does not allow causal relationships to be established among variables. For instance, lower neuropsychological performance scores in the CFS group does not confirm that CFS causes performance deficits. Alternative factors such as medication use or comorbid illnesses could also
account for such results. However, although the precise nature of the relationships between variables cannot be identified, causal relationships can be assumed to some degree using the sound theoretically derived conceptualisations of interactions among variables.

Self-report questionnaires were employed to assess CFS symptoms, fatigue, sleep disturbance, psychological distress, perfectionism, and motivation. Questionnaires were selected in favour of objective assessments due to the already arduous and time-consuming nature of the cognitive tests included in the study. However, self-report measures are subject to common limitations, such as variable response styles, social desirability biases, poor self-awareness, and dishonesty. Self-report measures may also be influenced by the participants’ emotional state and energy at the time of survey completion. Although there is no reason to assume that the participants in this study were especially susceptible to any one type of bias, the limits of data collected using subjective methods must be acknowledged and taken into consideration when interpreting the results. Wherever possible, studies in the future should include objective assessments of CFS symptom severity, fatigue, sleep disturbance, psychological disturbance, perfectionism, and motivation.

A number of the unexpected findings could be explained by limitations that potentially reduced the probability of detecting significant results. For instance, despite immense recruitment efforts, the final sample size was relatively small, and there was considerable within group variability on several outcome measures. These factors limit statistical power, reducing the probability of detecting significant effects. However, group differences were detected on several measures, and significant results have been reported in similar research with comparable sample sizes and standard deviations. Therefore, it seems unlikely that the nonsignificant
findings were caused exclusively by sample size and score variability. Nonetheless, future studies would benefit from including larger samples.

Some of the unexpected findings could be attributable to the setting in which the research was conducted. In accordance with certain test specifications, the assessments were performed within a laboratory. However, the nature of this setting may have caused participants to perform differently to how they normally function in naturalistic environments. In real world settings, cognitive performance may be vulnerable to the effects of distraction, divided attention, fatigue, and sleepiness. This may have been a particular problem for the patients in the current study given their high rates of fatigue, sleep disturbance, and attention difficulties. Everyday settings are also often monotonous and involve learning and recalling information over periods of days or weeks. In contrast, participants in the current study were required to complete tests of isolated cognitive functions using simple-to-follow tasks in a quiet laboratory environment. The assessment setting was also a novel, time-limited environment that required short periods of cognitive activity and focus. Further, the CFS patients may have been more motivated to perform well in the study compared to at school. As a consequence of these factors, the participants may have adopted an approach to performing cognitive tasks that differs from their usual methods, and they may have applied ongoing effort despite factors that inhibit their efforts under usual circumstances, such as fatigue and postexertional malaise. Therefore, the study may not have detected impairments that would normally be apparent in everyday settings. In order to control for these factors, future studies should be designed to assess functions that are similar to the demands of everyday cognitive tasks, and these assessments should be conducted in an environment that closely replicates naturalistic settings.
This study provides a potential opportunity for further research aimed at determining methods for reducing the impact of CFS in young people. Impaired cognitive flexibility, attention, and working memory could affect performance at school and limit opportunities for further education and career attainment, leading to associated problems with motivation, identity, and self-esteem. Further research could be designed to assess the effectiveness of interventions developed to treat or compensate for these cognitive deficits. Interventions such as these could significantly reduce the functional impact of CFS in young people.

Conclusion. This study provides an important contribution to the limited research in paediatric CFS. It presents a detailed description of the symptoms and impact of CFS diagnosed according to the paediatric definition and provides insight into the nature of how CFS affects neuropsychological and academic performance in young people. Previous research in CFS is limited and inconsistent due to the ongoing conceptual developments and epidemiological variability, particularly in young patients. Given that the cause of CFS remains unknown, treatments are often focused on minimising the impact of CFS by addressing the most debilitating symptoms. In young CFS patients, cognitive impairment is a common symptom that can cause devastating consequences in several functional and developmental domains. Therefore, research in this area is critical for developing appropriate treatments and reducing the impact of CFS in young populations.

The findings suggest that young people with CFS perceive themselves as cognitively impaired and have deficits in executive function, attention, and working memory. However, the CFS patients did not demonstrate impairment on academic tests, and academic performance was unrelated to the high rates of school
absenteeism. The CFS patients reported higher levels of motivation than controls, however both groups scored similarly on a measure of perfectionism, and motivation and perfectionism did not predict neuropsychological or academic test performance. Compared to adults with CFS, the young participants scored higher on a test of executive function, but were similarly impaired on measures of attention and working memory. The young CFS patients reported higher rates of sleep disturbance, psychological distress, and fatigue than controls, although these symptoms did not predict cognitive performance. Further research with a large, diverse sample of young CFS patients within a range of environments is required to verify these findings and clarify some of the inconsistencies between this study and previous research. Combined with the existing research, this study provides opportunities for developing new, focused interventions and might form a contribution to future research in young CFS patients.
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Appendix A
Definition of ME/CFS for Children (Jason et al., 2008)

I. Clinically evaluated, unexplained, persistent or relapsing chronic fatigue over the past 3 months that:
   A. Is not the result of ongoing exertion
   B. Is not substantially alleviated by rest
   C. Results in substantial reduction in previous levels of educational, social and personal activities
   D. Must persist or reoccur for at least three months

II. The concurrent occurrence of the following classic ME/CFS symptoms, which must have persisted or recurred during the past three months of illness (symptoms may predate the reported onset of fatigue).
   A. Post-exertional malaise and/or post-exertional fatigue.
      With activity (it need not be strenuous and may include walking up a flight of stairs, using a computer, or reading a book), there must be a loss of physical or mental stamina, rapid/sudden muscle or cognitive fatigability, post-exertional malaise and/or fatigue and a tendency for other associated symptoms within the patient’s cluster of symptoms to worsen. The recovery is slow, often taking 24 hours or longer.
   B. Unrefreshing sleep or disturbance of sleep quantity or rhythm disturbance.
      May include prolonged sleep (including frequent naps), disturbed sleep (e.g., inability to fall asleep or early awakening), and/or day/night reversal.
   C. Pain (or discomfort) that is often widespread and migratory in nature.
      - At least one symptom from any of the following: Myofascial and/or joint pain (Myofascial pain can include deep pain, muscle twitches, or achy and sore muscles. Pain, stiffness, or tenderness may occur in any joint but must be present in more than one joint and lacking edema or other signs of inflammation.)
      - Abdominal and/or head pain (May experience eye pain/sensitivity to bright light, stomach pain, nausea, vomiting, or chest pain. Headaches often described as localized behind the eyes or in the back of the head. May include headaches localized elsewhere, including migraines.)
   D. Two or more neurocognitive manifestations:
      - Impaired memory (self-reported or observable disturbance in ability to recall information or events on a short-term basis)
      - Difficulty focusing (disturbed concentration may impair ability to remain on task, to screen out extraneous/excessive stimuli in a classroom, or to focus on reading, computer/work activity, or television programs)
      - Difficulty finding the right word
      - Frequently forget what wanted to say
      - Absent mindedness
- Slowness of thought
- Difficulty recalling information
- Need to focus on one thing at a time
- Trouble expressing thought
- Difficulty comprehending information
- Frequently lose train of thought
- New trouble with math or other educational subjects

E. At least one symptom from two of the following three categories:

1. Autonomic manifestations: Neurally mediated hypotension, postural orthostatic tachycardia, delayed postural hypotension, palpitations with or without cardiac arrhythmias, dizziness, feeling unsteady on the feet—disturbed balance—shortness of breath.

2. Neuroendocrine manifestations: Recurrent feelings of feverishness and cold extremities, subnormal body temperature and marked diurnal fluctuations, sweating episodes, intolerance of extremes of heat and cold, marked weight change—loss of appetite or abnormal appetite, worsening of symptoms with stress.

3. Immune manifestations: Recurrent flu-like symptoms, non-exudative sore or scratchy throat, repeated fevers and sweats, lymph nodes tender to palpitation—generally minimal swelling noted, new sensitivities to food, odors, or chemicals.

III. Exclusionary conditions:

A. Any active medical condition that may explain the presence of chronic fatigue, such as:

1. Untreated hypothyroidism
2. Sleep apnoea
3. Narcolepsy
4. Malignancies
5. Leukemia
6. Unresolved hepatitis
7. Multiple Sclerosis
8. Juvenile rheumatoid arthritis
9. Lupus erythematosus
10. HIV/AIDS
11. Severe obesity (BMI greater than 40)
12. Celiac disease
13. Lyme disease

B. Some active psychiatric conditions that may explain the presence of chronic fatigue, such as:
1. Childhood schizophrenia or psychotic disorders
2. Bipolar disorder
3. Active alcohol or substance abuse—except as below:
   a) Alcohol or substance abuse that has been successfully treated and
      resolved should not be considered exclusionary.
4. Active anorexia nervosa or bulimia nervosa—except as below:
   a) Eating disorders that have been treated and resolved should not be
      considered exclusionary.
5. Depressive disorders

IV. May have presence of concomitant disorders that do not adequately explain
fatigue, and are, therefore, not necessarily exclusionary.

1. Psychiatric diagnoses such as:
   a) School phobia
   b) Separation anxiety
   c) Anxiety disorders
   d) Somatoform disorders
   e) Depressive disorders
2. Other conditions defined primarily by symptoms that cannot be confirmed by
diagnostic laboratory tests, such as:
   a) Multiple food and/or chemical sensitivity
   b) Fibromyalgia
3. Any condition under specific treatment sufficient to alleviate all symptoms
related to that condition and for which the adequacy of treatment has been
documented.
4. Any condition, that was treated with definitive therapy before development of
chronic symptomatic sequelae.
5. Any isolated and unexplained physical examination, laboratory or imaging
test abnormality that is insufficient to strongly suggest the existence of an
exclusionary condition.
Appendix B

Plain Language Statements and Consent Forms

DEAKIN UNIVERSITY
PLAIN LANGUAGE STATEMENT AND CONSENT FORM

TO: Participant Adult CFS

Plain Language Statement

Date: 19/10/2009

Full Project Title: Interactions between Sleep Disturbance and Cognitive Dysfunction in Adolescents with Chronic Fatigue Syndrome

Principal Researcher: Dr Greg Tooley

Student Researcher: Nina Katrina Frost

Associate Researcher: Dr Kathy Rowe

This Plain Language Statement and Consent Form is 5 pages long. Please make sure you have all the pages.

1. Your Consent

You are invited to take part in this research project.

This Plain Language Statement contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project so that you can make a fully informed decision whether you are going to participate.

Please read this Plain Language Statement carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative or friend or your local health worker. Feel free to do this.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project.

You will be given a copy of the Plain Language Statement and Consent Form to keep as a record.

2. Purpose and Background

My Name is Katrina Frost and I am currently undertaking a Doctor of Psychology (clinical) at Deakin University. As part of my course I am completing a research project under the supervision of Dr Greg Tooley, Associate Head of School, School of Psychology, Deakin University.

The purpose of this project is to investigate how chronic fatigue syndrome affects adolescents. Research tells us that both adults and younger people with chronic fatigue syndrome can experience symptoms that have a large impact on their daily lives. There has been lots of research examining the effect of chronic fatigue syndrome on cognitive performance in adults. Cognitive performance refers to thinking abilities such as memory and learning. There are almost no research studies that have looked at these things in adolescents with chronic fatigue syndrome, even though teenagers report having difficulties in this area. Our project aims to do just this.
Understanding the experience of adolescents with chronic fatigue syndrome is crucial in understanding this puzzling illness and overcoming the impact it has on the lives of those affected, especially at a time when educational achievement is so important.

We hope around 30 adults with chronic fatigue syndrome will participate in this project. We also hope around 30 teenagers with chronic fatigue syndrome and 30 teenagers without chronic fatigue syndrome will take part in this project. We also hope that 30 adults without chronic fatigue syndrome will participate. We are involving four different groups of participants so we can compare results and see if there are any differences between the groups. At the moment, it is not clear whether the cognitive difficulties experienced by adults with chronic fatigue syndrome will also be present in young people with the illness. Including an adult comparison group will enable us to investigate the differences in the way CFS affect adults and adolescents. In total, this research aims to include 120 participants.

You are invited to participate in this research project because you are aged above 20 and you have Chronic Fatigue Syndrome.

The results of this research will be used to help researcher, Katrina Frost to obtain a Doctor of Psychology (clinical) degree.

3. Funding

This research is totally funded by Deakin University.

4. Procedures

We would like you to come to an appointment at Deakin University. The appointment will take about 2 hours in total.

At the appointment, we would like you to fill out 10 questionnaires. Most of these are very short. The questionnaires ask about fatigue, sleep, physical symptoms and school attendance. There are also some questions about feelings, ideas, especially in relation to sadness and anxiety. The questionnaires will take about 45 minutes to fill out. In addition, you will be asked to complete a task of approximately 20 minutes that assesses your reading, writing, and mathematic skills. A similar task will be used to assess your vocabulary and pattern recognition skills. This should take approximately 10 minutes.

We will also ask you to do some tasks on a computer. The computer has a touch screen to make it easy for you to complete the tasks. The tasks look at things like memory and concentration. There are no right or wrong answers. The computer tasks will take about 45 minutes to complete. They are not a measure of your intelligence, but give us detailed information about memory, reaction time, and concentration.

You can take a break if you get tired. The questionnaires and computer tasks will happen at your own pace.

The information collected from you may be used to contribute to data for later research.

If you agree to taking part in this project, please contact Katrina Frost on 0430 224 449. We will try to organise a time that suits you best.

The researcher will be closely monitored by an experienced supervisor. The researcher will report back to the supervisor on a weekly basis to discuss the research and any problems that may have arisen. The supervisor will review the research and the procedures used by the researcher to ensure that the conduct of research conforms to the ethical guidelines.

5. Possible Benefits

For the wider CFS community, this research aims to increase understanding of adolescent CFS and validate anecdotal reports of cognitive dysfunction. This will provide insight into effective management
strategies, reducing the impact of CFS on patients. The group results of this research will be
communicated to the wider community, raising awareness of the impact of this illness on adolescents.
The more we know about this illness, the better we can manage and treat it.

6. Possible Risks
You may become upset when answering questions about sadness and anxiety, or thinking about
illness and its impact. The questionnaire and computer tasks can be tiring. If you do get tired, we can
take a break, or stop completely. If there are any concerns about your performance on the tasks, you
will be referred (if required) to someone who can help you.
The only inconvenience of participating is the time it takes to come to an appointment and complete
the questionnaire and computer tasks.
If you become upset or distressed throughout the procedure, we can take a break or end the testing
procedure entirely.

7. Privacy, Confidentiality and Disclosure of Information
We will enter the information you give us into a computer. Your name will not be entered with your
information and we will replace your name with a number code. All information that we keep on a
computer will be protected by a password. The original information will be stored in a locked cabinet
at Deakin University, in the School of Psychology for 6 years. After this time it will be shredded and
computer files will be deleted. Your consent forms will be kept separately from your information and
none of your information will be identifiable. We will be able to re-identify your information by
matching your code, however this can only be done by the researchers and will only occur if we need
to contact you regarding your information. No one, except the researchers involved in this project, and
The Deakin University Ethics Committee will have access to your information, except where otherwise
required by law. The Ethics Committee will only access your information if the project is audited. If we
talk or write about the results of the project, we will not use your name and we will refer only to the
results of the whole group, not individual people.

You may choose to withdraw from the study at any stage, and your information can be withdrawn at
your request.
Any information obtained in connection with this project and that can identify you will remain
confidential. It will only be disclosed with your permission, subject to legal requirements.

8. New Information Arising During the Project
During the research project, new information about the risks and benefits of the project may become
known to the researchers. If this occurs, you will be told about this new information. This new
information may mean that you can no longer participate in the research. If this occurs, the person
supervising the research will stop your participation.

9. Results of Project
When the project is finished, we will send you out a summary of the results. However, please note that
the project may not be finished for another 2-3 years. The summary that we send you will be about the
results of the whole group.

10. Participation is Voluntary
Participation in any research project is voluntary. If you do not wish to take part you are not
obliged to. If you decide to take part and later change your mind, you are free to withdraw from the
project at any stage. Any information obtained from you will not be used and will be destroyed.
However if your identifying details have been removed, we will be unable to withdraw your information.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect
any current treatment you are receiving or your relationship with Deakin University.
Before you make your decision, a member of the research team will be available to answer any questions you have about the research project. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

If you decide to withdraw from this project, please notify a member of the research team or complete and return the Revocation of Consent Form attached.

11. Ethical Guidelines
This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

The ethics aspects of this research project have been approved by the Human Research Ethics Committees of Deakin University.

12. Complaints
If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:

The Manager, Office of Research Integrity, Deakin University,
221 Burwood Highway,
Burwood Victoria 3125,
Telephone: 9221 7129,
Facsimile: 9244 6581; research-ethics@deakin.edu.au
Please quote project number: 2008-173

13. Reimbursement for your costs
You will not be paid for your participation in this project. However, you will be given a $20 gift voucher in appreciation of your time and travel expenses.

14. Further Information, Queries or Any Problems
If you require further information, wish to withdraw your participation or if you have any problems concerning this project, you can contact any of the researchers responsible for this project.

Principal Researcher: Dr Greg Tooley, School of Psychology, Deakin University, 221 Burwood Hwy, Burwood, Victoria, 3125. Phone: 03 925 17355/ 0400 995 057. Email: gregory.tooley@deakin.edu.au

Student Researcher: Miss Katrina Froel, School of Psychology, Deakin University, 221 Burwood Hwy, Burwood, Victoria, 3125. Phone: 0430 224 449. Email: klf@deakin.edu.au

Associate Researcher: Dr Kathy Rowe, Royal Childrens Hospital, Flemington Rd, Parkville, Victoria, 3052. Phone: 03 93445555. Email: kathy.rowe@rch.org.au
DEAKIN UNIVERSITY
PLAIN LANGUAGE STATEMENT AND CONSENT FORM

TO: Participant

Consent Form

Date: 19/10/2006

Full Project Title: Interactions between Sleep Disturbance and Cognitive Dysfunction in Adolescents with Chronic Fatigue Syndrome

I have read, or have had read to me and I understand the attached Plain Language Statement.

I freely agree to participate in this project according to the conditions in the Plain Language Statement.

I have been given a copy of the Plain Language Statement and Consent Form to keep.

The researcher has agreed not to reveal my identity and personal details, including where information about this project is published, or presented in any public form.

It has been explained that my involvement in this project may not be of any benefit to me.

Participant's Name (printed) .................................................................

Signature .................................................. Date ..............................
DEAKIN UNIVERSITY
PLAIN LANGUAGE STATEMENT AND CONSENT FORM

TO: Participant

Revocation of Consent Form

Date: 18/10/2008

Full Project Title: Interactions between Sleep Disturbance and Cognitive Dysfunction in Adolescents with Chronic Fatigue Syndrome

I hereby wish to WITHDRAW my consent to participate in the above research project and understand that such withdrawal WILL NOT jeopardise my relationship with Deakin University.

Participant's Name (printed) ..............................................................

Signature .......................................................................................... Date ......................

Please mail or fax this form to:

Katrina Frost,
Deakin University
School of Psychology,
221 Burwood Hwy
Burwood
Vic, 3125
Date: 19/10/2009

Full Project Title: Interactions between Sleep Disturbance and Cognitive Dysfunction in Adolescents with Chronic Fatigue Syndrome

I have read, or have had read to me, and I understand the attached Plain Language Statement.

I give my permission for .........................................................(name of participant) to participate in this project according to the conditions in the Plain Language Statement.

I have been given a copy of Plain Language Statement and Consent Form to keep.

The researcher has agreed not to reveal my child’s identity and personal details, including where information about this project is published, or presented in any public form.

It has been explained that my involvement in this project may not be of any benefit to my child.

Participant’s Name (printed) ........................................................

Name of Person giving Consent (printed) ...........................................

Relationship to Participant: ..........................................................

Signature ................................................................. Date .........................
Appendix C

Visual Analogue Scale

Please draw a single vertical line on the scale below to indicate how fatigued you feel at the present moment.

_Time 1_

No Fatigue |-----------------------------| Worst Possible Fatigue

_Time 2_

No Fatigue |-----------------------------| Worst Possible Fatigue

_Time 3_

No Fatigue |-----------------------------| Worst Possible Fatigue

_Time 4_

No Fatigue |-----------------------------| Worst Possible Fatigue

_Time 5_

No Fatigue |-----------------------------| Worst Possible Fatigue