Cognitive Deficits in Chronic Fatigue Syndrome

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The candidate confirms that the work submitted is her own and that appropriate credit has been given where reference has been made to the work of others.

Abstract

This thesis focuses on cognition in Chronic Fatigue Syndrome (CFS). Many patients report difficulties such as 'fuzzy' thinking, poor memory, reduced attention, and slowness of thought. Whilst much of the earlier literature presented conflicting results, more recently the theory that there is slowed processing has been suggested. Standard neuropychological tests have been used and been helpful in the description of this slowing, however an explanation for this slowing has not been postulated.

This thesis proposes a slowed processing theory of cognition in CFS focusing on representational weakness and global reductions in cortical activity as possible mediators of slowing.

Sixty-eight CFS patients (tertiary care clinic attendees) and 63 healthy controls participated in the study. They completed standard neuropsychological tests from the Weschler Memory Scale-R and measures of comorbid symptomatology, specifically the Hospital Anxiety and Depression Scale, The Fatigue Scale and the Profile for Fatigue Related Symptoms. They also completed a battery of tests designed to assess whether CFS patients had slowed performance; whether these problems could be attributed to representational weakness; whether there were differences in CFS and control participants' performance on perceptually and conceptually processed tasks, and tasks requiring conscious and non-conscious processing. The role of non-novel versus novel stimuli and interference is also discussed.

The results suggested that CFS patients' recall was worse than control participants' on the following measures: Paired Associate Learning - hard pairs, Logical Memory, and explicit memory. They were slower than controls for all levels of processing graded from perceptual to conceptual, and for semantic judgements of word pair relatedness.

The results are discussed as support for a theory of cognition in fatigue which is dependent on 2 factors; firstly, representational weakness and secondly global slowing of cortical activity. It is proposed that these two factors interact, and the performance of CFS patients on what may initially appear to be similar tests can be quite discrepant.

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Publications and Presentations

Fairhurst, D., Waterman, M., Lynch, S. (1998). Cognitive slowing and working memory difficulties in CFS, *Psychosomatic Medicine*, **59(6),** 638.

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Some of the work in this thesis has been presented else-where: portions of Chapter 5 in AACFS Conference Proceedings 1998, portions of Chapters 3 and 4 in Proceedings of the RCP Annual Meeting, 1998.

My gratitude also goes to the participants, especially those who though fatigued and ill, still managed to drag themselves from their beds to attend testing sessions, and to the control participants for springing up through the mists of despair and frantic worry; thank goodness I was saved the experience of clinical anxiety.

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....And finally, ok, I now acknowledge that effects of staying up all night to go beering do not constitute fatigue.

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Chapter

1

Chronic Fatigue Syndrome: definitions and methodological issues

1.1. Introduction

Fatigue, like depression and anxiety, is a ubiquitous phenomenon, the meaning of which is both widely and experientially understood. Recently, fatigue and more particularly excess fatigue have been the focus of much debate and research. Fatigue has been reported to be continuously distributed across the general population (Pawlikowska, Chalder, Hirsch, et al., 1994). Though estimates vary, reports suggest that 33% to 38% of the population report 'substantial' fatigue (Kennedy 1988, Pawlikowska, Chalder, Hirsch, et al., 1994), with about 18% reporting excessive fatigue of duration in excess of 6 months (Pawlikowska, Chalder, Hirsch, et al., 1994). Essentially such substantial unexplained fatigue of at least 6 months in duration, resulting in a 50% reduction in activity has been operationally defined as Chronic Fatigue Syndrome (CFS) (Sharpe, Archard, Banatvala, et al., 1991, Holmes, Kaplan, Gantz, et al., 1988, Lloyd, Wakefield, Bougton, & Dwyer, 1988, Schluederberg, Straus, Peterson, et al., 1992, Fukuda, Straus, Hickie, et al., 1994). In 1991, 24% of a questionnaire surveyed community sample reported consulting their doctor about fatigue (Lawrie, Manders, Geddes, & Pelosi, 1997), whilst prevalence rates for Chronic Fatigue Syndrome are estimated to be between 0.5% and 1% (Bates, Schmitt, Buchwald, et al., 1993).

Throughout the 1980s Chronic Fatigue Syndrome was popularly referred to as Yuppie Flu, Malingerers Disease, Postviral Fatigue Syndrome, and ME (myalgic encephalomyelitis). Media interest seems to have waned little over the past few years,

and sensationalist headlines are unabated, e.g. "*Royal college say there is no such thing as yuppie flu*" pg. 10, (Hawkes, 1996). The essence of the pervasive stereotype was, and to some extent still is, of a fashionable new disease that is 'all in the mind'. There is however, sufficient evidence to suggest that the clusters of symptoms found in CFS are not new. Diverse nomenclatures and aetiological theories, essentially describing the same clusters of symptoms, appear as early as the 18th century. These symptoms included fatigue and weariness, depression, forgetfulness, sore throats and headaches, amongst many others (Manningham, 1750, Straus, 1991, DaCosta, 1871, McEvedy & Beard, 1970b).

Fatigue can be considered to have both mental and physical components; it is therefore not surprising that in these syndromes where weariness is one of the primary symptoms that cognitive difficulties are reported. Hence, most of these early syndromes include cognitive complaints. These complaints ranged from the more specific forgetfulness (Straus, 1991) to the less specific decreased mental energy (Beard, 1869); whilst more recent accounts of symptoms include short term memory problems (International Federation for ME, 1994), concentration difficulties (Behan & Bakheit, 1991, International Federation for ME, 1994), and confusion (Holmes, Kaplan, Gantz, et al., 1988). In 1996, Komaroff, Fagioli, Doolittle, et al. (1996) reported that of Chronic Fatigue Syndrome patients (Fukuda, Straus, Hickie, et al., 1994), 86% had difficulty in concentrating, almost three quarters reported forgetfulness, 28% experienced confusion and over a third difficulty in thinking. As can be seen within this particular group these cognitive symptoms are apparently wide spread. Despite these differences being extensively reported subjectively, they have been somewhat more difficult to objectively confirm or define. Furthermore, although cognitive difficulties have been reported in CFS, they have also been reported in depression and anxiety (see section 1.5.4.). Given that many CFS patients experience psychiatric morbidity (Komaroff, Fagioli, Doolittle, et al., 1996) it has been suggested that the deficits do not actually exist and are merely a reflection of the persons depressive styles of thinking. This is extensively debated (Johnson, De Luca, & Natelson, 1996, and see Abbey & Garfinkel, 1991 for a review). That these symptoms may be the result of co-morbid symptomatology has been further compounded by a lack of correlation between subjective and objective measures of cognition; with the subjective symptom account positively correlating with low mood (Grafman, Schwartz, Dale, et al., 1993).

Additionally there is conflict within the cognitive literature regarding the results of specific cognitive measures, such as digit span, where performance ranges from worse (Krupp, Sliwinski, Masur, & Freidburg, 1994), to no different (De Luca, Johnson, Beldowicz, & Natelson, 1995) to better (Million, Salvato, Blaney, et al., 1989), further making a consensus of opinion difficult. A major factor here has been the confounding of research by methodological difficulties. These have included the use of: multiple case definitions; undefined criteria, e.g. fatigue; neuropsychological tests; as well as the psychiatric morbidity and vacillating symptom complex inherent within the syndrome. These confounding factors have presented many problems, both for replicability and comparability of current research and are particularly germane to earlier CFS work, where the syndrome was even less well understood. These problems have been particularly apparent in the literature on cognition and chronic fatigue syndrome; probably as a result of the numerous factors present which are thought to affect mental performance.

As the syndrome has become more clearly defined the awareness of methodological issues inherent in earlier pioneering research has increased. More recent studies have thus taken major confounds, such as depression, into account; though less emphasis has been placed on the role of other factors, such as anxiety. However, there is still a lack of consensus about what constitutes CFS, and determining its predictors, causes, mediators, characteristics and identifying potential treatment packages is therefore difficult. In the context of understanding, diagnosing and researching CFS comparability problems still remain. This is further compounded by a difficulty in defining and measuring the predominant symptom of CFS, fatigue, and in elucidating the role of comorbid depression and anxiety in cognitive symptoms.

Additionally, given the inherent variability in samples, resulting for example from: between and within variance in case definition or the profile of fatigue, heterogeneity between samples is to be expected. It should be no surprise that similar research studies may yield different results when using the same cognitive measures and similarly defined samples.

An understanding of the methodological issues, including different specifications of the criteria and their implications and the role of co-morbid symptomatology is thus important in order to interpret previous research, and adduce previous studies in a new

and more specific theoretical explanation. This chapter will therefore summarise the definitions of CFS and the issues entailed; with particular reference to cognitive aspects of the syndrome.

1.2 Chronic Fatigue: historical context, from the 1700's

Despite such wide differences in both the naming and understanding of fatigue what we recognise today as CFS shares many characteristics with Royal Free Disease, Icelandic or Akureyri Disease, Post Infectious Myelitis, (benign) Myalgic Encephalomyelitis (ME), yuppie flu, Post Viral Syndrome (PVS), Post Viral Fatigue Syndrome (PVFS), Chronic Mononucleosis Syndrome, Neurasthenia, abortive Poliomyelitis and Febricula. Although there are minor variations in symptom reports, each of these outbreaks has a main theme of general malaise and debilitating mental and physical fatigue of seemingly inexplicable cause. Symptoms are also said to include headache, myalgia, depression, sore throat, anhedonia, diplopia, blurred vision and breathlessness, amongst many others.

Perhaps the earliest analogue of this condition was Febricula, also known as nervous or hysteric fever; fever on the spirits vapours hypo or spleen (Manningham, 1750). The symptoms included low fever, lassitude and weariness, 'flying pains', low mood, delirium and forgetfulness (Straus, 1991). These symptoms were very similar to those reported fifty years later, in the early eighteen hundreds, popularly diagnosed as 'nervous exhaustion' (Straus, 1991). However, despite the popularity of the latter diagnosis (Straus, 1991), this term was superseded by Neurasthenia in 1869 when Beard redefined the condition (Beard, 1869). Again symptoms were of decreased physical and mental energy, general malaise and mild low mood in addition to which the existence of exclusion criteria for diagnosis were emphasised. Beard emphasised the aetiology as purely organic (Wessely, 1990) and perhaps for this reason neurasthenia became more influential in psychiatry in the Western World.

Some two years after Beard's first paper, in 1871, DaCosta (1871) defined an Effort Syndrome. Again fatigue was the main symptom, but observed in civil war veterans rather than in the general population. DaCosta suspected that such symptoms were caused by an irritable heart, but failed to find confirmatory evidence. Further interest arose post World War I when 60 000 cases were observed amongst the military (Lewis,

1940). Again identification of an organic cause was elusive, and in 1941 it was suggested that patients should be treated as 'psychoneurotics' (Wood, 1941).

Similarly during the first half of the twentieth century there was a shift in attitude towards neurasthenia. It was no longer seen as organic in cause, but as mental. Symptoms of anxiety, hysteria and obsessive compulsive disorder were ultimately excluded, with spinal irritation, headaches, dyspepsia, constipation and flatulence being taken as the main symptoms (Wessely, 1990). The difficulty of diagnosis and the recognition of the role of psychological factors led to the gradual disuse of the term neurasthenia. Although the term is still defined in the current ICD10 (International Classification of Disease), it is used more in Eastern medicine than in the US and Europe.

By the mid twentieth century a number of reports again began to see fatigue syndromes as organic or viral. Outbreaks were for example reported in: London in 1955 amongst patients at the Royal Free Hospital (McEvedy & Beard, 1970a, McEvedy & Beard, 1970b); amongst staff at Los Angeles County Hospital in 1934 (summary in McEvedy & Beard, 1970b); in the community of Akureyri (Iceland) in 1948 (Sigurdsson & Gudmunsson, 1956) and in soldiers post World War I (Lewis, 1940). These reports between the 1900s and the 1960s originated from different countries, populations and occupational groups. This together with the diverse history meant that the major classifications available to physicians in the mid 1900s could largely be attributed to particular outbreaks or historical theories.

Thus prior to 1959, when Acheson published a clinical and epidemiological review of 14 outbreaks (Acheson, 1959) they had not been viewed in an integrated manner. He defined both mild and severe forms. The more severe forms appeared to have abnormal upper motor neurone responses, accompanied by fatigue, muscle pain and emotional lability. These appeared to parallel some Central Nervous System (CNS) diseases, though as the CNS involvement was thought to be of a more benign type than polio and encephalitis, it was labelled 'benign myalgic encephalomyelitis'; the name implying the presence of myalgia and the role of the CNS in the disease state.

In the 1980s, however, a surge of reports suggested that Epstein Barr Virus may have been the mediator of this syndrome. The term Post Viral Fatigue Syndrome (PVFS)

(Behan & Bakheit, 1991) was thus introduced in an attempt to recognise that the mediator of this illness was not well understood and that causes may have been other than neurological (Behan, Behan, & Bell, 1985). Whilst this definition was wider, it did not consider that in many instances there was no history of a preceding viral infection. More recent work suggests that although CFS follows Epstein Barr infection for a few patients, these are rare cases (Wessely, Chalder, Hirsch et al., 1995). It has also been suggested that such discrepancies may have arisen as a result of confounding variables, such as recall bias (Wessely, 1995).

That viral infection was not a necessary precipitant of this illness was later recognised in the adoption of the London Criteria for ME (International Federation for ME, 1994). These are summarised in section 1.3.1. and as can be seen the focus of diagnosis shifted towards the fatiguing nature of the condition from that of a possible nervous system dysfunction.

By the mid-Eighties these isolated attempts at description had led to a diverse nomenclature for what were essentially the same symptoms, e.g. Neurasthenia, benign ME, ME, Febricula, PVFS, Royal Free Disease and Akureyri disease. These each reflected the slightly different stances on the origin, nomenclature and definition of excessive fatigue. Although historically, theories of contagion and hysteria were suggested, more recent neuromedical advances have led to additional suggestions of immunological problems, muscle disease and neurobiological disorders. A full review of these theories is beyond the scope of this thesis, for a review see Dickinson, 1997. Though aetiological debates have been diverse, some invoking solely physical causes and others solely psychological causes, few diseases can be distinctly attributed to one cause; more recently a holistic approach has been favoured (Wessely, 1997). This has been concomitant with a shift in CFS Criteria becoming more symptom based.

1.3. Operational definitions of Chronic Fatigue Syndrome

The use of so many differing criteria, suggesting different aetiology and symptoms has presented many problems, both for the replicability and comparability of research. This

lack of consensus about what constitutes CFS has resulted in difficulty in finding its predictors, causes, mediators and in identifying potential treatment packages.

In recognition of these problems, in 1987 the US Centres for Disease Control (CDC) convened a meeting to select an appropriate name and a working classification. This resulted in the CDC criteria for Chronic Fatigue Syndrome (Holmes, Kaplan, Gantz, et al., 1988). This nomenclature has since been revised, the current being the 1994 CDC criteria (Fukuda, Straus, Hickie, et al., 1994).

At the same time attempts were being made in the UK and Australia to supersede the medley of diverse definitions and provide more coherent, widely accepted and rigorous case criteria. This resulted in the Oxford Consensus Criteria (OCC) (Sharpe, Archard, Banatvala, et al., 1991) and the Australian criteria (Lloyd, Wakefield, Bougton, & Dwyer, 1988, Hickie, Lloyd, Wakefield, & Parker, 1990). These criteria are those primarily used in current research into cognition and CFS, however also of importance when evaluating previous research are the historically more recent case definitions of ME (International Federation for ME, 1994) and PVFS (Behan & Bakheit, 1991).

1.3.1. 'London Criteria', International Federation of ME Association Criteria (IFMEA)

The 'London criteria' (International Federation for ME, 1994) for fatigue arose from a meeting of the International Federation for ME, incorporating the views of the patient group as well as physicians and researchers. Essentially there was a recognition that the modified ME criteria (Manu, Lane, & Mathews, 1988) were misleading, particularly with respect to the heavy emphasis on organic causative factors. As McEvedy and Beard noted there seemed to be a '*total lack of objective evidence in support of the view that .. the brain and the spinal cord (were) the site of an infective, inflammatory disease process' pg. 15* (McEvedy & Beard, 1970b). The focus of the criteria became more symptomatic than aetiological, and it was acknowledged that there may be other triggers such as viral illness, immunisation and life trauma, or indeed that there may be none. The emphasis has also shifted to incorporate 'autonomic' symptoms (such as photophobia and disturbance of bowel motility) and 'immunological' symptoms (such as a low grade fever) in addition to both mental and physical fatigue. However whilst mental and physical fatigue are prerequisites no mention was made of underlying

physical or psychiatric features which may cause fatigue, nor are any of the accompanying symptoms required for a diagnosis (see table 1.3.1. below).

Table 1.3.1. Criteria for Myalgic encephalomyelitis, IFMEA.

The following **three criteria** must be present for at least 6 months ◆ disproportionate abnormal fatigue on exertion ◆ impairment of short term memory and concentration, usually accompanied by emotional lability, nominal dysphasia, disturbed sleep patterns, dysequilibrium or tinnitus ◆ fluctuation of symptoms, usually as a result of mental or physical exercise	
additional symptoms may be present, these include:	
autonomic symptoms	excessive night or day sweats Reynauds phenomenon or postural hypotension disturbances of bowel motility photophobia, blurred vision (accommodation related) hyperacusis frequency of micturition or nocturia
Immunological symptoms	subjective complaint of verifiable low grade fevers (<38.6°C) sore throat persistent or recurrent athralgia

1.3.2. Post Viral Fatigue Syndrome (PVFS)

In PVFS (Behan & Bakheit, 1991) the prerequisite of a severe preceding viral illness was identified, e.g. a sore throat, myocarditis or gastro-enteritis. Symptoms were again of unremitting fatigue, poor memory and concentration, low grade fever and changes in bowel motility. However, as well as inclusion criteria, the exclusion of other illnesses known to cause fatigue was required. Additionally it was recognised that disturbances in mood, sleep and appetite may also be present. Whilst this definition had several advantages over the ME definition, namely inclusion of psychiatric symptomatology and exclusion of other illnesses there were several inherent problems. Firstly, there should be adequate evidence that known causes for fatigue have been excluded, and secondly evidence of a viral precipitate is necessary. In fact in retrospective diagnosis this may be difficult. Furthermore, as previously mentioned, the majority of chronic fatigue patients have no viral precipitates (Wessely, Chalder, Hirsch, et al., 1995). This represented a problem for the criteria as these patients, though similar in symptomatology would have to be excluded from the case definition.

Table 1.3.2. Criteria for Post Viral Fatigue Syndrome

An initiating factor of severe viral infection, usually resulting in bed rest. the following **three criteria** should be present: ◆ A clinical or viral infection (sore throat, acute gastro-enteritis, labrinthytis or myocarditis) ◆ severe vacillating fatigue, exacerbated by exertion, not resolved by rest ◆ exclusion of other illnesses known to cause fatigue.
additionally **3 of the following symptoms** are required:
myalgia (usually neck and shoulder) depression (without anhedonia or guilt) subjective poor memory and concentration (intact on neuropsychological testing) sleep disturbance fluctuation in body weight intermittent low grade fever changes in appetite and bowel motility excessive (usually night) sweats

adapted from Behan & Bakheit (1991)

In recognition of these problems a modification of these criteria has been included in the Oxford Criteria. As summarised in section 1.3.5. these criteria include a subgroup of patients where symptoms follow a viral infection.

1.3.3. Centres for Disease Control case definition for Chronic Fatigue Syndrome

In recognition of the exclusion of those patients with similar symptomatology but no viral infection, dissatisfaction was growing in the US over the available case definitions for such fatigue. In addition there was a realisation that the assortment of criteria were proving obstructive for the comparability of research and the clinical evaluation of patients.

An informal working party involving researchers, clinicians and epidemiologists was convened to define the future research criteria (Holmes, Kaplan, Gantz, et al., 1988). The definition was '*intentionally restrictive*' pg. 388 and focused on the collection of

symptoms experienced rather than on the precipitant factors. Both major and minor criteria were included, these are summarised in table 1.3.3.1., below.

Table 1.3.3.1 Centre For Disease Control Criteria, 1988

♦ for inclusion both 2 major criteria must be present ♦ additionally: 6 or more symptom criteria and 2 or more physical criteria; or 8 or more symptom criteria	
Major Criteria	♦ At least 6 months of persistent or relapsing fatigue, of definite onset, disproportionate to the level of activity undertaken, resulting in 50% reduction in daily activities ♦ Other known causes for fatigue have been excluded, by history, lab findings and physical examination these include: malignancy, localised infection, bacterial, fungal and parasitic disease, HIV, Chronic psychiatric disease either new or previous (depression, anxiety neurosis, schizophrenia), medication side effects, chronic inflammatory, neuromuscular endocrine disease, drug dependency or substance abuse.
Symptom Criteria (for at least 6 months and not prior to onset)	mild fever (37.5 to 38.6 °C) sore throat painful cervical or axillary lymph nodes unexplained muscle weakness muscle discomfort or myalgia disproportionate post exertion fatigue, in excess of 24 hours headaches (new type, severity and duration) athralgia without swelling or redness neuropsychological complaints (at least one of: photophobia, transient visual scotoma, forgetfulness, excessive irritability, confusion, difficulty thinking, inability to concentrate, depression) sleep disturbance main symptom complex developing over a few hours to days
Physical Criteria (physician documented at least twice)	low grade fever 37.6 to 38.6 °C non-exudative pharyngitis palpable or tender cervical or axillary lymph nodes

adapted from Holmes, Kaplan, Gantz, et al. (1988)

Fatigue must have been of at least 6 months duration reducing activity levels by about 50% and not be the result of other illnesses, such as anaemia, local infections, auto-immune disease or HIV, for example. A number of serological tests were suggested to exclude these causes. Minor criteria were split into symptom criteria and physical criteria which must have been present for the same duration as the major criteria. These included sore throat, generalised muscle weakness, non-exudative pharyngitis and palpable or tender cervical or axillary lymph nodes (see table 1.3.3.1. for a full

description of major and minor criteria). At least 6 of the 11 symptom criteria and 2 or more physical criteria, or 8 symptom criteria were required for a diagnosis.

It is of note, given the cognitive focus of this thesis, that neuropsychological complaints, whilst listed as a minor criterion, were not required. The presence of depression and mood symptoms was accepted, though those of chronic psychiatric symptoms were reason for exclusion.

Problems were observed regarding the restrictive nature of these criteria. It was reported that in 135 consecutive clinic attendees, who had experienced fatigue in excess of six months, only 5% fulfilled these criteria for CFS (Manu, Lane, & Mathews, 1988). Concerns were also raised regarding the terminology of fatigue. It was suggested (David, Wessely, and Pelosi, 1988) that the criteria were ambiguous and more precise definitions of postviral and fatigue were required. These misgivings were raised at a National Institute of Health (NIH) workshop in 1991 (Schluederberg, Straus, Peterson, et al., 1992). Though primarily dissension had arisen over the very restrictive nature of these criteria, as well as the ambiguities present in case definition, there were additional problems. It was reported that a number of researchers differed in their application of the criteria, or that patients needed to be identified as an additional subgroup for analysis. This was particularly evident in those with comorbid psychiatric symptomatology or viral precipitates. It was also suggested that the physical selection criteria may bias the research sample to a more somatoform group (Schluederberg, Straus, Peterson, et al., 1992). Modifications were hence made (Schluederberg, Straus, Peterson, et al., 1992) to include patients with non-psychotic depression, panic disorders, generalised anxiety disorders and somatoform disorders; those reporting post viral onset were included as a separate subgroup.

These new criteria (Schluederberg, Straus, Peterson, et al., 1992) essentially differed from the original 1988 CDC criteria (Holmes, Kaplan, Gantz, et al., 1988) with respect to the specific exclusion of some severe psychiatric illnesses, unless, however, fatigue remained after effective treatment of these disorders. The inclusion of comorbid psychiatric symptoms independent of the time of onset was also stressed. In acknowledgement that psychiatric problems may accompany CFS and that fatigue may be an accompanying symptom of many psychiatric disorders, it was felt important to

delineate these two groups. Modifications were thus made in 1994 by the CDC (Fukuda, Straus, Hickie, et al., 1994) (described in table 1.3.3.2.).

Table 1.3.3.2. Centres for Disease Control Criteria revised

<table>
<tr><td colspan="2">For a definition of CFS patients must fulfil the following criteria:

♦ unexplained persistent or relapsing fatigue, of at least 6 months duration, of new onset.

♦ This fatigue should be disproportionate to the levels of activity undertaken, and not alleviated by rest, resulting in a reduction of function on educational/occupational and personal/ social levels.</td></tr>
<tr><td>Exclusion Criteria</td><td>active medical conditions known to cause fatigue, e.g. hypothyroid, sleep apnea, narcolepsy or medication side effects

previously diagnosed conditions, not adequately resolved, e.g. Hepatitis B

past or current psychiatric illness such as melancholic or psychotic depression, schizophrenia, delusional disorders, dementias and eating disorders

alcohol or substance abuse at least 2 years prior to fatigue onset</td></tr>
<tr><td>Inclusion Criteria</td><td>Fibromyalgia, neurasthenia, anxiety disorders, somatofom disorders and non-psychotic and non-melancholic depression

any condition that is adequately treated to asymptomatic levels

any condition which has been adequately treated and resolved.

unexplained physical or laboratory findings insufficient to suggest exclusionary criteria</td></tr>
<tr><td colspan="2">♦ The occurrence of 4 or more of the following 8 symptoms which have been present for at least 6 months, but do not predate the fatigue. These should result in a reduction of function on educational/occupational and personal/ social levels.</td></tr>
<tr><td>Symptoms</td><td>sore throat

tender cervical or axillary lymph nodes

muscle pain

multi-joint pain, without swelling or redness

headaches, new type severity or duration

unrefreshing sleep

post exertional malaise self reported impairment on tasks of short-term memory or concentration</td></tr>
</table>

adapted from Fukuda, Straus, Hickie, et al. (1994)

These suggest that the accompanying neuropsychiatric problems should be excluded unless they are manifest after the initial onset of fatigue. Past psychiatric diagnosis are

also considered to be reasons for exclusion. For the revised criteria only four out of eight symptoms are required for diagnosis, physical symptoms are no longer included. Additionally owing to the difficulty of objectively measuring fatigue present at least 50% of the time, this criterion was also abandoned. As for the previous CDC criteria although neuropsychological disorders are not necessary, they may be present (Fukuda, Straus, Hickie, et al., 1994).

1.3.4. Australian Criteria for Chronic Fatigue Syndrome

These criteria were essentially more relaxed than the original and revised CDC definitions. They arose from the investigation of the clinical laboratory features of 200 ME patients and 100 patients diagnosed with CFS (Lloyd, Wakefield, Bougton, & Dwyer, 1988). Whilst they agreed with the newer CDC terminology, they suggested that only 3 major inclusion criteria were necessary (Lloyd, Wakefield, Bougton, & Dwyer, 1988) (see table 1.3.4.1.).

Table 1.3.4.1. Australia Criteria for CFS

<table>
<tr><td colspan="2">Of 3 criteria the following 2 must be present
♦ generalised persistent or relapsing fatigue, of at least 6 months duration. It should be exacerbated by exercise and reduce activity.
♦ neuropsychiatric dysfunction on tasks of concentration and short term memory, disproportionate from premorbid levels</td></tr>
<tr><td colspan="2">♦ Abnormal cell mediated immunity may also be apparent (as indicated by lymphocyte subsets T4 and T8)</td></tr>
<tr><td>supportive symptoms
(at least twice after the initial illness onset)</td><td>myalgia
athralgia
headache
depression
tinnitus
parasthesiae
sleep disturbance (unexplained for 6 months)
lymphadenopathy
pharyngitis
localised muscle tenderness</td></tr>
</table>

Lloyd et al., 1988 adapted from (Lloyd, Wakefield, Bougton, & Dwyer, 1988).

Firstly, inexplicable fatigue of at least 6 months duration which may be vacillating; secondly, abnormal cell count of T8 and/or T4 lymphocytes and/or cutaneous anergy

and finally neuropsychiatric dysfunction, such as short term memory problems or impaired concentration. It was also acknowledged that other symptoms may be present such as depression, sleep disturbance and myalgia. The authors additionally state that with this definition only in 2 patients was an alternative diagnosis subsequently reached.

These criteria were simplified in 1990 (Hickie, Lloyd, Wakefield, & Parker, 1990) and are summarised in table 1.3.4.2.. Patients must have experienced at least 6 months of continuous or 3 months of vacillating fatigue. In addition to this 2 major criteria, or 1 major and 3 minor criteria, must be present. Major criteria included concentration or memory impairment, lymphadenopathy, cutaneous anergy or T4 or T8 lymphopenia.

Table 1.3.4.2. Modified Australian criteria

There must be persistent or recurrent debilitating **fatigue of at least 6 months** duration, And fulfil **2 major**, or **one major and three minor** criteria	
Symptoms (persisting over 6 mths or relapsing on at least 3 occasions within those 6 mths)	**Major:** concentration or memory impairment **Minor:** Myalgia, athralgia, depression, tinnitus, headache and parasthesiae
Signs (present at least once since the initial illness)	**Major:** lymphadenopathy **Minor:** pharyngitis, muscle tenderness
Immunological assessments	**Major:** cutaneous anergy, T4 or T8 lymphopenia **Minor:** hypoergy

adapted from Hickie, Lloyd, Wakefield, & Parker. (1990)

It is interesting to note the shift in the flexibility of these criteria. The most interesting change, from the perspective of this thesis, is that although neuropsychological or physical fatigue are included in the criteria, the neuropsychological symptoms are no longer necessary. This is also the case with T4 or T8 disturbances, marking a deviation from the earlier post viral or allergy hypotheses. Indeed though disorders of T lymphocyte cells have been reported, there is a great deal of overlap between cases, depressed patients and control patients. These findings are more likely to be coincidental (Wessely, 1995). Furthermore it has been suggested that high reports of viral illness are in most patients probably a result of recall bias (Wessely, Chalder,

Hirsch,et al., 1995). With increased flexibility came the loss of explicitly stated exclusion criteria, though patients with explicable fatigue were not included in the sample of this research team (Hickie, Lloyd, Wakefield, & Parker, 1990). These criteria are still prevalent in Australasia, but less widely so in Europe and the USA.

1.3.5. CFS Oxford Consensus Criteria (OCC)

The OCC arose from a meeting of researchers which aimed at achieving a consensus in the methods of investigating and disseminating future work with CFS patients (Sharpe, Archard, Banatvala, et al., 1991). Parallel to concerns expressed at the NIH workshop (discussed above), concerns were expressed in the UK. These centred on the restrictive nature of the criteria, the lack of explicit phenomenology and the presence of a subgroup of patients reporting preceding viral infection. Though the Australian criteria were perhaps excessively restrictive with respect to T lymphocyte disturbances or viral infection, it was acknowledged that there may be distinct subgroups of patients. They defined two broad syndromes: that of chronic fatigue syndrome; and a subgroup of post infectious fatigue syndrome.

Table 1.3.5.1 Oxford Consensus Criteria for CFS

The following criteria apply:

- the syndrome is of definite onset and not life long
- fatigue is the principle symptom (mental and physical), it is debilitating and of new and definite onset. It is present for at least 6 months, for at least 50% of the time.
- other symptoms may be present, particularly myalgia, mood and sleep disturbances

exclusion criteria	medical conditions known to cause fatigue e.g. anaemia psychiatric illness such as schizophrenia, manic depression, eating disorders, organic brain disease, substance abuse
inclusion criteria	psychiatric illness such as depressive illness, anxiety disorders, and hyperventilation syndrome.

adapted from Moss-Morris, Petrie, Large, & Kydd (1997)

The current case definition (described in table 1.3.5.1.) for Chronic Fatigue Syndrome states that: 'fatigue' must be of a minimum 6 month duration and definite onset. This fatigue should be present for at least 50% of these 6 months, and may be accompanied

by other problems such as disturbed sleep, myalgia and altered mood. Again diagnosis must exclude the possibility of fatigue from other known causes, such as anaemia, substance abuse and eating disorders. Patients with psychiatric diagnosis, such as schizophrenia and manic depression must also be excluded, though those with other disorders such as panic disorders and depressive illness may be included (Sharpe, Archard, Banatvala, et al., 1991).

Those with Post Infectious Fatigue Syndrome (PIFS) are defined as a subgroup of patients where the symptoms of CFS follow or are concomitant with a definite viral infection. These symptoms should have been present for at least 6 months. Since subjective accounts are unreliable, for example open to retrospective recall bias, laboratory investigations should be undertaken to ensure the presence of such a virus (Sharpe, Archard, Banatvala, et al., 1991).

Acknowledging the concerns raised about phenomenology (David, Wessely, & Pelosi, 1988) the following symptoms have been clearly defined by the Oxford Team: fatigue; disability; myalgia; mood disturbances and sleep disturbances. These should be complained of as persistent or recurrent problems which are distinct from their premorbid levels and reported as problems by patients.

Fatigue is defined as a subjective sensation, synonymous with tiredness and weariness and is both mental and physical in nature (Sharpe, Archard, Banatvala, et al., 1991). Physical fatigue is defined as lack of strength and mental fatigue as a lack of motivation and alertness (Sharpe, Archard, Banatvala, et al., 1991). Accompanying mood disturbances include depression, anhedonia, anxiety and irritability. Though the inclusion of anxiety, depression and anhedonia does increase the heterogeneity of the sample, as mentioned previously (see section 1.3.3.) earlier case definitions suffered from overly restrictive inclusion criteria. Furthermore, accompanying depression and anxiety are reported as correlates of many other diseases, e.g. Supra nuclear palsy (Giles, Esmonde, Gibson, & Hodges, 1996) and heart disease (Barefoot, Helms, Mark, et al., 1996). The type, severity, duration and frequency of co-morbid psychiatric symptoms should thus be noted, and their effects determined. Similarly the frequency, duration and severity of myalgia should be reported, where myalgia is pain or aching of the muscles disproportionate to the precipitating activity. Sleep disturbances should be

distinguished from tiredness and fatigue. They are defined as changes in the pattern of sleep, independent of *'external disturbances'* pg. 120 (Sharpe, Archard, Banatvala, et al., 1991) to the sleep wake cycle. These changes in sleep pattern should be persistent rather than recurrent.

Such clarification was aimed at minimising the problems inherent in operationalising the criteria. Though the criteria are still open to interpretation (discussed more fully in section 1.3.7.) clear definitions should be of benefit by increasing the homogeneity within and between research samples.

This is the operational definition used at the Leeds Fatigue Clinic and consequently will be used throughout the thesis.

1.3.6. Case definitions: summary and methodological issues

Despite a number of definitions being available, the OCC (Sharpe, Archard, Banatvala, et al., 1991), CDC (Fukuda, Straus, Hickie, et al., 1994) and Australian criteria (Hickie, Lloyd, Wakefield, & Parker, 1990) are those in primary use in CFS research at the current time. Whilst these largely concur, differences are apparent, primarily with respect to the inclusion of psychiatric symptoms and the phenomenology of fatigue.

Though there has been no formal investigation into the impact of differing case definitions on reported cognitive function, these definitions influence epidemiology estimates (Bates, Schmitt, Buchwald, et al., 1993) and, as mentioned in section 1.5.2.1., comorbid psychiatric prevalence rates. Estimates of point prevalence in primary care are 0.3%, 0.4% and 1%, using the CDC, Oxford and Australian criteria respectively (Bates, Schmitt, Buchwald, et al., 1993); thus the Australian criteria are far broader in scope. The differences between diagnostic criteria for CFS influence both between and within sample characteristics. Consideration of such variations are thus important in the evaluation and interpretation of previous research reports; as well as the theoretical approach to this research and its generalisability to other CFS populations. Where cognitive symptoms are required for example, all subjects are likely to be experiencing cognitive difficulty, at least subjectively. Groups where depression and anxiety are present may have additional or alternative symptoms characterised by these comorbid axis I disorders. The criteria fundamentally differ in the following ways: fatigue severity; fatigue duration; psychiatric symptomatology and cognitive symptoms.

1.3.6.1. Fatigue Severity

Fatigue, as mentioned previously can be defined mentally and physically. Variations in the specification of fatigue severity and duration may indirectly impact upon cognitive findings between groups, by the increasing of sample heterogeneity. Generally the criteria specify severe to debilitating fatigue, resulting in a reduction in function, or in activities of daily living. The CDC criteria (Holmes, Kaplan, Gantz, et al., 1988) further specify that this should represent a reduction of about 50% in activities. This restrictive criterion was later modified (see section 1.3.2.) to alleviate the potential biasing to more somatoform samples. It is, however, interesting to note the retention of the observable characteristic of fatigue level in most of the major criteria (Holmes, Kaplan, Gantz, et al., 1988, Schluederberg, Straus, Peterson, et al., 1992, Fukuda, Straus, Hickie, et al., 1994, Hickie, Lloyd, Wakefield, & Parker, 1990, Lloyd, Wakefield, Bougton, & Dwyer, 1988, Sharpe, Archard, Banatvala, et al., 1991). This helps to reduce heterogeneity by the inclusion of less subjective and more clearly defined characteristics. An observable functional change is required rather than a subjective interpretation on the part of the patient, and indeed the physician. Indeed the criteria of PVFS (Behan & Bakheit, 1991) and ME (IFME, 1994) are the only criteria which do not specify an observable change in activity as the correlate of reported fatigue. For the PVFS (Behan & Bakheit, 1991) and the ME (IFME, 1994) criteria, since only the subjective reports of experienced fatigue are required, fatigue that does not interfere with daily functioning, or is somatoform, may be included. A greater amount of within and between sample heterogeneity is therefore likely amongst the fatigue levels of patients defined by these criteria.

Neuropsychological deficits have been associated with functional impairment, in a similar way to that found in other medical conditions, such as MS (Christodoulou, DeLuca, Lange, et al., 1998). Groups with more severe physical fatigue may therefore be experiencing more symptoms of cognitive fatigue. A study with 53 CFS patients, with no prior axis I disorder and moderate to severe symptoms, showed a positive relationship between word list acquisition, free recall and activity (daily, social and general) over the preceding month. This association between cognitive function and physical function was independent of psychiatric symptomatology (Christodoulou, DeLuca, Lange, et al., 1998). Since the criteria of PVFS (Behan & Bakheit, 1991), ME

(IFME, 1994) do not specify an observable correlate of symptoms, these groups may be biased to the more somatoform, less physical and as a corollary, perhaps have fewer cognitive symptoms. For the ME group, where cognitive symptoms are required this factor is probably of less importance than for a PVFS definition.

1.3.6.2. Fatigue Duration

The vacillating nature and the duration of fatigue, both mental and physical, may also influence the results obtained. The criteria universally note that as well as persistent fatigue, in some patient it may be vacillating, relapsing or fluctuating; severity and activity levels varying over the course of the illness. At any one time a sample of patients will contain those who are experiencing high as well as low fatigue. These proportions will potentially differ between research samples; some degree of variation in the results obtained between similarly defined research samples should therefore not be unexpected.

All criteria, excluding PVFS, specify that this fatigue must have been present for at least 6 months; though the OCC (Sharpe, Archard, Banatvala, et al., 1991) and CDC (Holmes, Kaplan, Gantz, et al., 1988, Schluederberg, Straus, Peterson, et al., 1992, Fukuda, Straus, Hickie, et al., 1994) criteria are the only ones which express that this should not be life long. This arbitrary distinction has the added advantage of reducing the heterogeneity within these groups by excluding those individuals where a fatigue state is 'normal'. It also excludes those with acute fatigue symptoms which may differ phenomenologically from the more chronic forms as seen in CFS. Essentially for the PVFS criteria this lack of specification is another factor increasing between and within sample variability. Patients experiencing a short or long duration of post-viral fatigue may be included.

1.3.6.3. Psychiatric symptomatology

The presence of psychiatric symptomatology, in particular depression and anxiety, may result in further important differences in sample characteristics. As discussed later (see section 1.5.3.) both depression and anxiety are thought to affect cognitive function. The Australian (Lloyd, Wakefield, Bougton, & Dwyer, 1988, Hickie, Lloyd, Wakefield, & Parker, 1990), PVFS (Behan & Bakheit, 1991) and ME (International Federation for ME, 1994) have no explicit guidelines on the inclusion or exclusion of psychiatric

illness such as mania, or schizophrenia; though all criteria with the exception of the CDC (Holmes, Kaplan, Gantz, et al., 1988) criteria allow for the presence of psychiatric illness, such as depression and anxiety.

The Australian (Hickie, Lloyd, Wakefield, & Parker, 1990, Lloyd, Wakefield, Bougton, & Dwyer, 1988), PVFS (Behan & Bakheit, 1991) and ME (International Federation for ME, 1994) criteria may thus again suffer from increased sample heterogeneity. The problems may be further exacerbated by the difficulties encountered in elucidating the role of potentially large numbers of confounding psychiatric variables; sample sizes may be too small to detect such differences. The OCC (Sharpe, Archard, Banatvala, et al., 1991) and CDC (Schluederberg, Straus, Peterson, et al., 1992, Fukuda, Straus, Hickie, et al., 1994) criteria do allow for the presence of psychiatric symptoms. Within research samples the effects of these can be statistically measured and defined. It is only with the samples defined by CDC (Holmes, Kaplan, Gantz, et al., 1988) criteria that functioning may not be clearly attributable to comorbid psychiatric symptoms. However given that such samples are of a small subgroup of CFS patients, here generalisability is a problem, and as mentioned above has presented some problems. Therefore, it may be more informative to investigate function in a broadly defined group for which such variability in sample characteristics may be clearly controlled or specified.

1.3.6.4. Cognitive Symptoms

Given the cognitive focus of this thesis, it is relevant to note that whilst all criteria acknowledge the presence of mental fatigue (Fukuda, Straus, Hickie, et al., 1994, Schluederberg, Straus, Peterson, et al., 1992, Holmes, Kaplan, Gantz, et al., 1988, Behan & Bakheit, 1991, Hickie, Lloyd, Wakefield, & Parker, 1990), it is only a prerequisite for the OCC (Sharpe, Archard, Banatvala, et al., 1991), earlier Australian (Lloyd, Wakefield, Bougton, & Dwyer, 1988) and the ME criteria (International Federation for ME, 1994). This mental fatigue varies in definition between the classification systems. For the ME (IFME, 1994), Australian (Hickie, Lloyd, Wakefield, & Parker, 1990, Lloyd, Wakefield, Bougton, & Dwyer, 1988), CDC criteria (Schluederberg, Straus, Peterson, et al., 1992, Fukuda, Straus, Hickie, et al., 1994) and PVFS (Behan & Bakheit, 1991) criteria, it is specified as short term memory and concentration difficulties. Such precise definitions of as yet a largely unmeasured and undefined cognitive problem may serve to exclude those patients who experience other cognitive difficulties. In a questionnaire survey of 281 CFS patients cognitive

difficulties such as difficulty in thinking were also reported (Komaroff, Fagioli, Geiger, et al., 1996). Such restriction however, may have the advantage of increasing sample homogeneity making conflicting study results less probable.

The cognitive definitions used in the CDC criteria (Holmes, Kaplan, Gantz, et al., 1988) are somewhat wider, than those mentioned above. They define the symptoms as confusion, difficulty thinking, forgetfulness and an inability to concentrate. Again patients experiencing symptomatically different fatigue may be excluded, but a wider range of deficits may be observed. OCC (Moss-Morris, Petrie, Large, & Kydd, 1997) are also more encompassing with respect to cognitive symptoms. This fatigue is defined as a subjective sensation characterised by lack of motivation and alertness (Moss-Morris, Petrie, Large, & Kydd, 1997). In the absence of empirically defined neuropsychological deficits it allows the inclusion of all patients experiencing difficulties in mental function. Such defined samples are thus more likely to result in the detection of differences on a wider variety of cognitive measures, such as visual processing. Additionally, since according to the criteria all patients must experience some undefined type of cognitive difficulty, observable deficits are more likely than with CDC (Schluederberg, Straus, Peterson, et al., 1992) (Fukuda, Straus, Hickie, et al., 1994) criteria, where the type is specified but the presence not necessary. The objective characteristics of such reported mental sensations are, however, undefined by the OCC. The samples, for example may, or may not, include patients who express difficulties with memory, or with attention or concentration; between and within sample heterogeneity may thus be increased.

It is recognised that operationalising such 'fuzzy' definitions is inherently difficult. With all criteria this is a notable problem, since there are no objectively measurable discrete characteristics to define terms such as fatigue and the role of comorbidity is undetermined.

1.3.6.5. Conclusions

In summary, the criteria for diagnosis may have a significant impact on research findings. The three major case definitions state that: 'fatigue' is of a minimum 6 month duration results in a substantial or disabling reduction in activity. If subjective fatigue does reflect objective fatigue, then it is more likely that deficits will be found when

mental fatigue is a prerequisite for inclusion. Deficits are thus more likely in samples where OCC and ME criteria have been used rather than CDC (Schluederberg, Straus, Peterson, et al., 1992, Fukuda, Straus, Hickie, et al., 1994) or Australian (Hickie, Lloyd, Wakefield, & Parker, 1990, Lloyd, Wakefield, Bougton, & Dwyer, 1988) criteria, simply because this criterion for diagnosis differs. A more extensive variety of symptoms is also more likely in samples using the earlier CDC (Holmes, Kaplan, Gantz, et al., 1988) criteria and the more recent OCC (Moss-Morris, Petrie, Large, & Kydd, 1997) criteria, as symptom definitions are broader.

1.3.7. Operationalising the criteria: Defining and measuring fatigue

Ultimately the criteria are subject to some degree of interpretation on the part of the clinician, particularly when terms are undefined, as in the CDC and Australian criteria. For example; What is 'debilitating' fatigue? What constitutes mental fatigue or physical fatigue? Are the symptoms those of atypical depression or unexplained fatigue? For most of the case definitions these concepts are undefined and interpretation will thus vary between studies. From a research perspective assessing the severity of fatigue and accompanying depression and anxiety presents problems for comparability. As argued below such factors have effects on sample heterogeneity. They thus play a contributory role in the apparent conflict within the literature.

There are 2 primary sources for heterogeneity within the understanding of the concept of fatigue. The first arises from defining fatigue, reflecting differences in diagnosis. This may result in patients differing in fatigue between samples. The second relates to difficulties in measuring fatigue severity. An additional source of variation, specifically impacting on mental fatigue, is the difficulty in distinguishing it from comorbid symptoms.

1.3.7.1. Defining Fatigue

Defining fatigue is difficult, like pain and depression, the word 'fatigue' is in common use in the English language and is highly subjective in meaning. To illustrate, fatigue is reported to occur in the primary care sector at prevalence rates of 7 to 45%, this range primarily reflecting the differences in definition (Wessely, 1995). Synonyms for fatigue

include tiredness, weariness, languor, listlessness, lassitude, lethargy, exhaustion and being worn out or run down, to name but a few. Additionally fatigue varies with individual fitness and disease type (Barofsky & West Legro, 1991). Physiological definitions revolve around the concept of muscular fatigue, defining it as a failure to sustain muscle output, or fatigue resulting from abnormalities below the level of the neuro-muscular junction. The concept of fatigue outside the domain of physiology is of psychiatric origin. It has been conceptualised as central fatigue. This is fatigue that arises above the muscular level and is more phenomenological in nature. It is generally taken to mean that the patient tires abnormally easily or cannot sustain the same level of activity as is normal.

Dividing normal from abnormal fatigue is a major difficulty. For example, one would expect to be tired after a visit to the gym but not after making a cup of coffee, other tasks are less certain and reflect individual variations in fitness, such as a 'short' walk. Differences in such perceptions may be particularly evident in those patients with comorbid axis I diagnosis. Biases in the perception of fatigue severity may arise from over reporting or attendance to negative symptoms. Thus within those criteria where psychiatric symptoms are included further variance is likely, for example with OCC (Moss-Morris, Petrie, Large, & Kydd, 1997) and CDC (Schluederberg, Straus, Peterson, et al., 1992, Fukuda, Straus, Hickie, et al., 1994). This presents a further problem for the physician in that, excluding the CDC (Holmes, Kaplan, Gantz, et al., 1988) criteria, definitions focus upon the phenomenological rather than the objective nature of fatigue. This may result in increased within sample heterogeneity, as a result of patients individual differences in detection and reporting of symptoms of fatigue. In patients presenting with depression an additional problem for the physician is in separating fatigue from anhedonia; distinguishing it from low mood, or lack of interest may be difficult. Variability in the understanding and use of criteria on the part of the physician may thus result in differential diagnoses and compositions of research groups, affecting sample heterogeneity.

In an attempt to introduce a standard consensus in the use of fatigue as a symptom of classification for CFS, as mentioned previously, the OCC (Sharpe, Archard, Banatvala, et al., 1991) define fatigue. It is the first taxonomy to specify the nature of fatigue as a symptom in CFS. Mental fatigue is described as the" *subjective sensation characterised by lack of motivation and alertness*" pg. 120 and physiological fatigue as "*a lack of*

energy or strength and is often felt in the muscles" pg. 120. Fatigue should, be complained of, or reported as affecting functioning, be disproportionate to activity, represent a change from premorbid state, and be present for at least 50% of the time.

By specifying particular components of fatigue, sample heterogeneity arising as a result of differential understandings of fatigue should be reduced. However in practice the definition is probably too general to achieve this aim, and is to some extent still subjective. For example what is lack of motivation and alertness? If a patient reports lapses of concentration do these constitute mental fatigue? They may arise from attention difficulties experienced as reduced alertness, or from a more specific problem such as failure in retrieval strategies. As yet there is no consensus on what the objective problems are and indeed attempting to measure the subjective objectively may not be wholly possible.

1.3.7.2. Measuring Fatigue

At the current time there are two methods commonly used for assessing fatigue: the scheduled interview assessment and subjective self report questionnaires. As yet, interview assessments of fatigue severity and pattern have not been widely used in CFS literature and the majority of research in the last five years has used a self rated questionnaire assessment. There are probable reasons for this: firstly the length of time taken to implement such methods; secondly the possibility of experimenter bias in the case of unblinded research. In practice most assessment of CFS patients is in clinics or by referral from a clinic, blinded assessment of fatigue is therefore difficult to achieve.

Self rated scales of fatigue fall into two types uni-dimensional and multi-dimensional. Commonly used uni-dimensional scales of fatigue are: VAS visual analogue scales; the Tiredness scale (Montgomery, 1983) and the Fatigue Severity Scale (Krupp, La Rocca, Muir-Nash, & Steinberg, 1989). Commonly used multi-dimensional scales include: the Fatigue Scale (Chalder, Berlowitz, Pawlikowska, et al., 1993, Wessely & Powell, 1989); VAS fatigue (Wood, 1992); Profile of fatigue related symptoms (Ray, Weir, Phillips, & Cullen, 1992) and the Multi-dimensional fatigue inventory (Smets, Garssen, Bonke, & De Haes, 1995).

These self assessments are again open to individual variations in phenomenological experience. Some patients may rate their fatigue as more severe, whilst others rate

fatigue of the same levels less severely; these types of problems are inherent where an objective measure of the concept is as yet unknown. There will also be variation in the fatigue patterns assessed by the different scales employed.

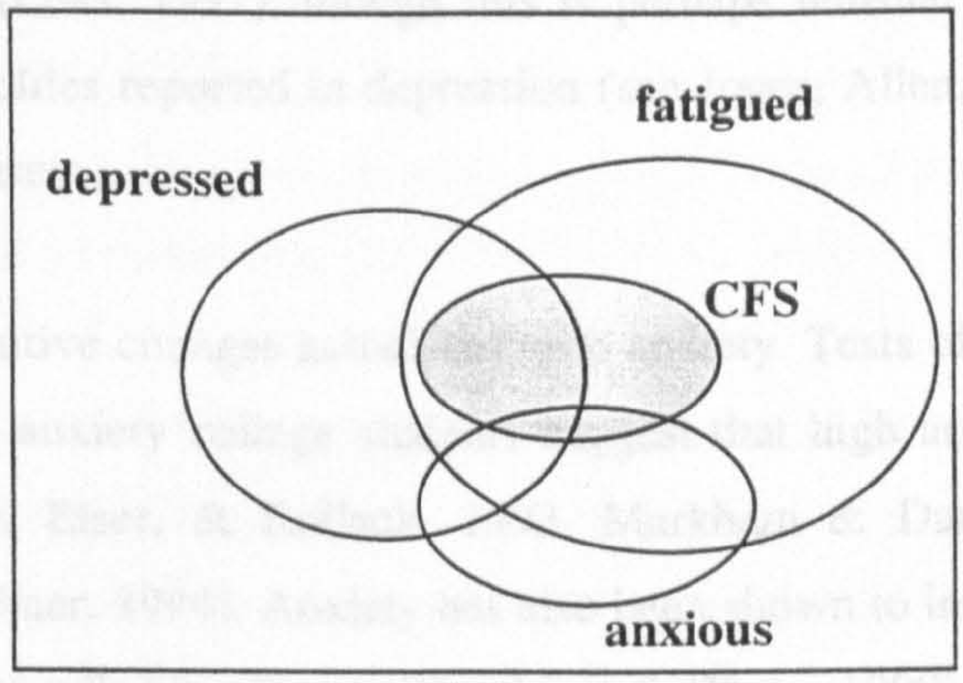
In chronic fatigue syndrome some individuals may feel more physically tired than mentally and vice versa; further this pattern may vary temporally within the individual. This pattern of fatigue is not addressed using the uni-dimensional scale. The case could be envisaged where fatigue was not detected since the fatigue pattern described in the questionnaire differed from that presented by the individual. Even with the multi-dimensional scales the fatigue assessed varies. For example the Fatigue Scale (Chalder, Berlowitz, Pawlikowska, et al., 1993) includes 3 broad questions such *as 'how is your memory?'* and 2 more specific such *as 'do you have difficulty finding the right word'*; whereas the PFRS (Ray, Weir, Phillips & Cullen, 1992) includes eleven more specific symptoms such as *'forgetting what you were trying to say'*.

Such differences between scales may result in variation in the estimates of fatigue severity and characteristics between studies and populations which differ in the type of cognitive fatigue experienced. When used to divide groups on the basis of fatigue severity or type, they may thus yield between study variance; or when entered as covariates into analysis result in differences in outcomes.

1.4. How unique is this pattern of fatigue, co-morbidity and neuropsychological deficits?

As stated in the criteria for CFS, fatigue is the major symptom; and there may be mental as well as physical components. The CDC (Holmes, Kaplan, Gantz, et al., 1988) criteria are the only which do not exclude concurrent psychiatric symptomatology; most definitions would allow that there is a degree of overlap between psychiatric and fatigue symptomatology as outlined in figure 1.4.1., below. This coexistence of fatigue with either or both mood and neuropsychological symptoms is not unique to CFS and has been reported in healthy controls and other patient groups, discussed below. It is important, however, to recognise that though these symptoms may often appear together, they are not necessarily dependent.

Figure 1.4. CFS and its relationship to comorbid depression and anxiety



adapted from Fukuda, Straus, Hickie, et al. (1994)

An investigation using the Profile of Mood States (POMS) in habitual exercisers, reported increases in mood disturbance when participants were deprived of exercise. The maximum score increase in depression coincided with that of reported confusion and fatigue (Mondin, Morgan, Piering, et al., 1996). In war syndromes such as Vietnam and the Persian Gulf, fatigue and exhaustion have been reported concurrently with muscle and joint pain, as well as forgetfulness and difficulties in concentration (Hyams, Wignall, & Roswell, 1996).

Changes of mood and cognitive function have been shown in the absence of mental fatigue. In Fragile X women significant differences have been reported between those who were depressed and non-depressed groups on some measures of cognitive function (Thompson, Rogeness, McClure, et al., 1996). In post traumatic stress disorder depressive symptoms are thought to be associated with cognitive changes (Barret, Green, Morris, et al., 1996). Mental and physical fatigue have also, for example, been shown to correlate with emotion before and after major joint surgery (Aarons, Forester, Hall, & Salmon, 1996).

Depression has been reported in a variety of diseases to be independent of changes in cognitive function and in others to be associated with it. Depressed patients have been reported to be impaired on computerised tests of neuropsychological function (Elliot, Sahakian, Herrod, et al., 1996). However in progressive supranuclear palsy cognitive performance and depression are reported, but depression does not correlate with cognitive measures (Giles, Esmonde, Gibson, & Hodges, 1996). Additionally

depression and lack of energy may occur together in the absence of cognitive fatigue, for example in fibromyalgia (Loas, 1997), though this is perhaps unusual given the prevalence of cognitive difficulties reported in depression (see Jones, Allen, Griffiths, et al. (1986) and references therein).

There is also a history of cognitive changes associated with anxiety. Tests of cognitive function and memory in high anxiety college students suggest that high anxiety may impair performance (Mueller, Elser, & Rollack, 1993, Markham & Darke, 1991. Rathus, Reber, Manza, & Kushner, 1994). Anxiety has also been shown to increase and decrease attention according to selective biases (Dalgleish & Watts, 1990). Research into the cognitive function of patients with obsessive compulsive disorder has suggested that these difficulties may extend to the clinical population (Lane, Manu, & Mathews, 1991).

As discussed in section 1.5.3., though delineation of mental fatigue symptoms specific to CFS given the co-morbid mood changes may be difficult, it is by this that a greater understanding of this syndrome will be derived.

1.5. Morbidity

1.5.2 Demographics

As stated in criteria for CFS some comorbid psychiatric symptoms may be present, though this is not always the case. The Royal College of Psychiatry report (RCP) (Wessely, 1997) suggests that approximately two thirds of patients experience comorbid psychiatric symptoms. Variable rates have been reported for each of these, again probably as a result of methodological discrepancies between studies.

1.5.2.1. Anxiety and depression

Estimated rates of depression suggest it is present in approximately 45% of the CFS population. Of 100 CDC (Fukuda, Straus, Hickie, et al., 1994) diagnosed chronic fatigue syndrome patients consecutively attending a tertiary care clinic, 45% experienced major depression, 11% of these were in remission (Farmer, Jones, Hillier, et al., 1995). Wessely and Powell (1989) report similar prevalence rates of 47% again in a tertiary care sample whilst Hickie et al. report that 45.8% of patients experience

depression at some time during the course of their illness (Hickie, Lloyd, Wakefield, & Parker, 1990). In CFS patients from a community sample, psychiatric caseness has been estimated at 48% using the GHQ (Lawrie, Manders, Geddes, & Pelosi, 1997). Comorbid anxiety has been reported at levels of between 23% (Farmer, Jones, Hillier, Llewellyn, et al., 1995) and 31% (Pepper, Krupp, Freidberg, et al., 1993).

Primary care rates of depression and anxiety are about 14.1% for major depression, and 20.5% for anxiety disorders (Leon, Olfson, Broadhead, et al., 1995), by comparison then, the rates of depression, generalised anxiety disorder and panic attacks amongst patients with CFS are high. Given this, it has been suggested that, CFS may be simply a somatisation of symptoms; physiological symptoms being reported as a corollary to psychological problems. This has been extensively debated (Johnson, De Luca, & Natelson, 1996) and discussion is beyond the scope of this thesis (see Abbey & Garfinkel, 1991 for a review). Additionally it is not new for syndromes with unknown aetiology to be thought if as 'all in the mind' (White & Moorey, 1997) or to suggest that subjective measures of fatigue may simply reflect depressive styles of thinking (Lane, Manu, & Mathews, 1991).

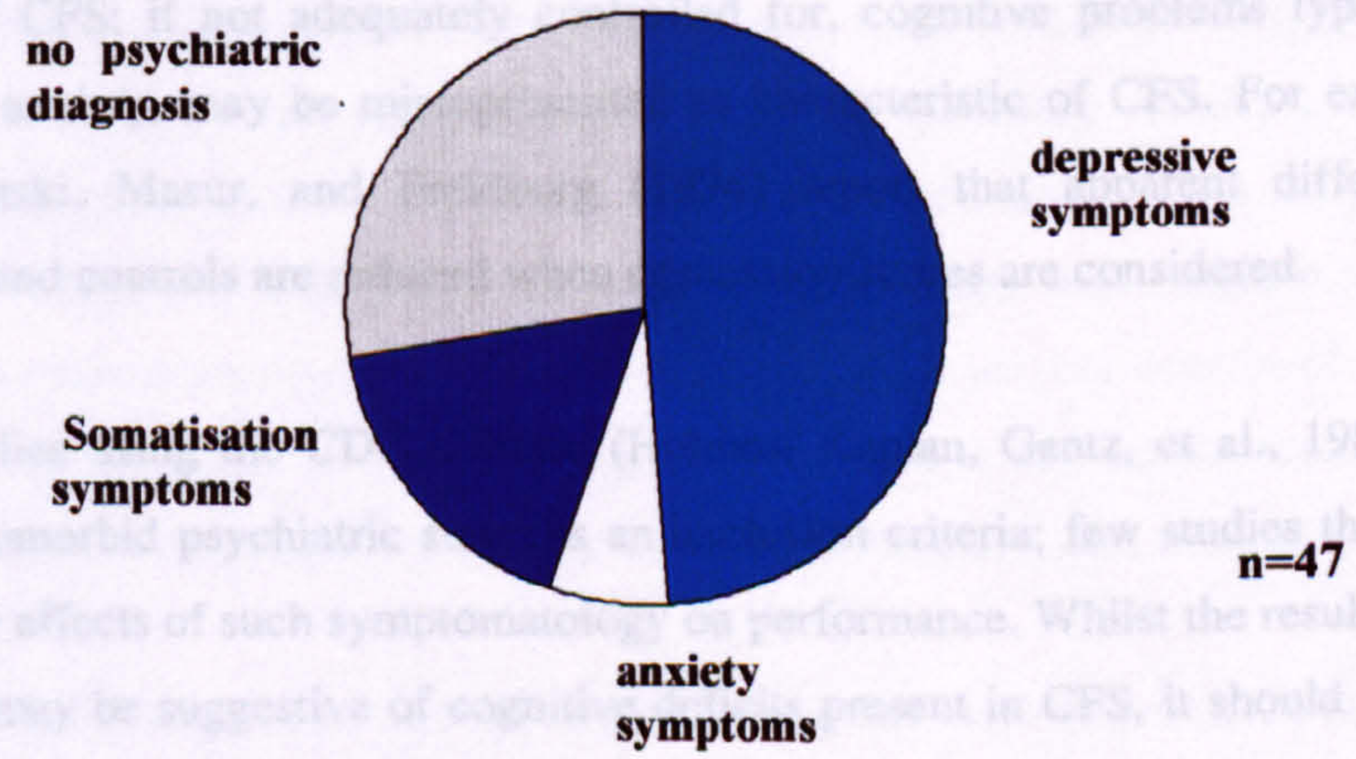
1.5.2.2. Somatisation

A number of studies have investigated somatisation in CFS, for example Lane, Manu, & Mathews, 1991 and Fischler, Dendale, Michiels, et al., 1997. Estimates of somatisation disorders vary between 0.02% (Hickie, Lloyd, Wakefield, & Parker, 1990) and 34%(Farmer, Jones, Hillier, et al., 1995). In a hospital sample referred for research self administered questionnaire responses showed somatic symptoms in 14.8% of patients whilst 15% qualified for the diagnosis of somatisation disorder (Wessely & Powell, 1989). Prevalence rates of 13% have also been reported (David, Wessely, & Pelosi, 1991). Of the psychiatric symptoms associated with CFS the point prevalence is most variable for somatisation, but is generally elevated above the 0.03% found in community samples (Escobar, Burnam, Karno, & et al., 1987). There are 2 issues of note here, one is the criteria used and the other of assessing somatisation . As can be seen in figure 1.5.2.2. somatisation accounts for a large proportion of psychiatric diagnoses. The high rates in this CFS group are of particular interest given that patients were selected using the original Holmes CDC criteria (Holmes, Kaplan, Gantz, et al., 1988). As mentioned in section 1.3.3. this may bias the sample to a more somatoform group.

The assessment of somatisation rates is generally problematic. Whether to attribute primarily physical symptoms as 'somatic' or 'real' complaints is entirely up to the physician. A study into somatisation disorder in CFS clinic outpatients reported that rates varied from 0 to 98%, depending on such decisions (Johnson, De Luca, & Natelson, 1996).

Given that many depressive scales include a large proportion of somatic complaints, we might expect that estimates of depression may vary according to these. However, as discussed later studies excluding somatic complaints from depressive criteria suggest that these have little impact on delineation of depressed and non-depressed groups. It has been reported that on the BDI the somatic subscale failed to distinguish between medically ill patients and depressed patients (Ray, 1991). This further suggests that problems with the potential to be described as somatoform are not necessarily characteristic of depression in this group.

Figure 1.5.2.2 Average prevalence of psychiatric symptoms in CFS using Holmes CDC Criteria



(adapted from David, Wessely, & Pelosi, 1991)

In summary then, though reports of prevalence vary, approximately 50% of patients report depressive symptoms, 25% experience other psychiatric problems and approximately 30% are free from psychiatric complaints. These symptoms are reported

at higher levels than found in general primary care populations, however as noted below, these elevated levels are not unique to CFS.

1.5.3. Depression, Anxiety, Cognition and CFS

Of particular note is the difficulty in attributing the reported neuropsychological symptoms of fatigue to either CFS or depression or anxiety. This is more especially the case given that case criteria do acknowledge the presence of affective disorders in these patients, and that neuropsychological problems are reported in such patients. The presence of cognitive deficits is widely accepted in both depressive illness (see Rush, Weissenburger, Vinson, & Giles, 1983, Elliott, McKay, Herrod, et al., 1996 and the references therein) and anxiety (Mueller, Elser, & Rollack, 1993, Markham & Darke, 1991, Coldwell, Milgrom, Getz, & Ramsay, 1997, Mogg, Bradley, & Williams, 1995). Furthermore, patients reports of mental fatigue have not always correlated with their objective measurement (Grafman, Schwartz, Dale, et al., 1993, McDonald, Cope, & David, 1993) but do correlate with mood (Grafman, Schwartz, Dale, et al., 1993).

A potential problem in CFS research is the separation of such co-morbid symptoms from those of CFS; if not adequately controlled for, cognitive problems typical of depression or anxiety, may be misrepresented as characteristic of CFS. For example Krupp, Sliwinski, Masur, and Freidburg (1994) report that apparent differences between CFS and controls are reduced when depression scores are considered.

For those studies using the CDC Criteria (Holmes, Kaplan, Gantz, et al., 1988) the presence of comorbid psychiatric states is an exclusion criteria; few studies therefore control for the effects of such symptomatology on performance. Whilst the results from these studies may be suggestive of cognitive deficits present in CFS, it should also be remembered that this group, without comorbid diagnoses, may not be typical of the larger group of CFS patients. In a study by De Luca et al. (De Luca, Johnson, Ellis, & Natelson, 1997) there were a greater number of psychiatric problems in CFS patients with gradual onset of fatigue, rather than definite onset. Additionally, it may be that unevaluated subclinical levels of depression, and anxiety impact on cognitive performance. For the remainder of criteria, comorbid depression is a recognised, but not necessary, symptom. Here then, the evaluation of the effects of depression on

performance is important if symptoms of depression are to be separated from symptoms of fatigue.

Within the literature a variety of methods have been used to assess the effects of these confounds on cognitive performance. These range from correlations of CFS mood ratings with performance, to comparison of the performance of CFS with depressed patients. As may be expected the use of differing CFS groups and statistical and experimental methods may produce inconsistent results. The relative paucity of research, together with the aforementioned methodological difficulties thus adds to the difficulty already inherent in assessing this confounding variable.

The specific results of these studies will be considered in chapter 2, in order to properly assess the effects of co-morbidity on cognitive performance in these groups. This will be done with respect to each of the following domains: attention/concentration, higher intellectual function, verbal and visual memory and information processing speed.

1.5.4. Medication, cognition and CFS

As a result of the high rates of concurrent symptoms of depression and anxiety, therapeutic drugs are widely used in treatment (Lynch, Seth, & Montgomery, 1991). As a consequence of such morbidity profiles these are generally antidepressants or anxiolytics. The effect of such medication on cognitive performance has long been a subject of investigation; since many patients on these drugs will maintain working status attempts have been made to reduce such effects, with varying degrees of success. A full review of the effect of drugs on cognitive function is beyond the scope of this thesis, but for review see Amado-Boccara, Gougoulis, Poireier Littré, et al. (1995).

Though the role of drugs in facilitating and inhibiting cognitive function has long been investigated in other populations, there are few placebo controlled trials on their use in CFS. Those studies that have been completed have more often concentrated on the effects of such drugs on the physical side of fatigue, rather than the cognitive or psychiatric symptomatology. Since the role of antidepressants and anxiolytics have been little evaluated, reference to effects in healthy populations may serve to illustrate possible effects. Reported improvements in only the psychiatric symptomatology of CFS patients may do little to illustrate probable influences on cognition. Unfortunately, it is equally plausible that if improvements are seen in comorbid psychiatric symptoms,

that these may positively impact on cognitive function or, that side effects may result in reduced function. Several studies have been undertaken looking at overall symptom evaluation, again these have not been specifically cognitively orientated. Conclusions can therefore, be little more than tentative or speculative as regards such effects on cognition.

One study has controlled for the effects of drugs on cognitive performance (Marcel, Komaroff, Fagioli, et al., 1996), this was by covariance, rather than a controlled trial. Patients on drugs performed significantly better on set shifting and worse on digit span forward tasks, with no effect being observed on category fluency and word monitoring tasks. Though it is stated that medication was primarily low dose antidepressants, specific types of drugs, e.g. anxiolytics versus antidepressants or subtypes of drugs, for example SSRIs (selective serotonin reuptake inhibitors) versus TCAs (tricyclic antidepressants), were not compared. As discussed below, such factors may differentially affect tests of cognitive performance.

For the population of patients tested in this thesis, SSRIs and TCAs are generally used for antidepressant therapy, or for the potential alleviating nature of their side effects. As in depression mono-amine oxidase inhibitors (MAOIs) are rarely used (British Medical Association & Royal Pharmaceutical Society of Great Britain, 1996); whilst the most commonly used anxiolytics are benzodiazapines. Potentially many of these drugs may have sedative side effects.

TCAs have long been regarded as having the capacity to be sedative, however despite this, a wide range of both negative and positive effects on performance have been documented in non-CFS patients. These effects range from the worsening to the improving of psychomotor performance, though improvements in cognition tend to be more apparent in depressed populations (Deptula & Pomara, 1990). Since TCAs are effective antidepressants, that they may improve cognitive function in depressed populations is not surprising; though they have also been associated with cognitive impairment in healthy controls (British Medical Association & Royal Pharmaceutical Society of Great Britain, 1996). Negative effects on cognition have been reported in non-depressed populations (Clayton, Harvey, & Betts, 1997) on tests of: reaction time and memory scanning with imipramine (Clayton, Harvey, & Betts, 1997); Critical Flicker Fusion Threshold (CFF); and increased tracking error and short term memory

with amitryptaline (Hindmarsh, 1998). In contrast, another study (Ferris, McCarthy, Reisberg, et al., 1980) showed no significant effects on tests of other cognitive functions, such as reaction time and digit symbol substitution, at single doses of 50mg imipramine or 100mg zimeldine.

There has been some controversy arising from anecdotal reports (Lynch, Seth, & Montgomery, 1991), over the efficacy of medication such as TCAs in CFS. It has been suggested that the drugs may have sedative and autonomic side effects. However, improvements in depressive symptoms of CFS patients have been noted with newer tricyclic drugs, such as lofepramin (Lynch, Seth, & Montgomery, 1991). It is equally plausible that since TCAs are effective antidepressants if used appropriately and effectively in the treatment of depressive symptoms in CFS, that cognitive function may be returned to near normal levels; alternatively they may result in reduced function as a consequence of side effects.

Given the lack of research into the sedative characteristics of TCAs in CFS patients, SSRIs such as Fluoxetine, are therefore more generally recommended than the TCAs (Vercoulen, Swanink, Zitman, et al., 1996). SSRIs are generally regarded to have fewer sedative side effects than TCAs. Again, as with the TCAs, there are few studies into the effects of such medication on objective or subjective cognitive symptoms of CFS patients. However, the effects of fluoxetine have been investigated.

Vercoulen, Swanink, Zitman, et al. (1996) conducted a double-blind placebo controlled comparison of fluoxetine in 44 depressed CFS patients and 52 non-depressed CFS patients. At the recommended dose for depressed patients (20mg daily), for 8 weeks, there were no differences from placebo on the ratings of fatigue or depression or on objective measures of cognitive performance. Specifically speed of information processing was measured using a complex reaction test with three levels increasing in difficulty, reaction time and motor speed were assessed separately. As the potential confounds of fatigue and depressive symtomatology did not improve, and cognitive performance showed no change it appears likely that the 20 mg dose of fluoxetine did not impact upon cognitive performance in this population. Supportive evidence comes from a more recent study. Again using a placebo controlled trial of fluoxetine (Wearden, Morriss, Mullis, et al., 1998) at 20mg doses, over 26 weeks, there were no significant effects on functional work capacity, at either week 12 or 26. A significant improvement in depression on week 12 was noted, but this was not present at week 26

of administration. These two studies, however, do not necessarily suggest that cognitive performance will be unaffected at doses of 20 mg. In the first study speed was measured and was unaffected; in the second study objective measures of cognitive performance were not made. It may be that doses resulting in attrition of symptoms were accompanied by other unmeasured cognitive improvements, or in side effects, concomitant with a reduction in cognitive performance.

Despite the rare use of MAOIs in CFS their impact on function has been assessed (Natelson, Cheu, Pareja, et al., 1996). A double blind placebo controlled trial over 3 two week periods was conducted on 18 CFS patients. Here patients on 15mg phenalzine daily showed improvement in subjective function on 11 tests incorporating measures of physical fatigue severity, confusion, activities of daily living and mood. Unfortunately the analysis was not performed on the cognitive sub items of these scales, so phenalzine effects on these symptoms are unclear. Interestingly, the authors report that these improvements were not attributable to an antidepressant effect since the depression component of the POMS showed no improvement. In a study into one of the newer reversible MAOIs (White & Cleary, 1997), moclobomide, at doses of 600 mg per day for 6 weeks, there was an improvement in fatigue, depression, anxiety and somatic symptoms; the largest improvement being seen in the depressed group. Again, there was no mention of the effects on cognitive symptoms.

More recently a newer selective nor-adrenaline re-uptake inhibitor (NARI), reboxetine has been available as an antidepressant. A study on the behavioural toxicity of reboxetine (single dose 4 mg) in a population of 10 healthy male volunteers (Hindmarsh, 1998), showed that it had no effect on cognitive performance of Critical Flicker Fusion Threshold (CFF) threshold, increased tracking error and short term memory, as compared to placebo. Sedative or negative effects do not appear to be present with the newer agents. There are as yet no studies on the effects of reboxetine in CFS, though they are used by patients within this group.

There are no studies on the effects of anxiolytics in CFS populations, on any aspect of functioning. Generally, within both healthy and anxious subjects, they are thought to result in sedation. Sedation has been reported to effect: reaction time, with 25 mg of diazepam in healthy controls (Unrug, vanLuijtelaar, Coles, & Coenen, 1997); and story recall, recognition and word recall, and at therapeutic doses of 0.50 and 0.75mg of

alprazolam in surgery patients (Coldwell, Milgrom, Getz, & Ramsay, 1997). However in contrast, clobazam is reported to have no sedative side effects on memory (digit span, telephone number recall, map route and information storage) (Hindmarsh, 1995) and no effects on psychomotor performance or driving (Hindmarsh, 1995). Within a CFS group it may be that cognition is affected by the sedative properties of anxiolytics or symptoms are alleviated by the therapeutic effects on the symptoms of anxiety.

The use of drugs in the research CFS population is therefore a major and poorly defined methodological issue. As reviewed above, there is little evidence that antidepressants result in a change in cognitive function in a CFS group. However, this may in part be a lack of effect on depressive symptoms impacting on secondary cognitive symptoms. With MAOIs improvements have been documented, though these do not seem to be a result of therapeutic gains in depression. With respect to anxiolytics no work has been completed, making speculation of probable effects difficult.

Given this lack of explicit medication effects within the population, it could be considered surprising that patients maintain medication during research. However, though in some studies patients may be 'drug' free, medication free research has some degree of risk associated with it (Carpenter, 1997), involving untreated depressive symptoms for example, hence it is preferable to maintain therapeutic medication. Although for the patient 'risk' is reduced, for the researcher this represents an additional source of error. Firstly, between study comparability may be reduced, due to the introduction of possible variance in drug use between studies. Secondly it may result in a possible unmeasured or un-measurable 'drug' effect, the latter as a result of small numbers and wide differences in medication use. The use of particular drugs may vary both between and within tertiary primary care centres, since the medication appropriate for one patient may be inappropriate for others; thus resulting in further comparability problems. Additionally the pattern of drug prescribing has been shown to vary over time; for example there was almost a 10 fold increase in the dispensing of prescriptions for SSRIs between 1990 and 1996, whereas TCA dispensing rose by only about 17% (Wilkinson & Statistics Division, 1998).

Given these possible, and as yet largely undefined additional sources of variability, the drug status of patients is important in the distinction of cognitive symptoms from

possible drug side effects. Where these have not been sufficiently considered in research, findings should be considered more tentatively.

1.6. General Sources of variability

As discussed earlier differences in criteria (section 1.36), individual differences in the comorbidity of patient samples (section 1.3.7.) impact on the results obtained by particular studies and add to apparent conflict in those reported. There are, however, a number of further sources of apparent differences in outcome between studies. Included amongst these are the multi-factorial aetiology, small sample sizes, biasing in sampling and the stability of diagnosis. Such factors need to be considered both when looking at conflicting results and in designing future research, since they will necessarily result in variation in sample characteristics and impact on results.

1.6.1. Multi-factorial aetiology

Many investigations have been made into the causes of CFS. Mechanisms have been postulated from the disruption of the hypothalamic pituitary axis (see Wessely, 1995 for a summary), to associations with pre-morbid life events (Masuda, Nozoe, Matsuyama, & Tanaka, 1994) and illness perceptions (Ray, Weir, Cullen, & Phillips, 1992, Moss-Morris, Petrie, & Weinman, 1996). As Butler and others (David, Wessely, & Pelosi, 1988, Butler, Chalder, Ron, & Wessely, 1991), have cogently argued the aetiology of CFS is likely to be multi-factorial, with no one factor being sufficient for development. This multi-factorial aetiology may compound the already high variability within and between research samples. Such high heterogeneity may impact on the already prevalent inconsistency in reported deficits. Given the sample sizes used, typically of the order of 20 to 30 CFS and controls (see appendix I for a summary of CFS studies), it is likely that the aetiology between and within particular CFS samples will vary more widely.

A recent study by De Luca et al. suggested that the cognitive performance of CFS patients varied according to whether the onset of fatigue symptoms was definite or more gradual (De Luca, Johnson, Ellis, & Natelson, 1997). Specifically, though both subgroups showed impairments they suggest that those with definite onset in addition

to showing processing difficulties may also experience impairment in memory performance. Since such onset factors may further affect the variability of patient characteristics conflicting results may be expected even when other facts such as differing criteria and morbidity levels are addressed. There is thus a need to look at the majority of reports with the expectation that results will show poor agreement simply because samples vary widely. If the majority of reports have sound method and design, then a consensus of deficits may be reached.

1.6.2. Power

Though power estimated for a single comparison between 2 groups of 25 subjects suggests a 29 % chance of type II error, for the CFS population this is likely to be an underestimate. Inherent within the CFS population, is variability in characteristics as mentioned above, and in cognitive performance. Greater variability, in the absence of significant between group differences in cognitive test scores has been reported in a number of studies (Grafman, Schwartz, Dale, et al., 1993, Fry & Martin, 1996).

Since power depends on the degree of overlap between the 2 distributions, i.e. the effect size, and this effect size is likely to be reduced with the large sample variance of the CFS group, power will be reduced. A recent study reported variations in power from 0 to 65%, depending on the test used (Marcel, Komaroff, Fagioli, et al., 1996). An additional problem with samples of the size typically used is that as mentioned above there is opportunity for a greater heterogeneity than would be expected with non CFS population. There is thus an increased chance that the null hypothesis may be incorrectly accepted, and there is a greater need for well defined CFS groups, larger sample sizes and a consideration of the possible confounding variables.

1.6.3. Sample Bias

There are two primary sources of bias operating in most studies into cognitive function: bias in population characteristics and bias in fatigue severity of presenting patients. These biases may result in differences in duration, severity, course and nature of fatigue, and results reported may therefore be specific to the group tested, rather than more generalisble.

Typically studies investigate problems in well-defined groups of CFS patients, who are attendees of tertiary care clinics. In part this is due to the difficulty of defining CFS in primary care as a 6 month duration is necessary for fulfilment of case criteria. Though such sample selection overcomes many difficulties involved in recruiting the number of patients needed to perform investigative studies, the features of such samples have been reported to differ (Euba, Chalder, Deale, & Wessely, 1996). Those patients in tertiary care are more likely to be from a higher socio-economic class, less likely to be married or cohabiting than the primary care sample. They also report higher functional impairment, fatigue levels and somatic symptoms than the non hospital group, and were more likely to attribute their symptoms to physical rather than psychological or psychosocial causes (Euba, Chalder, Deale, & Wessely, 1996). The results of studies of cognitive function may thus differ between primary and tertiary care. The results of those studies done in tertiary care should not be regarded as generalisable to the larger CFS population.

Although tertiary care samples are reported to experience greater severity of fatigue, it is still the case that patients with the most severe symptoms are still not tested. Studies using tertiary care populations have noted that failure to find large effects may be a result of patients who are experiencing more severe symptoms declining to participate (Lakein, Fantie, Grafman, et al., 1998, Marshall, Forstot, Callies, et al., 1997).

1.6.4. Stability of diagnosis

A further problem arises with respect to the stability of diagnoses according to these criteria. Concerns about the predictive validity have been raised (Lynch, Main, & Seth, 1991). It is reported that using the CDC criteria (Holmes, Kaplan, Gantz, et al., 1988), the Australian Criteria (Lloyd, Wakefield, Bougton, & Dwyer, 1988), and the OCC criteria (Sharpe, Archard, Banatvala, et al., 1991) 46 CFS patients were identified on initial assessment; however, at 18 month follow up only 73% of the patients still fulfilled the criteria for CFS. Whilst some decrement in numbers may be a result of spontaneous recovery, it is cause for concern that some of these patients developed other illnesses which retrospectively explained the initial symptom complex. These included schizophrenia and connective tissue disorders. These re-test figures are low and the results suggest a further possible source of heterogeneity within samples.

1.6.5. Neuropsychological test use

Well validated and reliable scales such as the WAIS and the WMS-R are often used in researching cognitive difficulties in CFS (for a review of studies see Tiersky, Johnson, Natelson, & De Luca, 1997 and Appendix 1.1). Such scales are accepted as useful tools in deciding what sub-processes may be difficult for patients, for example, digit span reflecting short term memory. However, there have been conflicting results reported in neuropsycholgical test results of CFS patients, as well as discrepancies in the cognitive theories deduced from these deficits. Though inconsistent explanations of cognitive problems in CFS partly arise as a result of differing methodologies, discussed earlier, culpability also rests on the complexity of the mental processes being assessed by these tests.

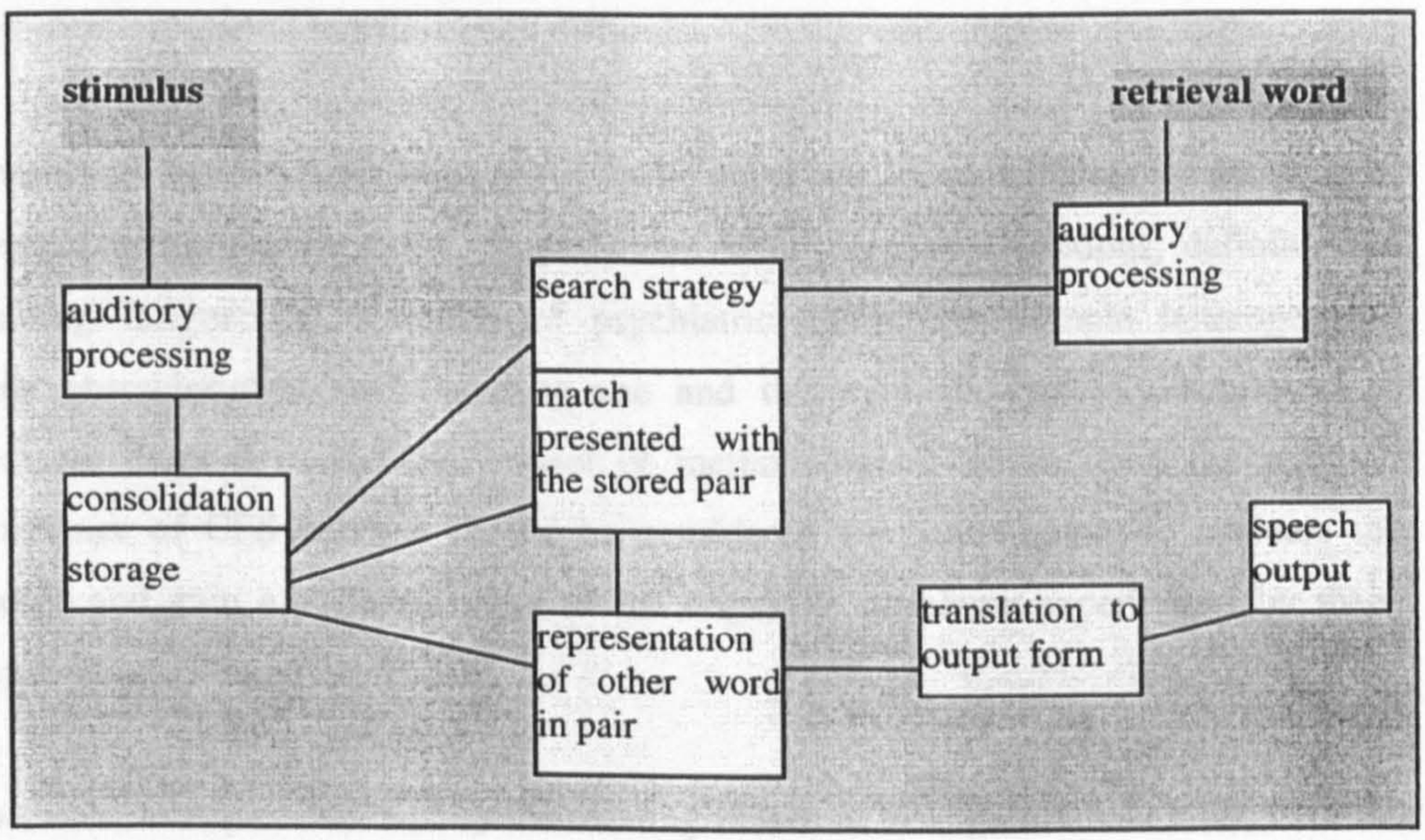
Processes as measured by standard neuropsychological tests are reasonably complicated, in that they involve the integration and use of a number of different functions (see the postulated processes involved in paired associate learning Figure 1.6.5.). Even the most simple tasks are multi-stage, or multi-process. It is therefore difficult to determine at which stage the problem has arisen in a particular functional deficit. Additionally some deficits may be sufficient to cause a describable disruption of function, but not necessary, further complicating explanation.

Caution is needed when such tests are used in attempting to define the processes underlying subjectively experienced difficulties in syndromes of a somewhat unknown nature. To illustrate, suppose that CFS patients showed problems on tests of Paired Associate Learning, we could adopt a classical approach and suggest that there are temporal lobe deficits or abnormalities as could be measured by SPECT, MRI. However, deficits may not be at consolidation levels or retrieval levels, but for example at output representation level. If a number of tests are used such factors may become apparent, however, in investigative research unitary tests are often used to infer particular problems.

These problems of interpretation can be clearly seen with the differing explanations of particular test scores in the CFS literature. For example significant differences between CFS patients and controls have been reported for the Digit Symbols test, suggesting problems with attention (Michiels, Cluydts, Fischler, et al., 1996), together with no

differences suggesting that there are no problems with visuomotor skills (Krupp, Sliwinski, Masur, & Freidburg, 1994). The Digit Span Subtest from the Weschler Adult Intelligence Scale Revised (WAIS~R) and the Weschler Memory Scale Revised (WMS~R), are used to assess attention (Clayton, Harvey, & Betts, 1997) or short term memory (Grafman, Schwartz, Dale, et al., 1993). Though there is consensus on the neuropsychological function measured by some tests, for example the trail making test as a measure of attention (Michiels, Cluydts, Fischler, et al., 1996, Riccio, Wilson, Thompson, et al., 1992, De Luca, Johnson, Beldowicz, & Natelson, 1995), since these processes are reasonably complicated, caution is needed when trying to infer explanations from poor test performance.

Figure 1.6.5. Simplified Schematic representation of processes involved in the Paired Associate Learning Task



Eight word pairs are read to the subject, these pairs are to be remembered. Retrieval is then initiated by the articulation of one word of the pair, the subject must then recall the second member of the pair. As can be seen, despite simplification, there are many steps involved.

To summarise, care should be exercised when using these clinical tools for investigative studies; standard neuropsychological tests are not deficit specific. It is important to remember that if neuropsychological tests show deficits these are not sufficient to infer particular unitary causes; though they may aid explanations. Given

the inadequate understanding of the causes of experienced difficulties in CFS, it is perhaps time to move from these tests to those designed to test specific theories. A probable corollary of neuropsychological test use is that explanations of cognitive fatigue conflict and as the recent RCP report (Wessely, 1997) notes, at present no particular pattern of deficits has been found.

1.7. Conclusions

Though CFS is often thought of as a relatively new disease, there is evidence to suggest that similar clusters of symptoms have been around for centuries, varying only in their appellations and more specific symptoms. Whilst the search for the physical and cognitive correlates of CFS has been more prevalent within the last 15 years, this work has been hampered by methodological issues and comparability problems. There are often discrepancies in outcome between studies and defining which aspects of cognition are impaired has thus been difficult.

A number of factors have been particularly important in contributing to the lack of consensus within the literature, in particular: multiple case definitions; defining and measuring fatigue; co-morbidity of psychiatric symptoms; sample heterogeneity; sample characteristics such as drug use and the methods typically employed to investigate these deficits. The impact of methodological issues upon the reported performance of CFS patients should be considered when attempting to evaluate the literature and gain a coherent view of the cognitive problems experienced by these patients.

Thus the next chapter will survey the existing literature in cognition and CFS, with the expectation of finding conflicting data. In this comparison between CFS and healthy controls it will discount those studies which suffer from a lack of control group (Altay, Toner, Brooker, et al., 1990, McDonald, Cope, & David, 1993, Schmaling, DiClementi, Cullum, & Jones, 1994); given that these are able to offer little insight into the problems experienced by patients. The latter two of these studies (McDonald, Cope, & David, 1993, Schmaling, DiClementi, Cullum, & Jones, 1994) will however be included in the evaluations of the effects of depression and anxiety on the performance domains reviewed. Where discrepancies are found between reports, methodological

confounds that are likely to impact upon performance will be considered in an attempt to gain valid conclusions on the cognitive difficulties experienced by these patients.

Chapter

2

Cognition and Chronic Fatigue Syndrome

2.1. Introduction

Despite the relative recency of studies into neuropsychological deficits, there has been research into a wide range of cognitive processes. Komaroff, Fagioli, Geiger, et al. (1996) suggested that 83% of CFS patients have difficulty concentrating, 71% experience forgetfulness, and 31% have difficulty thinking. Though there are subjective reports of impaired memory, concentration difficulty and dyslogia and these problems are included as diagnostic symptoms for the Oxford Consensus Criteria (Sharpe, Archard, Banatvala, et al., 1991) and the CDC Criteria (Holmes, Kaplan, Gantz, & et al., 1988) for CFS the underlying causes remain largely undetermined.

In many cases the comparability between studies is tenuous. Results of research conflict, or fail to find objective substantiation of complaints; probably, as discussed in the previous chapter, because of differing methodologies and sample characteristics. As may be expected the aforementioned methodological differences may result in inconsistency within the results. In this chapter, for clarity, the cognitive literature will be surveyed according to the following domains: higher intellectual function; visual and verbal memory; and attention and speed of information processing. The assessed role of depression and anxiety within these domains will be discussed, before domain conclusions are presented. The hypothesis that these cognitive problems may be a result of slowed processing will then be considered.

2.2 Higher Intellectual Functions

A wide range of higher mental functions have been assessed; these include time perception, set shifting, executive planning, problem solving, concept formation, and abstract reasoning. Whilst neuropsychological tests are accepted to be largely measures of these higher functions they are not specific to these functions. However in this context it is only if deficits are apparent that elucidating their composition becomes problematic. With few exceptions tests of higher order function have been reported to be unimpaired in CFS patients compared to controls.

Time perception has been assessed with Time Wall and Time Clock tests (Grafman, Schwartz, Dale, Scheffers, Houser, & Straus, 1993). The Time Clock Test requires the estimation of one minute of time, by the tapping of a key for every second of that minute. The Time Wall Test involves the 'disappearance' of a block half-way down a screen. Subjects are required to estimate when the block will reach the bottom of the screen. It is reported that there are no differences between CFS patients and controls on mean scores for either of these tests, though the CFS patients were more variable in their performance (Grafman, Schwartz, Dale, et al., 1993).

Tests of planning, reasoning and problem solving include block design, if visuospatial perception is excluded, object assembly, the Towers of London and Hanoi, Trail Making and 20 questions. There are no deficits reported on problem solution of the Tower of London and Tower of Hanoi when CFS patients are compared to controls (Grafman, Schwartz, Dale, Scheffers, Houser, & Straus, 1993). Indeed CFS patients solved more problems on the Tower of London task, though made more errors than the age and education matched controls (Grafman, Schwartz, Dale, Scheffers, Houser, & Straus, 1993). In contrast to the previously mentioned intact planning, a reduced strategy score for spatial working memory has been reported (Joyce, Blumenthal, & Wessely, 1996). Tests of categorisation require patients to discern the rules on which the categorisations are based and to discover new rule systems when arbitrary changes are made. CFS patients are reported to have intact performance on the Booklet category test (De Luca, Johnson, Beldowicz, & Natelson, 1995, Krupp, Sliwinski, Masur, & Freidburg, 1994, Joyce, Blumenthal, & Wessely, 1996) and the Wisconsin Card Sorting Test (Riccio, Wilson, Thompson, Morgan, & Lant, 1992, Sandman, Barron, Nackoul, Goldstein, & Fidler, 1993). Nor are there any reported deficits in CFS patients on

Symbol Digit Modalities Test, Block Design or Object Assembly subtests of the WAIS~R (Krupp, Sliwinski, Masur, & Freidburg, 1994).

Performance measures of verbal fluency include category naming, the Controlled Oral Word Association Test and graded naming tests. These show a generally unimpaired performance by CFS patients (Krupp, Sliwinski, Masur, & Freidburg, 1994, Cope, Pernet, Kendall, & David, 1995, Grafman, Schwartz, Dale, et al., 1993, Riccio, Wilson, Thompson, et al., 1992, Marcel, Komaroff, Fagioli,et al., 1996); with few studies reporting impairment in CFS patients (Joyce, Blumenthal, & Wessely, 1996, Marcel, Komaroff, Fagioli, et al., 1996).

2.2.1 Depression and anxiety:

For those deficits that have been noted, the authors report that the differences cannot be accounted for by depression. Specifically, since the CANTAB profiles for depressed patients differed from CFS patients (Joyce, Blumenthal, & Wessely, 1996), it was reported that impairments found were not likely to be attributable to depression. However the reduced strategy scores on spatial working memory (Joyce, Blumenthal, & Wessely, 1996) and impaired verbal fluency (Joyce, Blumenthal, & Wessely, 1996) were found in a group of CFS patients which was significantly more depressed and anxious than controls. Though the levels of comorbidity were sub-clinical they may still have affected performance and thus accounted for the observed deficits. In the study by Marcel, Komaroff, Fagioli, et al. (1996) covariance of global psychiatric with category fluency scores suggests that the verbal fluency deficits observed were not the result of depression or anxiety (Marcel, Komaroff, Fagioli, et al., 1996). Correlation analysis illustrated that greater variability of scores on Time Perception (Grafman, Schwartz, Dale, et al., 1993) was not attributable to depression scores of these patients.

2.2.2. Conclusions

As discussed above, and elsewhere (Tiersky, Johnson, Natelson, & De Luca, 1997), there are few differences reported in tasks of higher intellectual function. The majority of studies report that in tests of higher mental functioning CFS patients perform with no more errors than controls; visuomotor skills, time perception, problem solving, organisation, ordering and planning appear to be unaffected. Where deficits are

reported it is possible that these may be accounted for by presence of psychiatric symptoms.

2.3. Memory

A typical measure employed to assess memory in CFS patients has been the WMS-R (Wechsler, 1987). It has been reported that CFS patients have a general memory quotient lower than controls (Marcel, Komaroff, Fagioli, et al., 1996, Grafman, Schwartz, Dale, et al., 1993), though there may be no measurable differences on the analysis of specific subtests (Grafman, Schwartz, Dale, et al., 1993). Despite this a number of studies report differences between CFS and controls on subtests of the WMS, though there is disagreement between studies as to which subtests are impaired. Memory has also been studied with recourse to other measures, discussed below, which assess auditory and visual stimuli and use both verbal and non-verbal stimuli.

2.3.1. Non-verbal Memory

2.3.1.1. Pattern Memory

With the exception of one study (Marcel, Komaroff, Fagioli, et al., 1996) there are no deficits reported in item retrieval for non-verbal stimuli, though deficits have been reported in memory for location of such stimuli. Specifically, it has been reported that there are no deficits on visual memory subtests of the WMS-R (Riccio, Wilson, Thompson, et al., 1992). This is supported by Grafman, Schwartz, Dale, et al. (1993), who report no differences for either the Immediate or Delayed Visual Associate Learning subtests of the WMS-R. No differences are reported on the Graded Naming Test For Pictures (Cope, Pernet, Kendall, & David, 1995) or Pattern Memory (Joyce, Blumenthal, & Wessely, 1996). Nor are there any differences reported in pattern memory as measured by the Benton Visual Retention Test (Krupp, Sliwinski, Masur, & Freidburg, 1994), the Rey Complex Figure Test (De Luca, Johnson, Beldowicz, & Natelson, 1995, De Luca, Johnson, Ellis, & Natelson, 1997, Christodoulou, De Luca, Lange, et al., 1998) or as assessed by CANTAB (Joyce, Blumenthal, & Wessely, 1996). Furthermore CANTAB measures illustrated no deficits in simultaneous and

delayed matching to sample with patterns, nor in the spatial recognition of patterns or visual association learning (Joyce, Blumenthal, & Wessely, 1996). In contrast, Marcel et al. report that CFS patients are worse than controls on pattern recognition (Marcel, Komaroff, Fagioli, et al., 1996). Memory for the location of patterns has been reported to be impaired; CFS performing worse than controls (Michiels, Cluydts, Fischler, et al., 1996).

2.3.1.2. Face Recognition

Despite few documented instances of prosopagnosia in CFS, research has also looked at facial recognition. Much has been written about the 'specialness of faces' regarding their processing, recall and recognition (Farah, 1996, Bartlett, 1932) suggesting that facial recognition is separate from object recognition. The only set of reported results on face recognition in CFS (Cope, Pernet, Kendall, & David, 1995) used the Warrington Facial Recognition Test. This test involves the incidental learning of 50 faces by rating them for pleasantness, followed by a deliberate recognition task. The authors reports that there were deficits in CFS patients who performed worse than controls (Cope, Pernet, Kendall, & David, 1995).

2.3.1.2.1. Depression and anxiety

Though the CFS group in the above mentioned study (Cope et al., 1995) performed significantly worse than controls, they scored very similarly to the depressed group; whilst curiously sub-clinical levels of depression in CFS were associated with a reduction in deficits. These deficits were not correlated with anxiety and depression; statistical analysis for differences between CFS, CFS depressed, depressed and controls was not significant at the 5% level, ($F(3,58)= 1.9$, $p=0.14$), on this measure. Given the relatively small numbers in the above study, 26 CFS subjects split into two groups, and the analysis used; it is possible that performance may have been affected by comorbidity of psychiatric symptoms and not have been detected.

2.3.1.3. Conclusions Non-verbal Memory:

Given that there do not appear to be differences on tests of object and pattern recall, if there are deficits they are probably specific to faces, rather than representing a general visual memory problem.

2.3.2. Verbal Memory

Tests of verbal memory have generally relied on both visual and auditory presentations of word stimuli, thus reducing the potential interpretation problem of a general visual deficit. A standard approach to the measurement of verbal memory has been to use sub-tests from cognitive test batteries, such as the Wechsler Memory Scale-Revised. Despite the high validity and reliability of such measures mixed results are reported.

2.3.2.1. Paired Associate Learning Task

The Paired Associate Learning Test from the WMS-R tests cued recall for words. The test involves the subjects being read a list of eight word pairs. One word from each of the pairs is then presented, subjects are required to produce the other word from the pair. Word pairs are either semantically related (easy pairs), or unrelated (hard pairs).

Data conflicts for CFS performance measures on the Paired Associates Test. Three studies suggest that there are no differences in total Paired Associate recall between CFS patients and controls (Krupp, Sliwinski, Masur, & Freidburg, 1994, Wearden & Appleby, 1997, Cope, Pernet, Kendall, & David, 1995). In opposition three further studies suggest that there are differences in total performance (Sandman, Barron, Nackoul, Goldstein, & Fidler, 1993, Grafman, Schwartz, Dale, Scheffers, Houser, & Straus, 1993, Riccio, Wilson, Thompson, Morgan, & Lant, 1992); CFS patients recalling fewer words than controls. This inconsistency in total performance may arise as a result of the composite scoring system which summates recall of easy and hard pairs to a total score. When the analysis of hard and easy pairs has been separated the deficit appears to be only restricted to performance on unrelated or hard pairs (Joyce, Blumenthal, & Wessely, 1996). In a total score these deficits on hard pairs may be partially masked by intact performance on easy pairs. Inconsistent results in total performance may arise as a result of differences in the sample composition particularly with respect to fatigue severity. This assertion is supported by the work of McDonald, Cope and David (1993) where high fatigue CFS patients performed worse than low fatigue patients on hard associate learning, easy pair performance being no different.

2.3.2.1.1. Depression and anxiety

Deficits reported for total performance on this test do not appear to be attributable to depression as assessed by correlation (Joyce, Blumenthal, & Wessely, 1996, Grafman,

Schwartz, Dale, et al., 1993) or when compared with depressed patient performance (Sandman, Barron, Nackoul, et al., 1993); nor are they associated with general mood state (Grafman, Schwartz, Dale, et al., 1993, Riccio, Wilson, Thompson, et al., 1992). In a comparison of CFS patients with depressed patients, it was reported that reduced recall on easy pairs was related to depression (McDonald, Cope, & David, 1993); in contrast deficits on hard pairs were not depression-related (Joyce, Blumenthal, & Wessely, 1996). No studies comparing CFS with controls have assessed the possible role of anxiety. A study of CFS with case-control comparisons suggested that anxiety was not significantly correlated with degradation of performance (McDonald, Cope. & David. 1993).

2.3.2.2. Verbal List Learning

Memory for verbal information has been assessed using measures of word recognition and recall. Recognition memory for lists of words has been tested using the Hasher Frequency Monitoring Test (Grafman, Johnson, & Scheffers, 1991) the Warrington Verbal Recognition Test (Cope, Pernet, Kendall, & David, 1995), the Californian Verbal Learning Test of verbal list learning and memory (CVLT) (De Luca, Johnson, Beldowicz, & Natelson, 1995), and the Six Trial Version of Selective Reminding (Krupp, La Rocca, Muir-Nash, & Steinberg, 1989).

The Hasher Frequency Monitoring Test involves the subjects being read a list of to-be-remembered-words, some of which are repeated up to 7 times. Subjects are required to complete a recognition task from a list of heard words and non-heard distractors estimating how many times each word has previously been encountered. It has been reported that CFS patients do not differ from controls with respect to word recognition from a previously presented list (Grafman, Johnson, & Scheffers, 1991, Grafman, Schwartz, Dale, et al., 1993). This lack of decrement in recognition of word lists is supported by the absence of deficits on the Warrington Recognition Memory Test (Cope, Pernet, Kendall, & David, 1995), recognition on the CVLT (De Luca, Johnson, Beldowicz, & Natelson, 1995, Fiedler, Howard, De Luca, Kelly-McNeil, & Natelson, 1997, Johnson, De Luca, Fiedler, & Natelson, 1994, Schmaling, DiClementi, Cullum, & Jones, 1994) and the Six Trial Version of Verbal Selective Reminding (Krupp, La Rocca, Muir-Nash, & Steinberg, 1989). Though the majority of tests of recognition suggest that there are no deficits observed, deficits have been reported on recognition memory tests (Smith, Behan, Bell, Millar, & et al., 1993). These patients also made

fewer erroneous hits, and it is suggested that the CFS patients were more cautious in their response.

Several studies have assessed free recall of word lists. With one exception, (Smith, Behan, Bell, Millar, & et al., 1993), all studies report that in CFS patients free recall of word lists is worse than in controls (Marcel, Komaroff, Fagioli, & et al., 1996, Smith, Pollock, Thomas, & Llewelyn, 1996, DeLuca, Johnson, Ellis, & Natelson, 1997, Marshall, Forstot, Callies, Peterson, & Schenck, 1997). It has been suggested however that these differences may not reflect memory problems but problems in learning verbal material, i.e. acquisitional difficulties (DeLuca, Johnson, Beldowicz, & Natelson, 1995). Further analysis of the CVLT free recall condition (DeLuca, Johnson, Beldowicz, & Natelson, 1995) suggests that if these purported differences in acquisition are used as covariates deficits on delayed free recall are attenuated (DeLuca, Johnson, Beldowicz, & Natelson, 1995).

2.3.2.2.1. Depression and anxiety

General psychiatric status (Marcel, Komaroff, Fagioli, et al., 1996) has been reported to have no effect on CFS patient performance of the free recall task. Additionally it has been reported that depressed CFS and non-depressed CFS patients do not differ in free recall performance, neither group being impaired (Smith, Behan, Bell, et al., 1993). In contrast one study suggested that where free recall deficits were reported in CFS patients (Smith, Pollock, Thomas, Llewelyn, 1996), only those patients with sleep abnormalities were impaired; these sleep abnormalities were reported to vary with trait anxiety, emotional distress and somatic symptoms (Smith, Pollock, Thomas, & Llewelyn, 1996). It is thus possible that sub-clinical depression plays a role in free recall performance. Further support for this assertion is given by Marcel, Komaroff, Fagioli, et al. (1996), who reported that depression played a role in poor immediate recall performance. Conflict over the contribution of somatic symptoms may arise since where no deficits are observed the role of depression is difficult to determine, and a general psychiatric score may mask the effects of particular sub-types of axis I symptoms. With one exception (Marcel, Komaroff, Fagioli, et al., 1996) the role of sub-clinical anxiety has not been evaluated, and this study suggested that anxiety had no effect on free recall performance.

2.3.2.3. Paragraph Recall

The studies discussed to this point have considered the recall or recognition of a single verbal stimulus. These tasks are rare in activities of daily living. Bartlett (1932) was probably the first to suggest that tests of 'story memory' were more ecologically valid. There are large differences between encoding, storing and retrieving of single stimuli and prose. Beyond access to word recognition and meaning, there are reported to be three main levels of analysis in sentence comprehension; the analysis of parsing, of literal meaning and of intended meaning (Clark & Lucy, 1975). There are several competing theories to explain the extraction of meaning from a section of text. These range from the bottom-up processing approaches to the top down processing approach of McKoon (McKoon & Ratcliff, 1992; McKoon, Gerrig, & Greene, 1996).

It has been suggested (Kintsch & vanDijk, 1978) that propositional meaning is extracted, this micro structure is then integrated with the macro structure in a temporary store for the extraction of meaning or gist. It is argued that 'macro rules' are applied to these collections of propositions; this may involve the deletion of unnecessary sentences and the replacement of propositions by either a more general proposition, or the inferred meaning of a collection of propositions. However, this theory takes little account of the role of schema on text understanding and consequently consolidation and retrieval. Top-down theories of text comprehension focus more heavily on the schema within which an individual interprets the text and inferences are drawn for the construction of meaning.

More generally it is accepted that the understanding of prose involves the analysis of text at several levels (word, sentence and gist) and the analysis of the syntactic structure, literal meaning and intended meaning. Inferences may be drawn within the frameworks of both the schema of the individual and the internal schema of the text. Recall of information from presented text is generally regarded as a dynamic and sophisticated process involving the extraction of elements of the 'story' within the framework of personal schema, then their elaborative reconstruction in recall (Loftus, Miller, & Burns, 1978). Much information may be disregarded initially as unimportant, whilst at recall items are subject to memory distortion.

The recall of prose can be regarded as highly conceptual involving much elaboration. Single word recall or sentence recall is far less conceptual even when levels of

processing are manipulated. It is generally found that this increase in cues provided by elaboration, gist and episodic interpretation at encoding facilitate recall, and it is reported that the provision of schema and background knowledge facilitate both text comprehension and the amount of retrieval (Bransford & Johnson, 1972).

Investigations with CFS patients have included the use of the logical memory subtest from the WMS-R and story memory testing, involving subjects being read 2 stories and the number of story units immediately recalled being recorded. Results differ. Several studies have reported that there are no differences between CFS and controls (Grafman, Schwartz, Dale, Scheffers, Houser, & Straus, 1993, De Luca, Johnson, Beldowicz, & Natelson, 1995, Krupp, Sliwinski, Masur, & Freidburg, 1994) on the logical memory task. Two studies report deficits; Grafman et al. reported reduced recall of story units for the second story given, though patients were unimpaired on the logical memory task (Grafman, Schwartz, Dale, et al., 1993). Riccio, Wilson, Thompson, et al (1992) also reported that immediate logical memory was worse in CFS patients than in controls; however they did not control for the effects of comorbid sub-clinical depression or anxiety levels.

2.3.2.3.1. Depression and anxiety

It is possible that these observed deficits and apparent conflict arise from patient differences in depression and anxiety. This is substantiated by the results of 2 studies. Krupp, Sliwinski, Masur, & Freidburg. (1994) report that there were differences in the number of story units recalled on this subtest of the WMS-R, but when they controlled for depression these were reduced. Comparisons of depressed-CFS patients with non-depressed also show that deficits in logical memory are restricted to depressed patients (Wearden & Appleby, 1997). Additionally, the combined anxiety and depression score is reported to correlate with memory scores (Wearden & Appleby, 1997).

2.3.2.4. Cue Provision

There are several methods typically thought to increase the amount of information retrieved from memory. Two of these are evident in the CFS research: increasing the conceptual information at study, as in paragraph recall; and increasing the number of cues at retrieval. As mentioned previously (section 2.3.2.3.) the reading, processing and retrieval of text represents a sophisticated process of a highly conceptual nature. This

may have provided CFS patients with additional information for the acquisition of material or additional conceptual routes available for retrieval; resulting in no measurable differences. Difficulties, however, have been exhibited by CFS patients when the external information available to aid retrieval is increased. The provision of cues at retrieval should aid performance on memory tasks. Healthy subjects typically demonstrate improved performance on cue provision particularly when the processing types between study and retrieval condition are matched. It should also be remembered that if CFS performance is worse than controls, this may be a result of failure to benefit from retrieval aids rather than a retrieval deficit.

On tests of retrieval using word pairs the provision of cues which increasingly overlapped with items given at study phase were of increasingly less benefit to CFS subjects (Sandman, 1992). They showed less benefit across a series of tests where the degree of cue provision was increased from partial to complete, where the word pair was given for recognition (Sandman, 1992). This lack of facilitation to retrieval has also been noted with performance on the paired associate test when a free recall task is also given. It was also reported that CFS patients recalled fewer words than controls in a cued recall condition though were not impaired in a free recall condition (Grafman, Schwartz, Dale, et al., 1993). A more recent study examined the differences between CFS and controls (Wearden & Appleby, 1997); though the ratio of cued to free recall was lower for CFS non-depressed than controls, these deficits were not significant (Wearden, 1998).

It has been suggested (Sandman, 1992) that this failure to benefit from the provision of external cues at retrieval illustrates an encoding deficit; since it would appear that the information is not there to be retrieved despite increasing cues. CFS patients may be performing at ceiling on the free recall tests, and therefore fail to benefit from cue provision. This is supportive of the acquisition difficulty proposed by De Luca *et al.* (De Luca, Johnson, Beldowicz, & Natelson, 1995). It has also been noted that CFS patients show an increased susceptibility to pro-active interference (Johnson, Lange, De Luca, Korn, & Natelson, 1997), which would impact on acquisition and speed of response, particularly in tests involving word pairs[1].

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[1] since the capacity of a cue to activate memory of the pair is associated with speed (see section 2.6.)

2.3.2.4. Depression and anxiety

These differences do not appear to be related to levels of comorbid depression. It is reported that there are no differences between CFS and depressed subjects (Sandman, Barron, Nackoul, et al., 1993). This is supported by a lack of correlation of depression and mood with performance (Grafman, Schwartz, Dale, et al., 1993). A further study reported that depressed-CFS patients were worse on free recall tasks rather than cued recall tasks and that this was probably a result of poor motivation (Wearden & Appleby, 1997).

2.3.2.5. Verbal Memory: Conclusions

It is generally reported that recognition memory for word lists is intact in CFS patients, this contrasts with performance on free recall measures. However free recall problems in CFS patients have been associated with sleep abnormalities and depression. Despite these comorbidity issues, the consistency of this documented deficit in free recall suggests that CFS patients may demonstrate deficits in tests of verbal list free recall. Caution is however needed regarding the possible role of depression in free recall tasks. Additionally it should be considered that these free recall difficulties may arise as a result of acquisitional problems rather than impairments in retrieval.

There are probably deficits in the hard paired associate measures, with CFS performance on easy pairs remaining intact. However, performance on easy paired associates may be impaired in the presence of comorbid depression. CFS patients have been reported to benefit less from the provision of cues at retrieval. This lack of benefit of context to retrieval may appear to directly conflict with the intact recognition performance on single word lists. However it should be considered that CFS patients demonstrate more susceptibility to interference at study, and may thus be worse when a word pair is given rather than a single word. It has been reported that these apparent difficulties with cueing are likely to be the result of problems with acquisition of information. It should also be remembered that problems with acquisition do not just involve attentive acquisition, but the creation and manipulation of representations for storage.

2.3.3. Implicit Memory

Most studies have concentrated on explicit memory performance, instances where the participants are aware that information is to be stored and will later be tested. Perhaps deficits on such tests are less apparent or differ from those experienced in real life situations where an advanced warning that material will later need to be retrieved is rarely given. Work done by Brindle, Brown, Brown, et al., 1991 suggests that implicit memory may have more to do with the subjective experience of memory than had been previously thought.

Only one study to date has measured performance on tests of implicit memory. Word stem completion was measured (Cope, Pernet, Kendall, & David, 1995). Priming scores were calculated by the subtraction of un-primed baseline response from primed completion response rates. There were no overall differences reported between either controls, depressed patients, CFS patients or CFS patients with concurrent depression. However there were no reported differences between groups on implicit or explicit memory performance generally. As there were no differences on explicit memory performance the author reports that there was perhaps little prospect of demonstrating a dissociation on word stem completion in this experiment. Furthermore, there was no correlation between subjective cognitive performance and implicit or explicit memory scores (Cope, Pernet, Kendall, & David, 1995).

2.3.4 Memory: Conclusion

Whilst there is disagreement as to whether there are deficits in memory, it is consistently reported that subjective cognitive deficits do not correlate with, or are not consistent with, their objective measurement (Cope, Pernet, Kendall, & David, 1995, McDonald, Cope, & David, 1993, Ray, 1993, Grafman, Schwartz, Dale, et al., 1993, Altay, Toner, Brooker, et al., 1990). Nor is meta-memory indicative of performance (Grafman, Schwartz, Dale, et al., 1993, McDonald, Cope, & David, 1993, Lakein, Fantie, Grafman, et al., 1998). Free recall performance deficits are probably the result of comorbidity. Recall and recognition of non-verbal stimuli appears to be unaffected, though memory for location of such patterns is impaired. There are no differences between CFS and controls on the recognition of word lists. Studies conflict over scores on the logical memory task. It is likely that levels of anxiety and depression may

contribute partially or totally to impaired performance. There are deficits apparent on paired associate learning tasks, these appear to result from performance problems on hard pairs. Patients appear to benefit less from cue reinstatement. To date there has been only one investigation on implicit memory in these patients; this found no differences between groups (Cope, Pernet, Kendall, & David, 1995). Overall it appears that CFS patients have problems with some tasks of explicit verbal memory; these appear to be restricted to those tasks where the processing and formulation of new representations is required, such difficulties may manifest as an acquisitional problem.

2.4. Attention and Information Processing

Attention has been assessed using a number of tests traditionally used for this purpose. Specifically measures have included: the Digit Span subtest from the WMS-R; cognitive vigilance tasks; reaction time measures; Trail Making Tests A & B and the Classic Stroop. Some of the tests included here are also considered to be tests of information processing hence the integration of attention and processing in this section.

Though Digit Span loads on both working memory and attention it loads most heavily on the attention/concentration factor (Wechsler, 1987). Several studies have reported that there are no differences between CFS patients and controls on Digit Span measures (De Luca, Johnson, Beldowicz, & Natelson, 1995, Krupp, Sliwinski, Masur, & Freidburg, 1994, Smith, Behan, Bell, Millar, & et al., 1993, Johnson, De Luca, Diamond, & Natelson, 1996, Cope, Pernet, Kendall, & David, 1995). However two studies report that performance is worse (Michiels, Cluydts, Fischler, Hoffman, LeBonner, & De Mierlier, 1996, De Luca, Johnson, & Natelson, 1993) and one further study that performance is worse solely on Digit Span backwards (De Luca, Johnson, Ellis, & Natelson, 1997).

Vigilance and visual motor cancellation tasks have also been used to assess attention. People with CFS are reported to be impaired on target detection in a task of cognitive vigilance (Smith, Behan, Bell, Millar, et al., 1993, Smith, Pollock, Thomas, & Llewelyn, 1996). This is supported by performance on the star cancellation tests (McDonald, Cope, & David, 1993) when test results are compared to standard norm tables, and intact performance on a sustained cognitive vigilance task (Marshall,

Forstot, Callies, et al., 1997). However, CFS patients have also been reported to make more errors and take longer than controls on tasks of sustained attention (Vollmer-Conna, Wakefield, Lloyd, et al., 1997).

Tests of focused and divided attention have also been undertaken. There are no differences reported between CFS patients and controls on the embedded figures test (Ray, 1993); a test of focused attention. CFS patients show no differences from controls on tests where the switching or shifting of attention is required (Joyce, Blumenthal, & Wessely, 1996, Marcel, Komaroff, Fagioli, et al., 1996). It has also been reported that CFS patients were no worse on tests of divided attention (Vollmer-Conna, Wakefield, Lloyd, et al., 1997), this is consistent with the absence of deficits on tracking tests discussed below.

The Trail Making Test requires subjects to join consecutively numbered circles (part A) and to alternate between consecutive numbers and letters for part B. This task should be done as quickly as possible. It is therefore taken as a measure of both divided attention (maintaining alphabet and counting orders, whilst alternating between tasks) and of speed of visual information processing. There are generally no deficits reported on Trail making A & B (DeLuca, Johnson, Beldowicz, & Natelson, 1995, Krupp, Sliwinski, Masur, & Freidburg, 1994, Sandman, Barron, Nackoul, et al., 1993) (Riccio, Wilson, Thompson, et al., 1992) though Michiels, Cluydts, Fischler, et al. (1996) report that CFS were significantly worse. In this latter study not all patients fulfilled criteria, despite the fact that 14.2% of this sample were clinically depressed the deficits do not appear to be related to depression (Michiels, Cluydts, Fischler, et al., 1996). Overall the pattern is one of intact performance; this has been taken to mean that CFS patients are unimpaired on tests of divided attention and complex parallel visual processing

Whilst a number of studies have reported deficits in measures of both simple, and choice reaction time (Scheffers, Johnson, Grafman, & Dale, 1992, Smith, Behan, Bell, Millar, & et al., 1993, Prasher, Smith, & Findley, 1990, Marshall, Forstot, Callies, Peterson, & Schenck, 1997), two studies have reported that CFS were no worse than controls (Fiedler, Howard, DeLuca, Kelly-McNeil, & Natelson, 1997, Grafman, Schwartz, Dale, Scheffers, et al., 1993). This may be simply a result of type II error given the high standard deviations of patient scores on these measures, and the relatively low subject numbers. A lack of impairment in motor speed combined with

differences in choice RT would suggest that the impairments are at a more complex cognitive processing level than a simple motor response. However, it is undetermined as to whether these deficits arise, either in part or, in total as a result of motor slowing. There are no impairments noted in the performance of CFS patients on the Grooved Peg Board test (Fiedler, Howard, De Luca, Kelly-McNeil, & Natelson, 1997, Riccio, Wilson, Thompson, et al., 1992). No results were reported for the finger oscillation test (Krupp, Sliwinski, Masur, & Freidburg, 1994). However performance on finger tapping (Michiels, Cluydts, Fischler, et al., 1996) and tests of motor speed (Marshall, Forstot, Callies, et al., 1997) are reported to be slower than controls; these do not appear to be related to depression (Michiels, Cluydts, Fischler, et al., 1996), or affective disorders (Marshall, Forstot, Callies, et al., 1997).

The Classic Stroop (Stroop,1935) is considered to be a test of attention and distractibility. Several studies have reported slowing on this measure (Ray, 1993, Smith, Behan, Bell, Millar, & et al., 1993, Smith, Pollock, Thomas, & Llewelyn, 1996, Marshall, Forstot, Callies, Peterson, & Schenck, 1997). This has been taken to suggest that these patients are more distractible and have impaired concentration (Smith, Behan, Bell, Millar, et al., 1993, Schmaling, DiClementi, Cullum, & Jones, 1994). In contrast one study has reported no differences on the interference condition of the Stroop (Marcel, Komaroff, Fagioli, et al., 1996). On further analysis it would appear that all conditions of the Stroop have been reported to be slowed (Ray, 1993, Marshall, Forstot, Callies, et al., 1997). Two further studies suggest that when slowing in non-interference conditions of the Stroop is considered, CFS are not proportionally slower on the interference condition (Marshall, Forstot, Callies, et al., 1997, Ray, 1993). Furthermore in one study where deficits on the interference condition were noted it was only in those patients who also exhibited sleep disorders (Smith, Pollock, Thomas, & Llewelyn, 1996). It is probable that there may be a generalised slowing, but attention impairments, such as increased distractibility, are unlikely.

The pattern of results considered so far, particularly the general slowing, is not inconsistent with an underlying problem that manifests as, or is the result of, problems with speed of information processing. Problems with speed of information processing have been assessed with Event Related Potentials (ERPs), the PASAT (Paced Auditory Serial Addition Test), the PVSAT (Paced Verbal Auditory Serial Addition Test), time restricted tests and the previously considered Trail Making Test.

It is thought that speed of information processing may be directly investigated by measuring ERPs. These are small fluctuations in the electrical activity of the brain. They are time-related to both definable internal and external events such as auditory stimuli or motor activity and are thus divided into exogenous and endogenous ERPs, respectively. The cognitive processes involved in processing and responding to a stimulus result in an ERP known as the P3 wave. Diminished P3 amplitude is thought to reflect attention deficits relating to the amount of information processed; whereas delayed P3 are thought to reflect delayed information processing (Scheffers, Johnson, Grafman, & Dale, 1992, Prasher, Smith, & Findley, 1990, Johnson, De Luca, & Natelson, 1996). This prolonged latency has been reported to be affected by a number of factors such as ageing (Brown et al., 1972, Picton, Stuss, Champagne, & Nelson, 1984, Crawford, Parker, & McKinlay, 1997) and task complexity (Brown et al., 1972).

There have been three studies looking at P3 responses in CFS sufferers. The results of these are not consistent. Prasher, Smith, and Findley (1990) used a visual discrimination task and reported that P3 waves were delayed or diminished, implying that speed of information processing was slowed and the amount of information acquired was reduced. Scheffers, Johnson, Grafman, and Dale (1992) used an oddball reaction time paradigm, increased variability of P3 wave was reported, but with no significant difference between groups. The most recent study, using an auditory tone discrimination paradigm supports the lack of differences between CFS and controls (Polich, Moore, & Wierderhold, 1995). Though they report deficits on some measures they suggest that the lack of consistency with other measures cast doubt on reliability.

This lack of consistency is typical of the literature and is probably attributable to methodology. None of these studies control for both age and education. As mentioned above these factors are highly correlated with speed of processing. Furthermore Scheffers, Johnson, Grafman, & Dale. (1992) used CDC criteria where mental fatigue may be present but was not necessary. They report increased variability which may be the result of a more heterogeneous sample where fatigue forms were mixed.

A further measure of speed of processing is the Digit Symbols sub-test from the WAIS-R. Two studies have reported that there are deficits on this test which do not appear to be the result of depression (Krupp, Sliwinski, Masur, & Freidburg, 1994, Pepper,

Krupp, Freidberg, Doscher, & Coyle, 1993). However, though slowing of performance was noted (Pepper, Krupp, Freidberg, et al., 1993), there were no differences reported in the number of errors made (Pepper, Krupp, Freidberg, et al., 1993). One further study reported no difference in errors between CFS and controls (Fiedler, Howard, DeLuca, et al., 1997). It would appear that the CFS patients were able to complete the task, but the processes involved took longer.

The PASAT is generally used as a test for focused attention, however it is reported to be highly dependent on processing capacity which is in turn highly dependent upon speed (Crawford, Parker, & McKinlay, 1997). Increasing the rate of digit presentation quickly results in performance errors. Studies consistently report that CFS performance on this measure is impaired (DeLuca, Johnson, Beldowicz, & Natelson, 1995, De Luca, Johnson, & Natelson, 1993, DeLuca, Johnson, Ellis, & Natelson, 1997, Marshall, Forstot, Callies, Peterson, & Schenck, 1997, Johnson, DeLuca, Diamond, & Natelson, 1996, Johnson, Lange, DeLuca, et al., 1997). These deficits do not appear to be related to comorbidity of depression (DeLuca, Johnson, Beldowicz, & Natelson, 1995, DeLuca, Johnson, & Natelson, 1993, Johnson, Lange, DeLuca, et al., 1997). Research using the Paced Visual Serial Addition Test suggested that whilst patients were impaired on the verbal measure of this test there appeared to be no deficit on the visual form (Johnson, De Luca, Diamond, & Natelson, 1996). This restriction of deficits to the processing of verbal or auditory complex information may explain a lack of differences on the Trail Making Task and the time taken to do a non-verbal mental control task (Cope, Pernet, Kendall, & David, 1995). A restriction to auditory or verbal processing deficits is, however, inconsistent with impaired performance reported on the Digit Symbols subtest. With respect to impaired Paced Serial Addition Tests the authors (Johnson, De Luca, Diamond, & Natelson, 1996) suggest intact performance on the visual form may be a result of different input and response modalities. For the auditory form, information must be input in verbal form and output in this modality, hence there may be interference and worse performance.

2.4.1. Attention and Information Processing Conclusions

CFS patients vary in performance on these measures. They appear to have intact performance on measures such as tracking, and impaired performance on tasks of vigilance. Problems with slowing are particularly apparent, and it has been suggested

that these are problems with the speed of information processing. Deficits have been demonstrated in these areas. Though it has been suggested that problems with slowed processing have been restricted to the auditory processing of information several studies show impairments when CFS patients are assessed on visual measures.

2.5. Impairments in CFS Summary

There are few deficits reported on tests of higher intellectual function. Tests of visual memory suggest that impairments are restricted to facial recognition and memory for location. Deficits are apparent on tests of verbal memory, specifically tests of hard paired associates and where cue reinstatement is provided. Performance decrements on paragraph recall tasks and free recall of word lists may be in part or total due to comorbid psychiatric symptoms. Performance decrements have been noted on tests involving speeded processing. Slowing is reported on all conditions of the Stroop and reaction time measures. ERP data conflicts, but performance on the PASAT, together with intact performance on other attention measures such as digit span, focusing and switching of attention and trail making, suggests that speed of information processing may be slowed. Alternatively the intact performance on the PVSAT and impairment on digit span may suggest that the processing deficit is not restricted to the auditory domain, but arises as a result of modality interference. Deficits appear to be restricted to problems with acquisition, interference of representation or modalities and slowing.

There are a number of possible cognitive explanations for the deficits observed in memory attention and processing, these are discussed in the section 2.7., before which an explanation of what is meant by speed of processing is presented.

2.6. Speed of Information Processing

The observed deficits in CFS are consistent with slowed speed of information processing. The theory of slowing to speed of information processing is not unique to CFS; it has, for example, been reported in ageing and depression (Weckowicz, Nutter, Cruise, & Yonge, 1972), hypertension and cerebro-vascular disorders (Junque, Pujol, Vendrell, & et al., 1990). As has been previously argued (Fairhurst, Waterman, &

Lynch, 1997) it is of importance to elucidate the features of such slowing. Slowed processing has been investigated for a number of years using different paradigms and theoretical interpretations of differing specificity; though historically it has generally been regarded as a global concept (Stankov & Roberts, 1997). Definitions have included: mental processing speed[2], neuro-physiological efficiency[3], and related to this basic units of information processing (BIPs). However much of the work measuring speed of information processing has been equated to the time taken to perform particular cognitive tasks.

Research using a definition of 'performance time' has been undertaken in a variety of areas from intelligence in healthy subjects (McGeorge, Crawford, & Kelly, 1996), to ageing (Allen, Smith, Jerge, & Vires-Collins, 1997, Brown et al., 1972) and clinical populations such as schizophrenia (Mialet, Pope, & Yurgelun-Todd, 1996) and depression (Sabbe, Hulstijn, VanHoof, & Zitman, 1996, Sobin & Sackeim, 1996). Researchers investigating speed and its relationship with general intelligence have suggested the potential for a factor model of speed, though empirical support is weak (Stankov & Roberts, 1997). The basic conceptualisation is that as cognitive processes may be hierarchically arranged from perceptual processing to more complex and effortful processing then so may speed. Models of speed conflict as to whether individual differences in slowing are restricted to certain domains or affect global intellectual function (Rabbitt, 1996, McGeorge, Crawford, & Kelly, 1996). Some empirical support for a separation of speed related to task and complexity can be seen in the clinical domain of depression. Analysis into sub-components of processing illustrate that depressed patients have greater difficulty in tasks of effortful processing rather than automatic processing (Mialet, Pope, & Yurgelun-Todd, 1996). This is not to say that slowing may not be global. Indeed deficits have been demonstrated in this population both peripherally and centrally (Mialet, Pope, & Yurgelun-Todd, 1996), but that the relative importance to tasks differing in complexity may vary, or that some processing types may be affected to a greater extent than others. Demonstrations of slowed speed of information processing have been made in a number of clinical populations using a variety of mental tasks. The issues of global versus specific processing deficits, or early versus late stage deficits are pertinent to the clinical

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[2] i.e. how quickly a cognitive task can be performed

[3] i.e. how quickly the neurones or systems of neurones are able to process information

populations. As yet, though slowing in performance has been demonstrated in CFS patients, this has been restricted to tests which are reputed to load heavily on speed of processing or less complex tasks such as simple reaction time.

An analysis of the work at this level suggests that the time taken for some patients to do particular tests is longer and that this slowing may affect a variety of domains; it however does no more than describe slowing, rather than explain possible cognitive mechanisms. Just what is meant by information processing and by its slowing? There are two principal definitions of information processing: one in the artificial intelligence paradigm; and the other from more traditional box models of cognitive processes. The latter approach involves the dividing of the cognitive system into smaller units each representing a defined processing stage. Information flows through these sub-units from input to output. More recent models are in the framework of connectionism and artificial intelligence. They postulate that information processing involves the transformation of representations by sets of structured rules. Such ideas are more specifically defined by levels of cognitive architecture such as that of Fodor & Pylyshyn (1988). They suggest that cognitive states are representational states upon which a cognitive architecture is superimposed. These representational states are implemented by an implementation architecture (akin to processing). Such models have representational, organisational and processing levels and may therefore offer a more explanatory level of description.

Insight into slowing of information processing at such levels of description can be derived from traditional experiments in learning and memory. Memory records are assumed to have a property called 'strength'. Early work on conditioning (Pavlov, 1928) demonstrated that on repeated presentation of the conditioned stimulus with the unconditioned stimulus (i.e. practice), the strength of the association increased and learning was acquired. The ideas of increased practice or use of representations resulting in an increased representational strength have been extended to human memory. A considerable body of research has been undertaken, demonstrating that the more each item is presented, the greater the likelihood of its retrieval. For example, in a study by Anderson (1981), subjects were presented with 20 paired associates over seven occasions, the probability of correct recall increased as a function of practice.

In other words: $[representational\ strength]^{[Practice]} \propto [retrieval]$

Further support can be cited from work in priming related to the incremental learning hypothesis (Becker, Moscovitch, Behrmann, & Joordens, 1997). Here it has been suggested that responses are more accurate and faster (on priming tasks) where the same input pattern is given (Becker, Moscovitch, Behrmann, & Joordens, 1997), rather than when similar primes are used. This is compatible with the notion of a stronger representation. The effect of practice on trace strength and speed to retrieve is evident over the whole learning process. As practice increases speed of performance increases, tasks being performed more quickly (Anderson, 1981). Even when maximal retrieval has been achieved performance still shows improvement by a reduction in retrieval time (Anderson & Pirolli, 1985).

Hence [*Speed*] $\propto$ [*representational strength*] $^{[Practice]}$

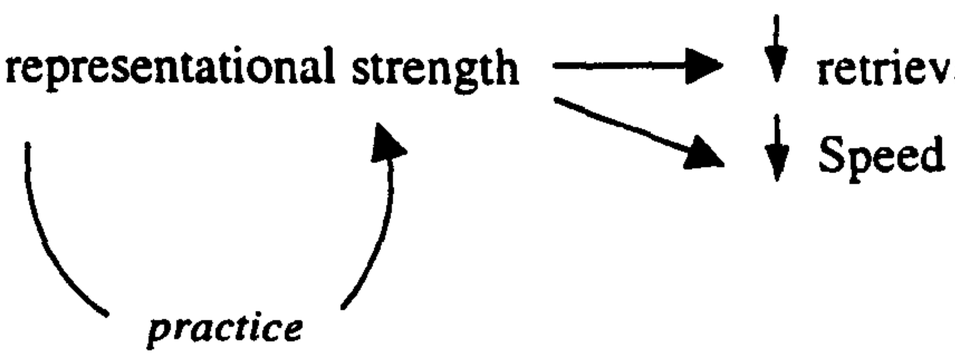
In other words speed of retrieval is proportional to the amount of practice which determined strength of the representation. Hence a potential definition of what is meant by *'slowed speed of information processing'* may be proposed. If speed is slowed (for some as yet undefined reason) this may be related to a decrease in the strength of representation and thus with retrieval difficulties. Critically the impact of representational weakening on retrieval may depend upon the existing strength of the representation. If representations are sufficiently weakened they may fail to be retrieved; whereas if representations are already strong, then their retrieval may be possible with only a small boost to strength. Hence a possible delineation between novel inputs and inputs of information already known (old inputs) may be found, with retrieval for old information being better than retrieval for novel information.

Correlations between components such as strength, speed and retrieval speed and content are all very well, but we need to consider the notion from a more theoretical perspective.

As depicted below (figure 2.6.1.) it is possible that slowed processing speed may result in weakening of representations or memory traces. Here a problem with creating and maintaining representations impacts on retrieval content and the speed to retrieve. Items which already exist as representations may need less practice for retrieval, as the representational strength may be high enough for a small boost to strength to impact positively on retrieval. For those representations that need to be created this small boost

to representational strength may be totally, or partially, insufficient for retrieval; this may result in either failure to retrieve, or in partial recall, with slowing.

Figure 2.6.1. Impact of representational strength



Information taking longer to input may allow for interference between weak representations which are being input and dealt with almost simultaneously. Such problems are more likely to be apparent for new information where there is no existing representation, since for old representations a boost to strength may be sufficient. Studies in priming using category exemplars have shown that activation and retrieval of several items/representations in a category of words, such as fruit, seems to inhibit the subsequent retrieval of other members of the category (Blaxton & Neely, 1983). Additionally Rundus et al. (1973) suggested that the retrieval of each representation increases its strength relative to other items in the category group, and the probability of their recall from semantic memory decreases. These studies suggest support for interference of associated representations in a recall task in a healthy population. If speed is adversely affected, this potential for interference of representations may be heightened. Since processing takes longer, the processing of the representational information from one input may not be completed when the next input arrives. There is thus a potential for numerous competing inputs. This interference would result in the further weakening of representations and in subsequent retrieval difficulties. Such an interference effect is also likely to be more apparent in processes where input of representations take longer, in other words more complex or cognitively demanding processes. It has been reported in experiments on priming that perceptual processes are used earlier and more quickly than conceptual processes (Weldon, 1993). Hence a potential for performance differences on tasks differing in 'levels of processing' may be seen. It would be expected that those representations with a higher conceptual load may have weaker and less coherent representational formation, and thus worse retrieval than those which were perceptually processed.

Obviously recall is not just about representational strength and numerous studies (e.g. Blaxton, 1989, Morris, Bransford, & Franks, 1977) have demonstrated the importance of 'transfer appropriate processing[4].' Essentially this states that recall is enhanced when the conditions present at encoding are reinstated at retrieval. The greater the match between study and test, the better performance. For example, Blaxton (1989) illustrated that performance was improved for conceptual/semantic information when participants generated rather than read study items; performance on perceptual tasks was improved when subjects read rather than generated items at study. Additionally, factors such as modality and typography were shown to be important for determination of match between study and retrieval (Blaxton, 1989). A primary factor here must be both the existing representation and the new representation initiating retrieval; in effect what exists for overlap. If these representations are weak, then the extent to which processes overlap becomes redundant, there may be insufficient of the weak original for processes to be reinstated and for transfer appropriate processing to occur. Recall would thus be impaired, and more so given that retrieval representations are also likely to be weakened. Such weakening would render whether or not type of processing is matched or mis-matched, redundant. Impairments are likely to manifest globally, irrespective of the extent of overlap or local context.

At a higher level could representational differences exert differential influence on conscious and non-conscious processes? Here an inspection of the neuroanatomy of memory, incorporating consciousness is instructive. Typically memory can be divided into the unconscious implicit and the conscious explicit. Implicit memory can be thought of as enhanced performance at retrieval without conscious awareness, as a result of exposure to previously relevant material. Explicit memory can be regarded as retrieval with conscious awareness. There are currently 3 accounts for this division of explicit and implicit (which will be discussed more fully in chapter 6): The Processing Account as expounded by Roediger (Roediger, 1990a & 1990b); the Systems Account as explained by Schacter (Schacter, 1987, 1990, 1992), and the Component Processing Account as proposed by Moscovitch at al. (1991, 1993). For the moment I will concentrate on the Component Processing Theory (CPT), a combination of the afore mentioned theories.

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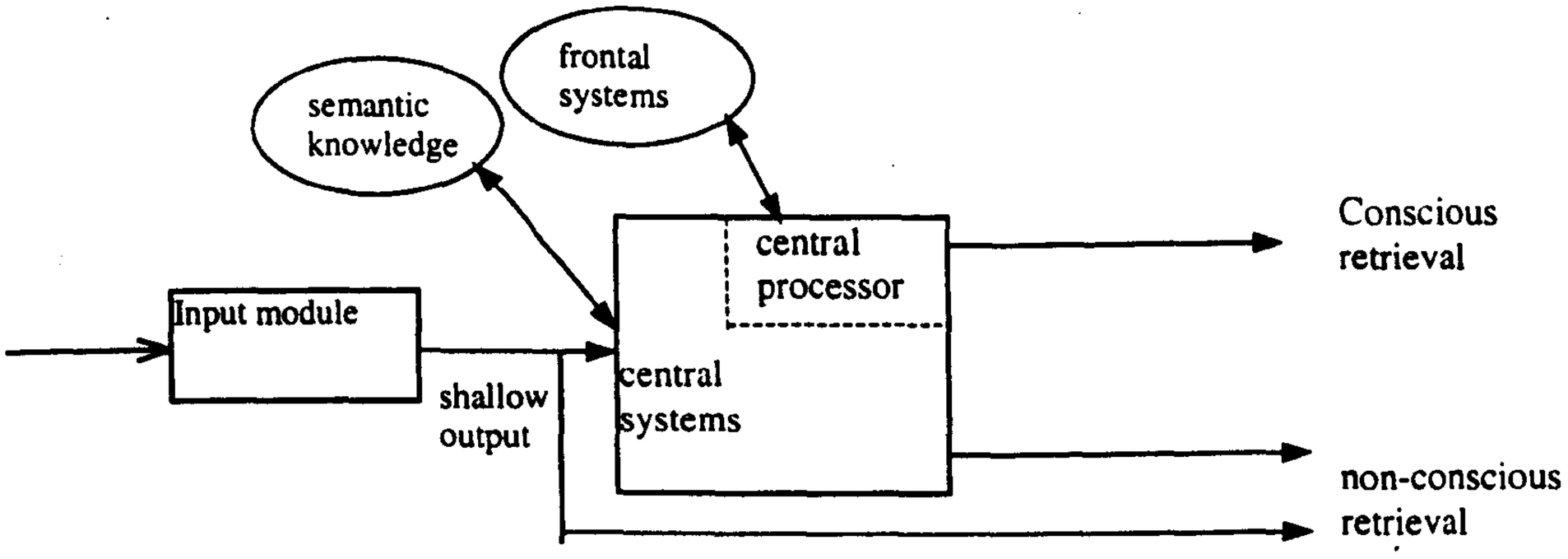
[4] see chapter 6 for further discussion of transfer appropriate processing and memory

This CPT proposes that memory tests are composed of sets of processes. As in the Transfer Appropriate Processing frame work priming occurs if 'critical' processes involved in study are reinstated at test. However these sets of processes may also be regarded as separate modules or 'structural units' performing different functions. For example it is suggested that perceptual information is input to the posterior cortex, encoding and retrieval then occurs in the medial temporal lobes and hippocampus, and explicit recall then occurs with some frontal lobe function. The crucial assumption here seems to be that explicit memory is associated with conscious processing and implicit memory with non-conscious processing.

Moscovitch & Umilta (1991) (as summarised in figure 2.6.2) proposed that external information, as detected by vision for example, is input to *input modules* which deal with components of processing. These *component processes* or input modules are *domain specific* (i.e. deal only with one type of information) and have a shallow output (i.e. not available for semantic or conscious interpretation). The output of these component processes is thought to be received by central system processes, where it can be consciously or non-consciously processed. It is postulated that there are 5 central systems, one of which is the *central processor* which mediates consciousness. These central systems are implicated in semantic memory and higher order functions, such as planning. A comprehensive description of the system is beyond the scope of the thesis, but in summary may be divided into non-conscious and conscious processes. As mentioned previously, explicit memory is thought to be conscious and implicit memory to be unconscious. Explicit tests of memory are thought to be associated with hippocampal and neocortical areas; the hippocampus integrating input cues and stored memory records, which form memory traces. The output from the hippocampus projects to the central processor where it becomes accessible to conscious interpretation. The mechanism for the strategic recall of information differs in that rather than relying on external cues it relies on frontally mediated internal cues. Again these are accessible to conscious evaluation, interpretation and planning. According to this model implicit memory, without awareness, must be independent of the central processor which mediated consciousness. Here it is proposed that the shallow level output of the input modules may activate hippocampal processes, resulting in the facilitation of performance, without awareness. However researchers have demonstrated that there may also be a conceptual element to implicit memory (Blaxton,

1989). This would thus require access to semantic knowledge and 'higher order processes' thought to be mediated by central systems operating without activating consciousness.

Figure 2.6.2. Summary of Moscovitch & Umiltas (1991) Model of Memory



Moving to a more neuro-anatomical perspective Petri and Mischkin (1994) proposed that again there are two circuits, one implicated in explicit memory and one in implicit. That involved in implicit memory is thought to involve the basal ganglia, this receives information from the neocortex and projects to premotor areas; and also receives and projects to the subtantia nigra. Explicit memory circuits are thought to be composed mainly from limbic structures. Ascending projections (cholinergic, serotonergic and dopaminergic) are thought to output to the hypothalamus and the neocortex. These neocortial areas are believed to be active during encoding (ventrolateral) and during retrieval (dorsolateral). One of the crucial differences from Moscovitch & Umilta's (1991) model is that memory is considered to depend upon the level of activations across the system. The Basal Forebrain is responsible for approximately 70% of cholinergic projections to the forebrain, as well as projecting other fibres. These ascending fibres are thought to be implicated in activation, and their lesion results in amnesia. Projections from serotonergic fibres in the mid-brain and noradrenergic fibres in the hind-brain are together thought to be implicated in maintaining cortical activation. Their lesion produces global disruption to intelligent behaviour as mediated by the neocortex. These areas are thought to operate by maintaining cortical activation so cells can function normally rather than being responsible for memory or higher order functions per se. They are also thought to be more fundamental for explicit rather than

implicit memory. They may not be dissimilar from either the central processor (thought to mediate consciousness) or central systems (thought to mediate conceptual processing) as proposed by Moscovitch & Umilta (1991).

In the account of slowing with weak representations, as proposed above, the activation level of the representations may be insufficient to support the cortical activity required for conscious processing. Representations may be sufficiently weakened for output to be insufficient, or too shallow, to activate either central systems and/or the central processor responsible for consciousness. This would impact on semantic retrieval and conscious explicit retrieval, but perhaps less so on strategic processes (retrieval and planning) which are dependent on strong existing frontal representations. Implicit memory would be expected to remain largely intact. Since it is less reliant on the maintenance of cortical activation, being independent of consciousness. However, if central processes were affected, it is possible that conceptual implicit memory may be impaired.

To summarise, an overall model of the effects of process slowing can be proposed on three levels. Firstly initial input may result in weakened representations, perhaps as a result of interference. Secondly there may be a levels of processing effect, perceptual and conceptual processes being differentially impaired. As conceptual processes take longer these representations are likely to be weaker and less distinct from other representations. These weakened representations may result in novel representational activity being insufficient to form the appropriate overlap with an existing representation. If these existing representations are too weak, they may also be insufficient to activate ascending systems and conscious awareness. Explicit retrieval failure would be expected, whilst implicit retrieval is less likely to be problematic. Conceptual or semantic processing is thought to be dependent on central systems. Conceptual representations are probably weakened to a greater extent than perceptual representations, and these processes should thus show greater impairment. Since strategic retrieval and planning are thought to be frontally mediated these would probably remain intact; representations already exist and are therefore likely to be strong and distinct.

2.7. Theoretical Explanations for Deficits Observed in the Literature

Given the evidence, and in light of the above explanation of what speed of information processing might mean, it seems that a number of theoretical explanations might account for the cognitive impairments found in CFS sufferers from a speed of information processing framework.

In CFS patients there may be a weakening of representations resulting in a diffuse reduction in processing speed; this giving rise to many of the subjective deficits reported by CFS patients. A slowed speed of information processing hypothesis is thus attractive in its ability to explain the lack of deficits in tasks less dependent on speed (e.g. planning (Grafman, 1993) and strategic recall (Lakein, Fantie, Grafman, et al., 1998)) as well as the presence of deficits on tasks more reliant on speed (e.g. PASAT see De Luca, Johnson, Beldowicz, & Natelson. (1995) and the Stroop, see Ray. (1993), Marshall, Forstot, Callies, Peterson, & Schenck. (1997)).

Additionally, taking a transfer appropriate processing perspective (Morris, Bransford, & Franks, 1977) a slowed speed of information processing hypothesis is also able to explain results previously thought of as counterintuitive. A lack of benefit to recall from cueing has been reported in CFS samples (Million, Salvato, Blaney, et al., 1989, Sandman, Barron, Nackoul, et al., 1993, Grafman, Schwartz, Dale, et al., 1993, Riccio, Wilson, Thompson, et al., 1992). This is unusual as cue provision generally aids recall, by the provision of context, additional routes to retrieval and an overlap in active processing representations. Transfer appropriate processing states that if the processes involved in encoding are reinstated in retrieval then recall is maximal. If process overlap is large then recall is improved as compared to conditions where overlap is slight (Jacoby, 1991). Cueing should provide retrieval via partial reinstatement of the content or the reinstatement of the processing involved at encoding, or both.

It has been shown (above) that the strength of association between cue and memory is related to speed and that this is independent of elaboration. As strength increases so does speed and the capacity of a cue to activate a memory. Perhaps as speed is affected by strength then the associations between the representations may be weakened.

Therefore retrieval would be sub-optimal in a CFS group. In this scenario it is of no significance whether the overlap between encoding and retrieval is large or whether it is small. The strength of association between representations is weakened to a critical degree. Cueing therefore provides no direct benefit.

Alternatively there may be a temporal processing effect. Perceptual encoding and retrieval generally take less time than conceptual encoding and retrieval (Weldon, 1993). In more conceptual tasks the additional time taken may allow interference from other active representations. This would be particularly apparent in tests requiring a number of active representation, or of a particularly conceptual nature. Increased proactive inhibition has been reported in these patients. Problems on conceptual tasks might be greater since patients undertaking a conceptual encoding task would need longer in absolute terms to extract content representations than for perceptual encoding tasks; performance on conceptually encoded tasks would be impaired. If this is the case difference should be apparent when manipulating processing at retrieval and encoding, conceptual cues should be less useful than in control populations.

A further possibility may be that the content representations themselves are weakened with problems in their generation, maintenance or manipulation. Such problems would manifest as difficulties in the acquisition of information, and speed to complete tasks. Slowing may arise in a number of ways, for instance as a lengthening in the time to generate and manipulate representations. Problems in generation would also affect the amount of information acquired, particularly in tests where speed is crucial. In tests of verbal memory it has been reported that CFS patients exhibit problems with the interference of representations, or the acquisition of information. Additionally, performance decrements have been noted on tests involving speeded processing. Slowing is reported on all conditions of the Stroop and reaction time measures. The performance of CFS patients on the PASAT, together with intact performance on other attention measures suggests that speed of information processing may be slowed.

The theory of slowing to speed of information processing is not unique to CFS only by further investigation will it be possible to suggest a possible underlying mechanism in this population; for example are they impaired on tasks requiring more conceptual processing? If impairments of conceptual tasks are found, are they restricted to memory domains or do they generalise to processing speed? The possible explanations outlined

above are not mutually exclusive and it seems plausible to suggest that several components of cognitive processing might be affected.

Hence issues to be addressed with respect to describing the nature of speed in the CFS population are: firstly, whether slowing in performance can be demonstrated and whether this is a result of representational weakening; secondly, whether tasks differing in processing are affected differently; and thirdly, whether such slowing or weakness impacts differently on conscious and non-conscious processes.

2.8. Aims of the Thesis

The principal aims of this research were:

1. to move from a traditional neuropsychological approach to testing and to characterise the speed of information processing problems that are purported to be the underlying problems in cognitive symptoms experienced by these patients.
   Specifically investigations were designed to:
   - determine whether there are deficits in the speed at which CFS patients processed information.
   - determine whether slowing of performance could be attributed to representational weakness.

2. to determine whether differences as a result of processing style (e.g. deep versus shallow processing) are also present in the cognitive domains of implicit and explicit memory; and additionally to determine whether there are effects in implicit and explicit memory tasks which can be related to the idea of speed and consciousness.

3. to consider the previously undetermined effects of anxiety symptoms on the cognitive problems exhibited by these patients. Additionally to consider the effects of comorbid depressive symptoms, both clinical and sub-clinical.

The traditional tests of speed are unitary measures and though can be placed on a more global continuum, inferences may be limited as task demands as well as cognitive

complexity differ greatly. Tests of processing were therefore devised which would exploit speed of processing differences between a CFS population and control population (as presented in chapter 4), and determine whether slowed processing can be attributed to representational weakness (see Chapter 5). Implicit and explicit memory tasks differing in processing and overlap were then devised for the assessment of conscious and non-conscious processes (see chapter 6). Since the underlying theory for test development differed for each test, test design and development will be considered within separate chapters. The general methods employed, CFS patient characteristics and their performance on standard tests will be presented in the next chapter. The chapters following this will then consider the investigations into processing and memory.

Chapter

3

General methods and patient characteristics

3.1. Introduction

There are a number of ways in which cognitive tests may be manipulated to highlight a between group difference in speed of information processing. As discussed previously slowed speed of information processing has been generally inferred from the results of tests of complex reaction time and slower performance on the Stroop and neuro-psychological measures such as PASAT.

A variety of interesting questions may be posed if such slowing is indeed manifest. At what point does the nature of the task produce a large change in response? Is the relationship between processing requirements and slowing linear? Are there different effects of slowing on perceptual and conceptual processing? Are representations weakened? Addressing such issues is difficult with respect to a single measure of one complex reaction time. Though it should be possible to obtain an absolute difference in RT between CFS and controls groups, it may be more beneficial to have a picture of slowing relative to processing requirements, or a number of absolute differences in slowing over tasks with incremental processing requirements. Such specification is of greater utility in making a more complete description from which to make explanatory inferences. As stated in chapter 2, section 2.6, a model of the processes involved in memory may be proposed, from a low level representational perspective to the higher level of consciousness.

In order to facilitate data collection a battery of tests was devised; designed to assess speed and memory from these different perspectives. Though these were administered

in one session, their design rationales are different, testing 3 levels of the proposed model. They will thus be considered in separate chapters.

Two tests were designed to specifically characterise the nature of slowed performance in CFS patients. The first test was designed to evaluate whether or not CFS patients were slowed in speed of information processing. As discussed in section 2.6., the effects of slowing on perceptual and conceptual processing may differ. Perceptual tasks should require the activation of fewer representations and less processing than conceptual tasks. The study thus involved an evaluation of the effects of incremental conceptual processing on speed of performance. This study is reported in Chapter 4.

As previously noted, that information processing is slowed presents only a partial picture, slowing may arise as a result of representational weakness. This second study thus involved the determination of the effect of strength of semantic association of word pairs on speed of response, since differences in the strength of association have been reported to differentially affect response speed (Collins & Quillian, 1969, Rosch, 1975). Since words and word pair representations already exist in memory, they should all be weakened to a similar extent. It may therefore be expected that there will be global slowing, relative impairment in speed being no different across associational levels. Whether such slowing can be accounted for by the combined motor speed and word recognition elements of the task is also considered. This study is reported in Chapter 5.

A further problem arises in that if there is slowing, how does this relate to performance of other cognitive tasks? Representational weakness, manifesting as slowed performance, may differently effect perceptual and conceptual processing tasks, and may also be associated with poor performance on cued recall tasks. Additionally there may be an impact on conscious rather than non-conscious processing. Implicit and explicit memory performance from a transfer appropriate processing perspective, is therefore reported in Chapter 6.

In attempting to measure a particular deficit and move away from standard neuro-psychological tests there is a danger that these results will not be comparable to previous literature. Given the heterogeneity of the disorder and the multiple case definitions currently in use, the possibility of drawing comparisons with other groups

of differently and similarly defined CFS samples would be useful. Comparisons will serve to illustrate how greatly the group differs from existing patient samples and to some extent the generalisabilty of these findings. Sub-tests from the WMS-R have been used in a number of studies; those used frequently have been the Paired Associate Learning Test, Logical Memory and Digit Span. Measures of CFS performance on these tests will be made, since comparability is a key issue. These tests also have the additional benefit of varying in conceptual requirements and the cues available for recall, thus aiding explanations in later chapters.

The following measurements will therefore be used in an attempt to investigate the main study hypothesis of slowed speed of information processing: complex reaction time tests, graded in terms of processing requirements (see chapter 4); timed response tasks graded in terms of semantic relation (discussed in chapter 5); tests of both implicit and explicit memory (discussed in chapter 6); and standard neuropsychological tests of digit span, paired associate learning and logical memory sub-tests from the WMS-R (discussed later in this chapter).

This chapter will firstly outline the general methods of this research; the specific design of the tests of processing and implicit and explicit memory will be considered in subsequent chapters. The chapter then aims to give an overall picture of the comparability of the neuropsychological performance of this CFS group with those tested in other studies. Psychiatric and fatigue characteristics as well as demographic information will thus be presented, and the results of standard neuropsychological tests considered.

3.2 Method

3.2.1. Participants

All participants were native speakers of English. There were 68 CFS patients as defined by the OCC (Sharpe, Archard, Banatvala, et al., 1991), with a mean age of 40.7 years. Forty-one were female, 27 were male. They had a median educational level equivalent to A-level. The majority of patients were taking medication with 45.6 % being medication free. These patients were matched with a group of 63 healthy controls, who had a mean age of 41.0 years, 41 were female and 22 were male. Mann Whitney non parametric tests were used to establish that there were no significant differences

between CFS and control participants in: education[1] (z=-1.9170, p=0.06); sociodemographic group[2] (z=-1.9179, p=0.06); or age (z=-0.153, p=0.878). Chi squared showed that there were no significant differences between CFS and control participants in sex χ^2 =0.317, p>0.05 or handedness χ^2 =0.018,p>0.05.

CFS patients rated themselves as significantly more depressed (z=-8.35, p<0.0001) and anxious (t(126)=5.2, p< 0.01) than controls on the HAD scale. CFS patients also experienced significantly higher levels of fatigue, as assessed by the Fatigue Scale (z=-9.043, p<0.0001). On analysis of the specific fatigue subtypes, as rated on the Profile for Fatigue Related States (PFRS), CFS patients experienced significantly more symptoms of both mental (t(128)= 128, p< 0.01) and physical fatigue (t(128)=14.95, p<0.01) than controls.

3.2.2. Materials

3.2.2.1. Fatigue Scales

As discussed in Chapter One, there are a number of confounding factors which need to be considered when attempting to objectively assess cognitive impairments in CFS. Differences in fatigue characteristics, anxiety symptoms and depression levels are especially pertinent in this population. There are a number of methods currently available to measure fatigue (as discussed in section 1.3.7.2.), in this study self assessment scales were adopted. These questionnaires have the advantage of being quick to administer, are free from experimenter bias and avoid the lack of uniform comparability in responses obtained from traditional interview methods. Fatigue symptoms were assessed in two ways. Firstly a questionnaire assessing subjective symptoms for diagnostic clinical screening was used, and secondly a measure characterising the fatigue described.

3.2.2.1.1. The Fatigue Scale

The Fatigue Scale (Chalder, Berlowitz, Pawlikowska, et al., 1993). is a 14 item two-dimensional self-rating questionnaire. Eight questions assess physical fatigue and six questions assess mental fatigue. Response is via a 4 item scale from 'better' to 'much

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[1] 2.0 CFS vs. 2.4 for controls, where 2.0-2.9 is equivalent to 'A' level.

[2] 2.6 CFS vs. 2.3 for controls, where 2.0-2.9 is equivalent to Intermediate.

worse'. Patients are asked to compare the symptoms of fatigue they are currently experiencing with those prior to illness onset. The scale is scored via the GHQ method. It has high internal reliability and acceptable validity. The scale also has good discriminant validity providing support for the use of sub-scores of physical and mental fatigue. Factor analysis (Morris, Wearden & Mullis. in press) has yielded 4 factors: cognitive difficulties which accounted for 36.5% of the variance, sleep difficulty which accounted for 15.2% of the variance, objective physiological measures (7.9% of the variance) and depressive symptoms (7.5% of the variance).

The Fatigue Scale has been widely used both in primary care and tertiary care to screen for Chronic Fatigue (CF). Patients with scores of above 9 are commonly regarded to be suffering from CF. Though this is a useful measure, assessment for CFS was supported with physician diagnosis. The use of the fatigue scale, in this study, was primarily for comparison with existing research. Though this scale has been designed for use as a screening tool for CFS (Chalder, Berlowitz, Pawlikowska, et al., 1993) it does not assess psychiatric history or physical health. Additionally patients may potentially underrate fatigue severity, since severe fatigue may be the normal state. In order that OCC criteria were fulfilled it was thought important to have diagnosis obtained from the Physician and Psychiatrist at the Leeds Fatigue Clinic.

3.2.2.1.2. Profile For Fatigue Related Symptoms (PFRS)

The PFRS (Ray, Weir, Phillips, & Cullen, 1992) is a 54 item subjective rating questionnaire and has 4 dimensions; emotional distress (anger, anxiety and depression), cognitive difficulty, general fatigue and somatisation. Ray reports that these factors account for 83% of the variance. The convergent validity with other measurements of fatigue is good, correlations ranging from 0.76 to 0.88; the scale also has high reliability (test retest correlations of 0.86 to 0.97) (Ray, Weir, Phillips, & Cullen, 1992). It has been validated for use as a research tool. Response is made via a 6 item numerical scale equating to what extent symptoms have been experienced during the past week. The scale yields 4 scores; the mean responses for each dimension.

CFS patients vary greatly in the type, severity and overall pattern of fatigue they report experiencing. As discussed in section 1.3.7.2., whilst some patients may report high mental fatigue and low physical fatigue others may report the reverse. Given that CFS performance on meta-memory tasks is unimpaired it seems probable that those patients who report no symptoms of mental fatigue will be largely intact in objective cognitive

performance measures. In order to assess the variation of subjectively experienced fatigue types, a multi-dimensional assessment of fatigue was necessary. The use of scales designed for use in one population may not validly generalise for use in another population. The PFRS besides offering good validity and reliability and specificity for a CFS population has several advantages. Firstly, it separates fatigue into 4 dimensions so the differing of patterns of subjective fatigue can be addressed, as can the relationship of the individual dimensions to objective data. A further advantage of this scale is the avoidance of the term 'fatigue', here problems resulting from a lack of consensus over meaning are avoided. It should therefore be possible to dissociate validly the experience of mental fatigue and physical fatigue, for comparison with objective symptoms.

3.2.2.2. Hospital Anxiety and Depression Scale (HAD)

The HAD (Zigmond & Snaith, 1983) is a well validated scale and has been widely used in the CFS literature. It assesses anxiety and depression using 14 items; 7 anxiety and 7 depression. Using a Likert scoring system from zero to three, scores are summated. A score of 11 or more is regarded as clinically significant. (Joyce, Blumenthal, & Wessely, 1996). Internal consistency is good at 0.80 and 0.81 for the anxiety and depressive scales respectively (Herrman, 1996).

The HAD scale was chosen for the assessment of depression and anxiety. This self-rated scale was chosen as it is quick and easy to administer, with good reliability and validity (Zigmond & Snaith, 1983). The scale has the advantage of avoiding the possible inflation of depressive score by excluding somatic symptoms of depression, such as fatigue. It is also widely used in the literature and thus aided comparability.

3.2.2.3. WMS~R sub-tests

Neuropsychological tests of digit span, logical memory and paired associate learning (PAL) were included in order to increase the comparability of this research with that done previously.

The immediate Logical Memory Test requires the remembering of 2 successively read stories. Patients hear a short story which they are asked to remember, then repeat to the researcher using the same words. The total number of units correctly recalled is recorded (for scoring criteria see Wechsler (1987)). The participants are then read a

second story for which the same is required. A total recall score for the 2 stories is then calculated.

For the PAL test participants are read a list of eight word pairs which they must remember. Four of these are semantically unrelated (hard pairs) and four related (easy pairs). Participants are then given the first word of the pair as a recall cue for the second word; if they are unable to recall an item the correct answer is provided. The task was repeated three times (with the same word pairs in different orders) giving a maximum possible score of 12 for easy pairs and 12 for hard pairs.

The Digit Span Test is composed of Digit Forward and Digit Backwards Tests. Participants are read a string of numbers which they repeat either forwards or backwards depending on the test. The test uses incremental strings of digits. The participants are required to repeat two strings of equal length. If they are successful in repeating at least one string, they proceeded to the next string, greater in length by one digit. When the participant is unable to correctly repeat a string of numbers on the two successive occasions the test is discontinued. Results are the number of strings correctly repeated for forwards performance and backwards performance.

3.2.2.4. Implicit and Explicit Memory Tests

These are described in more detail in Chapter 6. The implicit and explicit memory tests differed only in retrieval intentionality. A two (perceptual study, conceptual study) by two (perceptual retrieval, conceptual retrieval) design was used. For the implicit study phase, judgements of utility were made for ten words (conceptual study) and of the number of vowels in 10 words (perceptual study). In the implicit recall phase participants were asked to 'think up words', 10 of these were cued with word stems (perceptual retrieval) and 10 with semantic clues (conceptual retrieval). There were thus ten items with matched study and retrieval processes, five conceptual and five perceptual, and ten where processes were mismatched. For the explicit test, which followed, participants were asked to remember the study list whilst they rated the words and counted the vowels. They were then asked to use the cues on the retrieval list as clues to help them remember study items (tests are included in appendix 3.1).

The rationale for the inclusion of the test of memory has been briefly dealt with in section 3.1. and will be considered more fully in the chapters considering each study.

3.2.2.5. Computerised Test Semantic Pairs

This test is discussed more fully in chapter 4. Stimuli were presented and responses recorded via a Toshiba 1900 portable personal computer programmed in C. The test was composed of two parts. For the first part participants were randomly presented with 27 pronounceable non-words and 48 words. They were required to make a lexical decision for each word as quickly and as accurately as possible, before moving to the next. The second part involved the presentation of semantically related items. There were eight pairs each of strongly related, moderately related, slightly related and unrelated, in each of these categories 4 were presented as word-word pairs and four as word-picture pairs. Thus 16 word-word pairs were presented and 16 word-picture pairs. All items had been encountered previously in the lexical decision task. Participants were required to make yes/no judgements, as quickly and accurately as possible, as to whether items were related. Responses and response times were recorded.

3.2.2.6. Computerised Test Graded Reaction Time

Participants were presented with 20 trials using a Toshiba 1900 portable p.c., via which responses were also made. For each trial a statement was presented followed by an item. Participants were required to make yes/no judgements on whether or not the statement was a true description of the item. These questions were graded from perceptual to highly conceptual in their processing requirements. Participants were asked to respond as quickly and accurately as possible, responses and response times were recorded. This test is described more fully in Chapter 5.

3.2.2.7. Background Details

CFS patients were questioned briefly assessing age, sex, which hand they usually use, occupation (current or most recent), highest educational level, current medication, illness duration and length of time as clinic attendees. Control participants were questioned briefly to assess their age, sex, handedness, occupation (current or most recent), highest educational qualification and current medication (schedule in appendix 3.2.).

Intelligence has been reported to vary with processing speed (Kane, Proctor, & Kranzler, 1997, McGeorge, Crawford, & Kelly, 1996). In order to compare the CFS

group with the control group an estimate of intelligence levels which would be unaffected by the deficits present in CFS was required. Premorbid intelligence has traditionally been estimated in a number of ways, for instance the use of demographic information, lexical decision tasks, subtest scatter methods, reading ability and spared performance on some WAIS-R sub-tests. Estimates of intelligence in CFS have been made using the NART (Cope, Pernet, Kendall, & David, 1995, Riccio, Wilson, Thompson, Morgan, & Lant, 1992, Joyce, Blumenthal, & Wessely, 1996) and subtests from the WAIS-R (Krupp, Sliwinski, Masur, & Freidburg, 1994, Michiels, Cluydts, Fischler, Hoffman, LeBonner, & De Mierlier, 1996, Marshall, Forstot, Callies, Peterson, & Schenck, 1997, Schmaling, DiClementi, Cullum, & Jones, 1994). Longitudinal studies in healthy participants have shown the NART to be a reliable estimate of earlier intellect (Berry, Carpenter, Campbell, & Schmitt, 1994); however, caution has been advised against its use when the effects of the disease state on performance are still undetermined (O'Carroll, 1998). The same criticism may be levied at a variety of the available methods, given that the effect of CFS on these tests has not yet been longitudinally determined.

As there is still debate about the problems experienced in CFS, educational level was taken as an index of premorbid intellect in this study. Previous educational attainment would not have been affected by disease state and such methods usually account for about 50% of the variance in intelligence (O'Carroll, 1998). Educational Level was categorised according to the highest educational level attained, in a paradigm similar to that used in the General Household Survey (Social Survey Division, 1995). There were five categories, ranging from no education to postgraduate degree, see Table 3.2.2.7.a..

Table 3.2.2.7.a. Categorisation of educational levels.

Educational Status	highest qualification attained
0	no qualifications
1	GCSE, O level, skilled apprenticeship or equivalent
2	A level, HND, City and Guilds or equivalent
3	Degree or equivalent
4	MSc, MPhil, DPhil or equivalent

It has been reported that tertiary and primary care CFS samples differ in demographic characteristics, with those attending tertiary care centres tending to be higher in socio-demographic group (Euba, Chalder, Deale, & Wessely, 1996). For issues of

comparability and generalisability an index of socio-demographic group was determined. This was categorised according to occupation using the Registrar Generals Categories, see Table 3.2.2.7.b., as used by the Central Statistics Office (Government Statistical Service, 1996). For CFS participants who were retired due to ill health, the previous occupation was taken as an index.

Table 3.2.2.7.b. Categorisation of Occupations

GROUP		Examples from the studied population
I	Professional	Dentist, accountant, doctor
II	Intermediate	nurse, manager, school teacher
IIIN	Skilled non-manual	secretary, clerk, customer services advisor
IIIM	Skilled manual	electrician, joiner, technician
IV	Partly skilled	foster parent, crane operator, aromatherapist
V	Unskilled	cleaner, domestic, bread delivery person

3.2.2.8. Counterbalancing

Given the length of the testing schedule it was thought that order effects may be particularly prevalent; time on test affecting fatigue levels, or repetition of movements affecting response times. Additionally it was important to control for sequence effects which may have arisen as a result of test items presented in a specific order, (for example to be remembered words). The cognitive tests were therefore counterbalanced (see appendix 3.3. for counter-balance schedule), with the exclusion of implicit memory which always preceded explicit memory. It is thought that in the reverse scenario awareness may contaminate implicit memory performance. Additionally the order of stimuli presented in each of the designed tests varied between participants.

3.2.3 Recruitment

There were 2 phases to CFS participant recruitment. The first was by letter (see appendix 3.4.), on November 1, 1996 where CFS patients previously seen at the Seacroft Leeds Fatigue Clinic during the period November 1995 to November 1996, were contacted and invited to take part in study. There were 82 of these, 48 of whom did not respond, though one address did not exist. Of the 33 that did respond 7 declined to participate owing to practical difficulties or illness severity. This gave a response

rate of 31.7%. A further 2 patients had altered in diagnosis and 2 were awaiting their next clinic appointment; thus appointments were made with twenty-two patients. Of these owing to administrative difficulties and staff illness at the clinic, 4 patients appointments were cancelled, impacting on research appointment attendance. A further 3 failed to arrive giving no reason. This resulted in the testing of 15 patients, 19.0 % of those 79 CFS patients approached.

Of those patients contacted in phase one of recruitment, 8 were tested in phase two. Six of those who had made no response to the initial letter agreed to participate. One person whose clinic appointment had been cancelled, re-appointed. One person who was too ill in the first phase of recruitment participated 17 months later.

The second phase was undertaken between October 1996 and May 1998. Consecutively seen clinic attendees of the Leeds Fatigue clinic who fulfilled OCC criteria were invited to participate. This involved the attendance of the researcher at the Seacroft Fatigue Clinic on Thursday mornings and the General Psychiatric Clinic at St. James University Hospital on Monday afternoons. The CFS diagnosis was made according to Oxford Consensus Criteria (Sharpe, Archard, Banatvala, et al., 1991). Firstly, illnesses known to cause fatigue were excluded by a consultant in Infectious Diseases and Tropical Medicine. Secondly, patients with psychiatric disorders considered to be exclusion criteria as diagnosed by a consultant in psychiatry, were excluded from the study. Patients were invited to participate in the study then followed up by letter, unless they requested an appointment on the day.

Eighty-four patients were invited to participate (of these 8 had been approached in phase one). Of those approached 19 failed to respond to follow up letter, one no longer fulfilled criteria, 4 declined to participate (see appendix 3.5. for further details), 3 had incorrect addresses in the patient records and one was awaiting clinic appointment. This resulted in the appointment of 56 patients of whom two cancelled and 1 did not arrive, This resulted in the testing of 53 patients, 63.1% of those approached in clinic.

As can be seen in table 3.2.3. Mann Whitney tests showed participants did not differ according to recruitment phases 1 and 2. for age, education, socio-demographic group, or the duration of their illness, $p<0.05$.

Table 3.2.3. Mann Whitney Tests for differences between CFS on demographic characteristics according to phase

VARIABLE	U	Z	P
Education	284.5	-1.9467	0.0516
Age	285.0	-1.2408	0.2147
Illness Duration	318.0	-1.1793	0.2383
Sociodemographic	320.5	-0.436	0.6629

15 participants from phase 1 and 54 participants from phase 2 recruitment

In total 158 patients were approached, 3 no longer fulfilled the Oxford Consensus criteria for CFS (Sharpe, Archard, Banatvala, et al., 1991). Sixty-one patients did not respond and letters were posted to 4 incorrect addresses. This resulted in a response of 90 patients of whom 77 were finally appointed, (for non-participation reasons see appendix 3.5.). Of these 77, five appointments were cancelled and 4 patients did not arrive. This resulted in the testing of 68 CFS patients, giving an overall response rate of 43.9% of available participants.

Control participants were recruited between November 1996 and June 1998. These participants considered themselves to be healthy and free from psychiatric problems, fatigue, depression or anxiety. The participants were recruited from two areas: friends or relatives of patients or controls; and staff or students from the University of Leeds, United Leeds Teaching Hospitals or the Mary Morris International Residence Limited, because this was a convenient and varied source of control participants. They either volunteered whilst accompanying patients to Clinic, or responded to advertisements posted in newspapers and around the University Campus.

3.2.4. Testing Procedure

Both groups of participants were tested in clinical and non-clinical settings and at different times of the day, depending on the mutual convenience of the researcher and participants. Testing took place either at the Seacroft-Leeds Fatigue Clinic, Saint James' University Hospital, or at the School of Psychology. Participants were given the Information Sheet (appendix 3.6.) and any questions that arose were answered.

Participants then gave written consent (Consent Sheet appendix 3.7.). For confidentiality participants were then allocated a participant number, according to the counterbalance schedule, which was recorded on all test items. There then followed a short interview to assess background details. Participants then completed the self rated questionnaire measures, assessing fatigue, depression and anxiety. These tasks were administered in the order determined by the counter balance schedule (appendix 3.3.). Neuropsychological tests then followed. Participants completed these tests, again in the order given by the counterbalance schedule. Following testing participants were asked if they had further questions. When these had been satisfactorily answered they were given a debrief sheet (appendix 3.8.).

3.2.5. Statistical Methods

All data were analysed using SPSS for Windows, version 6.1. Data of ordinal or categorical levels were analysed using non parametric statistics. Data of interval and ratio levels were analysed using parametric statistics. Standard deviations are presented in parentheses after the means. Where there were differences in the homogeneity of variance between CFS and control participants according to Levenes F Test, non parametric alternatives were used. Except when adjusting for multiple comparisons, and unless otherwise stated, a strict level of $p=0.05$ was taken for statistical significance, and all values above this were considered to be non-significant. For tests where expected effects were not significant, post hoc power analyses were calculated to determine the potential for Type II error.

3.2.6. Ethics

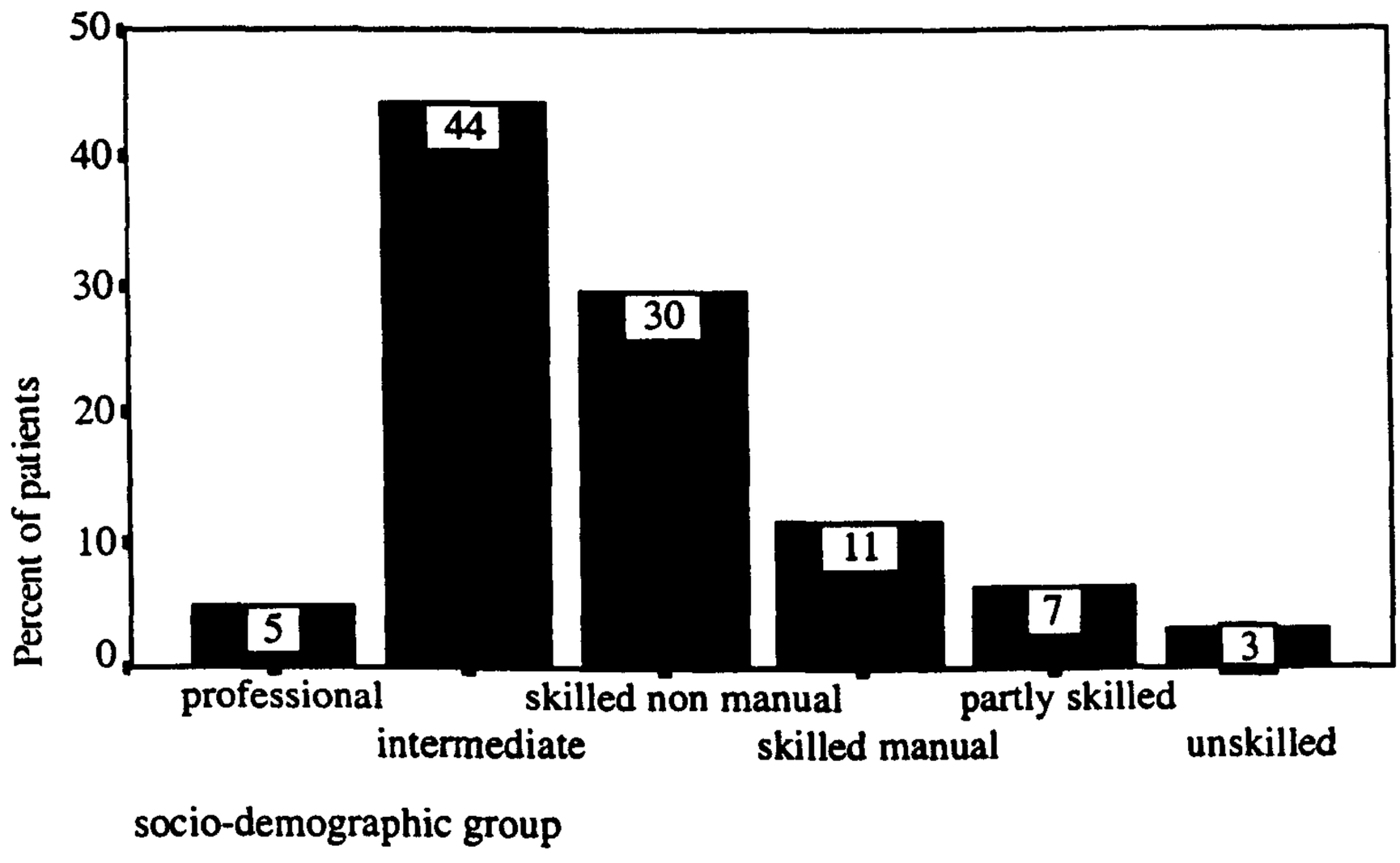
This project was approved by the St James's University Hospital NHS Trust Clinical Research Ethics, project number 95/288, and by the Leeds General Infirmary Research Ethics Committee, project number CA96/028.

3.3. Patient Demographics

3.3.1. General Characteristics

Patients were from 18 to 66 years old, with a mean age of 40.7 (11.5) years and a quartile range of 32 to 50 years. The largest proportion (35.3%) of these CFS patients were educated to degree level, with 14.7% having no formal qualifications or equivalent training, and 5.9% having a higher degree.

Figure 3.3.1.1.a. Distribution of socio-demographic group



The percentage of patients in each category is inset into each bar.

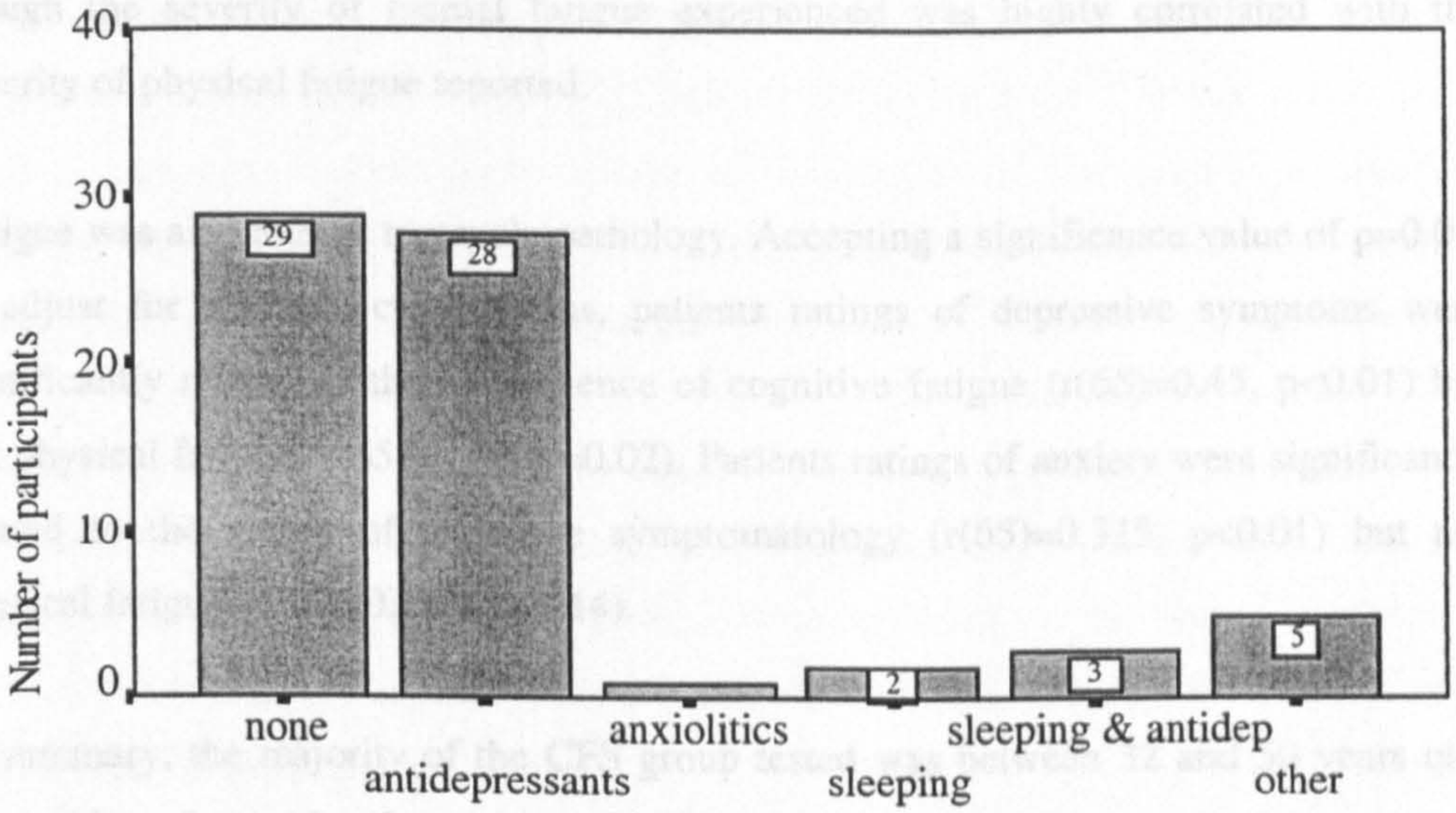
The majority of patients were in socio-demographic group II, with only 9.9.% being in social group IV and V. Seven patients were not entered into the analysis, 6 of whom were students and one for whom data was missing. The percentages of patients in each class are represented in figure 3.3.1.1.a. above.

An illness duration of less than or equal to 5 years has been arbitrarily used for inclusion of patients in some of the CFS literature; 60.3% of these patients fulfilled such criteria. Duration of illness ranged from 10 months to 288 months, and duration of clinic attendance from 0 (first attendance) to 96 months. These upper values represent

outliers and thus were excluded from mean calculation; this resulted in a mean duration of 24.7 (16.3) months of clinic attendance and 67.8 (43.19) months for illness length.

Excluding HRT or the oral contraceptive, 57.7% of patients were taking prescribed medication. Sleeping tablets and anxiolytics were taken by some patients, though the majority were using antidepressants, see figure 3.3.1.1.b. below for numbers.

Figure 3.3.1.1.b. Medication use in CFS patients.



The number of patients in each category are inset into each bar.

3.3.2. Psychiatric Variables

Anxiety and depression were assessed with the HAD scale, this gave separate scores for anxiety and depression. Taking the accepted value of eleven, or above, for denoting clinical levels of anxiety or depression, 36.9% of patients were clinically anxious, and 24.6% experienced clinical levels of depression, with 4.6% of these experiencing both anxiety and depression.

3.3.3. Fatigue Characteristics

Using the Fatigue Scale (Chalder, Berlowitz, Pawlikowska, et al., 1993), a maximum score of 28 could be obtained. The mean score was 19.1 (6.3), with a quartile range of 15.75 to 24.00. The mean score for healthy controls was 2.30 (4.090), providing an

anchor for the relative severity as assessed by this scale. A cut off of four for Chronic fatigue has also been used with this scale (Pawlikowska, Chalder, Hirsch, Wallace, Wright, & Wessely, 1994).

In the week prior to and including testing, 69.1% of patients reported having experienced cognitive symptoms of fatigue to a moderate or extreme extent. Experience of physical symptoms to a moderate or severe extent were reported by 80.9% of patients. Generally, patients experienced more physical than mental fatigue, though the severity of mental fatigue experienced was highly correlated with the severity of physical fatigue reported.

Fatigue was also related to psychopathology. Accepting a significance value of $p=0.01$, to adjust for multiple comparisons, patients ratings of depressive symptoms were significantly related to their experience of cognitive fatigue ($r(65)=0.45$, $p<0.01$) but not physical fatigue ($r(65)=0.29$, $p=0.02$). Patients ratings of anxiety were significantly related to the extent of cognitive symptomatology ($r(65)=0.315$, $p<0.01$) but not physical fatigue ($r(65)=0.185$, $p=0.14$).

In summary, the majority of the CFS group tested was between 32 and 50 years old, educated to degree level and in sociodemographic group2. They had a mean illness duration of 67.8 months, and had been attending clinic for 16.3 months. The majority of participants reported cognitive symptoms in the week prior to testing, though experienced more symptoms of physical fatigue. More than half the tested group was taking prescibed medication, though those patients exhibiting clinical levels of anxiety and depression were in the minority

3.4. Neuropsychological Sub-Test Performance

Tests of paired associate learning have been used widely in the research on CFS and cognition. Though existing results have been conflicting, there are general underlying trends for performance. The discrepancies that are apparent may be the result of differences in sample characteristics or sample sizes between studies. The following tests were undertaken firstly, for comparability with the existing research and secondly,

in an effort to investigate whether differences could be attributed to symptoms of depression or anxiety.

3.4.1. Logical Memory Test, WMS-R

3.4.1.1. Hypotheses and Methods

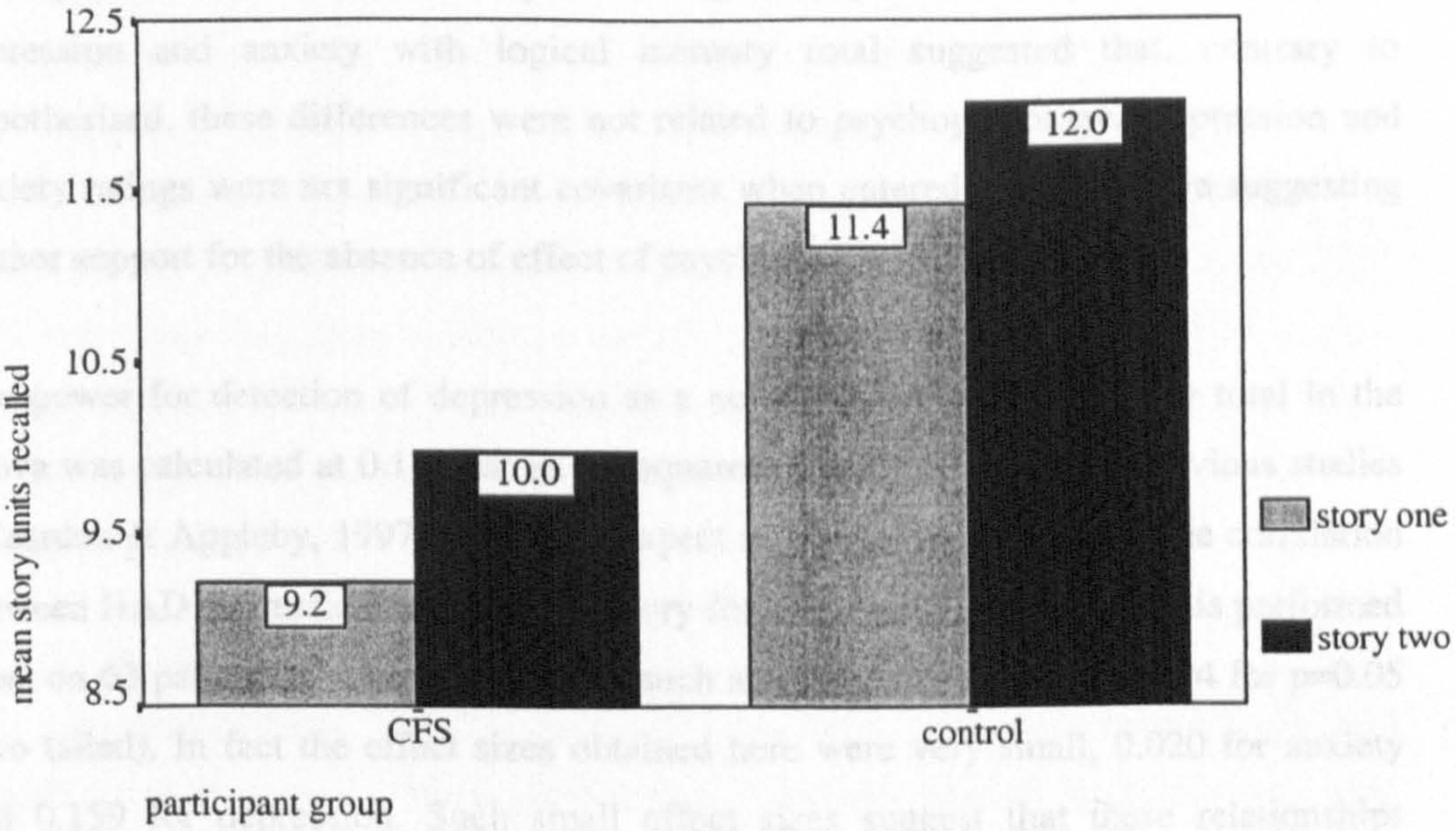
As mentioned in chapter two (section 2.3.2.3.) logical memory performance in CFS has been reported to vary with psychopathology, and comparisons between CFS and control patients have yielded mixed results. It was hypothesised that there would be differences between controls and CFS patients. However such differences may be, in total or part, due to comorbid symptoms of depression and anxiety; this is consistent with the significant correlation of anxiety and depression scores with total memory score. Time on test effects are often expected as a result of increased fatigue over the testing period. However, no differences were expected between controls and CFS on repeated testing since story two immediately followed story one; though both groups were expected to improve as a result of practice for second story recall. The test, described in section 3.2.2.3. was administered according to the method detailed in section 3.2.4. Data on logical memory performance was available for 66 CFS patients and 63 control participants.

3.4.1.2. Results

The total logical memory score of CFS patients did not correlate significantly with depression ($r(63)= -0.16$, $p=0.21$) or anxiety symptoms ($r(63)=0.02$, $p=0.89$) nor with the total HAD score ($r(63)=-0.08$, $p=0.55$). An independent t-test illustrated that there were significant differences between CFS and controls such that control participants remembered more story units than CFS patients ($t(127)= -3.59$, $p<0.01$). As can be seen in figure 3.4.1.2. participants recalled more units on the second story than on the first.

A post hoc stepwise multiple regression analysis using all measures of psycho-pathological and fatigue symptoms was performed to establish which factors were contributing to performance on this test. As can be seen in Table 3.4.1.2. below only PFRS-F (extent of physical symptoms) was entered into the equation of patient symptoms upon logical memory.

Fig 3.4.1.2. Performance of CFS and controls on the Logical Memory Test



A change of one standard deviation in the PFRS-F score of subjective fatigue ratings being associated with a change of 0.319 standard deviations in logical memory total. This is supported by consideration of the Pearsons correlation coefficient of PFRS-F with logical memory total ($r(66)=-0.28$, $p=0.025$).

Table 3.4.1.2. Results of stepwise multiple regression

Variable	Beta	T	Sig. T
PFRS- F/physical	-0.319	-2.563	0.01
HAD-depression	-0.0960	-0.774	0.46
HAD-anxiety	0.0291	0.230	0.82
PFRS-cognitive	-0.0807	-0.548	0.59
PFRS-emotional	-0.0003	0.003	1.00
PFRS- somatic	-0.1213	0.718	0.48
Fatigue Scale	0.1212	0.922	0.92

3.4.1.3. Conclusions

There were significant differences between CFS and control patients such that CFS recalled fewer story units than controls. Both CFS and controls improved performance on the second story, suggesting that both groups increased with practice, the lack of

interaction effects of participant group with test presented suggest that the CFS participants were not differentially benefiting from practice. Correlation analysis of depression and anxiety with logical memory total suggested that, contrary to hypothesised, these differences were not related to psychopathology. Depression and anxiety ratings were not significant covariates when entered into the anova suggesting further support for the absence of effect of psychopathology.

The power for detection of depression as a covariate on logical memory total in the anova was calculated at 0.172 for an eta squared of 0.07. Referring to previous studies (Wearden & Appleby, 1997) we would expect an effect size of 0.45 for the correlation between HAD depression score and memory for story units. For the analysis performed here, on 63 patients, the power to detect such an effect size was good, 0.94 for p=0.05 (two tailed). In fact the effect sizes obtained here were very small, 0.020 for anxiety and 0.159 for depression. Such small effect sizes suggest that these relationships obtained here are probably not of profound importance and would require extremely large groups for their detection. CFS patients do significantly differ from controls, having worse recall, and these results are not attributable to depression or anxiety as measured by the HAD. The regression analysis suggested that a large proportion of the variance in logical memory total could be related to the patients ratings of their physical symptoms of fatigue, and was not related to symptoms of emotional distress, somatisation, anxiety, depression, nor even cognitive fatigue.

3.4.2. Digit Span

3.4.2.1. Hypotheses and methods

Five studies have reported that there are no differences in Digit Span performance between CFS and control participants, contrary to 3 studies reporting differences (see section 2.4). For studies where differences have been found it may be that the results obtained are not representative of the larger CFS population; for example, in one study not all of the patients fulfilled the CFS criteria used for recruitment (Michiels, Cluydts, Fischler, Hoffman, LeBonner, & De Mierlier, 1996). In another study only 12 patients were tested (De Luca, Johnson, & Natelson, 1993), and further studies by this research group with larger numbers did not detect differences between CFS patients and controls (De Luca, Johnson, Beldowicz, & Natelson, 1995, De Luca, Johnson, Ellis, &

Natelson, 1997). It is therefore expected that CFS and control patients will perform no differently on tests of forward and backwards digit span.

The digit span test was described in section 3.2.2.3 and the testing procedure in section 3.2.4. In this research, the Digit Span Test was administered as a distractor task between study and recall conditions of implicit and explicit memory tests. Thus the test was administered twice, and the time between first and second presentation of the Digit Span Tests was subject to individual variation. Given that the typical period of time elapsing between tests was 5 minutes, time on test effects were not expected. Eight cases were rejected because of missing data, thus 63 CFS patients and 62 controls were entered into the analysis.

3.4.2.2. Results

As can be seen in Table 3.4.2.2. CFS participants had a mean performance lower than controls on all measures of the digit span test. A 2 (CFS, control) by 2 (time one, time two) by 2 direction (forwards, backwards) anova illustrated that there was a significant main effect of participant type ($F(1,123) = 11.86$, $p<0.01$). However, depression as measured by the HAD scale was a significant covariate ($p=0.01$), though anxiety was not. When the analysis was calculated using depression as a covariate, there was no significant effect of participant type ($F(1,121) = 0.74$, $p=0.39$); the performance of CFS patients was not significantly different from controls.

Table 3.4.2.2. Mean performance on the Digit Span Test.

Digit Span Test	CFS	control
forwards time one	7.89 (2.27)	9.21 (1.73)
backwards time one	6.25 (2.37)	7.48 (2.04)
forwards time two	8.12 (2.42)	9.16 (2.03)
backwards time two	6.49 (2.54)	7.56 (2.19)

Again with depression as a covariate, there was a significant main effect of test direction ($F(1,121)=0.08$, $p<0.01$) such that performance on digit span forwards was better than digit span backwards. There was no significant interaction of type by test direction, ($F(1,121)=0.48$, $p=0.49$). There was no significant difference between presentation at time one and time two ($F(1,121)=0.98$, $p=0.32$), and no significant interaction with type, $p>0.05$.

3.4.2.3. Conclusions

Though differences were apparent in initial inspection and analysis between CFS and controls, these differences were attenuated when depressive symptomatology was controlled for. Any differences between the groups are probably attributable to depression; the effect of anxiety was not significant. Thus in support of existing research there were no differences between CFS and control patients, controlling for depression. Additionally there were no effects of repeated presentation for either group, illustrating that neither group had benefited from practice. As would be expected performance on Digit Span Forwards tasks was significantly better than performance on Digit Span Backwards (Wechsler, 1987) for both groups.

3.4.3. Paired Associate Learning

3.4.3.1. Hypotheses and methods

As discussed in section 2.3.2.1. there have been some discrepancies in the results of Paired Associate Learning when CFS patients are compared with controls. It was hypothesised that there would be differences in both easy and hard pairs of the paired associates task, and thus in total performance. However if there were differences between CFS and controls on easy pairs these would probably be attributable to the comorbid symptoms of depression, whilst symptoms of anxiety would not be related to performance. Differences between CFS and control participants on hard pairs would remain when considering comorbidity factors. The paired associate test was described in section 3.2.2.3 and the testing procedure in section 3.2.4. Excluding missing data there were 128 participants available for analysis, 65 CFS patients and 63 controls.

3.4.3.2. Results

As can be seen in table 3.4.3.2. below, mean CFS patient performance was lower than that of controls. An independent t-test revealed that there were significant differences between CFS patients and control participants in the total performance on this task ($t(125)= -3.74$, $p<0.01$).

Table 3.4.3.2. Paired Associate Learning Performance (means)

Paired associate measure	CFS	Controls
Total	16.17 (4.21)	18.65 (3.19)
easy pairs	10.46 (1.87)	11.11 (1.09)
hard pairs	5.72 (3.18)	7.54 (2.70)

Performance on the sub-components of the test was analysed using a 2(CFS, controls) by 2(easy pairs, hard pairs) anova. This revealed a significant effect of participant type ($F(1,126)=13.76$, $p<0.01$), such that CFS patients performance was worse than that of controls. There was also a significant interaction of patient type by the sub-task (easy or hard pairs), ($F(1,126)=5.43$, $p=0.02$). Both depression and anxiety as measured by the HAD were significant covariates, and were thus entered into the analysis. Ancova revealed that the effect of participant group remained significant ($F(1,122)=4.37$, $p=0.04$), as did the interaction of participant group by easy/hard pairs ($F(1,122)=4.62$, $p=0.03$). Post-hoc analyses showed that the differences between CFS patient and control participant performance on easy pairs was not significant, but that there were significant differences between groups on hard pairs $p<0.01$. CFS participants performed significantly better on the hard pairs task than on the easy pairs task, $p<0.01$.

3.4.3.3. Conclusions

There were differences in performance between CFS and controls on all measures of the Paired Associate Learning Test. Though, some of the variance could be accounted for by the effects of comorbid depression and anxiety, differences still remained when these symptoms were controlled for. The deficit in CFS performance on hard pairs was greater than that for easy pairs. Contrary to the effects hypothesised anxiety did significantly covary with performance, and in fact accounted for more change than depression. This conflicts with the previously reported absence of association of anxiety with performance (McDonald, Cope, & David, 1993). This is probably the result of differences between the analyses between the studies. In this research the inclusion of control participants, the majority of whom had low anxiety, would increase the spread of possible anxiety scores and be more likely to result in a significant correlation in the spread of anxiety symptoms; whereas the study by McDonald et al. (McDonald, Cope, & David, 1993) included only CFS patients, most of whom experienced anxiety symptoms.

3.4.4. Neuropsychological Test performance: Conclusions

On the neuropsychological tests both Logical Memory performance and Paired Associate Learning Performance were impaired in the CFS group, even when depression and anxiety were considered. When depression was controlled for there were no differences between CFS patients and controls on Digit Span performance. From a traditional neuro-psychological perspective this would suggest that these patients do not exhibit memory difficulties. The absence of deficits on the Digit Span Test suggests that attention is probably spared. However, such a statement is descriptive rather than explanatory. If we consider these deficits in the light of existing research, as reviewed for example by Tiersky, Johnson, Natelson, & De Luca (1997) and in chapter 2, a more explanatory framework may be articulated.

Generally it has been reported that in CFS patients higher intellectual function is spared, whilst they exhibit difficulty with some tests of memory and speed of processing. However, the current literature together with the results here are consistent with an explanation of slowed processing to describe the deficits observed in CFS.

CFS patients performance on hard paired associates is impaired whilst their performance on easy pairs, remains intact. As was discussed in chapter two, the strength of association between cue and memory is associated with speed, and as strength increases so does speed and the capacity of a cue to activate a memory. If speed of information processing is generally slowed in CFS patients, we would expect that the strength of association between cue and memory would be weakened, and recall reduced. It may be that the representations between the novel relations are weakened to a greater extent than those representations which already exist. Hence CFS patients were no worse than controls on easy pair performance, using existing representations, which do not have to be created, just strengthened. In contrast performance on hard pairs was significantly worse for CFS patients as compared to controls. Here novel representations needed to be created and may be insufficiently active, or too weak, for effective recall.

Interestingly these differences are not just apparent when cues are provided externally as in paired associate learning, but also when conceptual cues are provided internally, as in the case of the logical memory task. As has been noted previously speed of processing problems are likely to impact on memory performance, particularly where

cues to retrieval are provided. Transfer appropriate processing states that if the processes involved in encoding are re-instated in retrieval then recall is maximal. If process overlap is large then recall is improved as compared to conditions where overlap is slight (Jacoby, 1991). Cueing should provide retrieval via partial reinstatement of the content or the reinstatement of the processing involved at encoding, or both. If however representations are weakened, cues may provide no direct benefit, representations being too weak to overlap sufficiently. The significantly lower logical memory score of the CFS patients may suggest that slowing impacts globally on representational strength; new representations being weak, and old representations not be sufficiently strengthened. This would consequently affect the overlap of the representation at retrieval with the representation from study. From a transfer appropriate processing perspective this would impact on retrieval performance.

3.5. Study Comparability

The mean age of CFS respondents in this study was 40.7 years. This is comparable with other reported results in this area, mean ages of CFS participants ranging from 30 to 44.5 years. The ratio of male to female patients was 1:1.5. These figures are similar to those reported in previous studies of neuro-psychological function in CFS tertiary care clinic attendees, for example Vollmer-Conna, Wakefield, Lloyd, et al. (1997) report a ratio of 1:1.33, and Wearden & Appleby (1997) a ratio of 1:1.38. This value is more balanced than the ratio which would be found in a primary care population, for example 1:5.66 (Joyce, Blumenthal, & Wessely, 1996), and probably reflects a bias of referral (Euba, Chalder, Deale, & Wessely, 1996). The duration of fatigue was 67.8 months, with 60.3% of patients having an illness duration of less than sixty months as has been specified in some studies. The range of illness duration was comparable with that found in other research reports (Sandman, Barron, Nackoul, Goldstein, & Fidler, 1993, Vollmer-Conna, Wakefield, Lloyd, et al., 1997); additionally there are reported to be no differences in illness duration between tertiary and primary care clinic attendees (Euba, Chalder, Deale, & Wessely, 1996).

This sample is less biased to a higher socio-demographic group than previous tertiary care samples, and contrary to what would be expected as a result of referral bias (Euba, Chalder, Deale, & Wessely, 1996). The majority of patients were in social group II,

with social group IIIn being the next most represented. This may be advantageous in that results will be more comparable with the wider population of CFS patients. Educationally 35.3% of the sample were educated to degree level. This is not atypical of tertiary care populations (Euba, Chalder, Deale, & Wessely, 1996), for example in a study by Vollmer-Conna, Wakefield, Lloyd, et al. (1997) 47.6% of patients were educated to degree level. In contrast primary care samples report the education of most participants to be of O/A level (McDonald, Cope, & David, 1993). In the main this group is more highly educated and has a more equal representation of female and male participants than would be expected in a primary care sample. These biases are typical of those found in patients at tertiary level care (Euba, Chalder, Deale, & Wessely, 1996). This group is lower in socio-demographic status than would be expected for a tertiary care sample and is thus comparable to a primary care population in this, as well as age and illness duration. Results may thus, with caution regarding sex and education, be more generalisable to the wider CFS population.

A variety of inclusion criteria for study have been detailed in the literature, ranging from the exclusion of all patients with depressive symptomatology, to only those with clinical symptomatology, to the inclusion of all CFS patients irrespective of comorbidity. The latter, whilst potentially confusing results, does at least mean that results are generalisable, and that there is the potential to evaluate the effects of comorbidity. The results obtained here are consistent with previous literature reporting that fatigue is related to anxiety, depression or somatisation (McDonald, Cope, & David, 1993, Lane, Manu, & Mathews, 1991). The majority of this sample report symptoms of moderate to extreme cognitive (69.1%) and physical fatigue (80.9%). Generally hospital samples report significantly higher fatigue than primary care samples (Euba, Chalder, Deale, & Wessely, 1996). This group had a mean cognitive fatigue severity rating and physical fatigue severity ratings on the PFRS comparable to that of a tertiary care study (Ray, Weir, Phillips & Cullen, 1992) (3.5 vs. 3.8 for cognitive, and 4.2 vs. 4.0 for physical symptoms). This translates to experience of symptoms to a severe, but not extreme, extent. These patients thus probably represent those at the more severe end of the spectrum of CFS, and symptoms may be greater than those observed in primary care populations.

In support of most existing research, there were no differences between CFS and control participants on digit span performance, once the effects of depression had been

considered. As previously mentioned deficits in performance have been described in 3 studies. However, these studies had small sample sizes, or considered of the effects of only clinical symptomatology, or not all patients suffered from cognitive symptoms. Consideration of comorbid symptoms of psychopathology for example, may change the significance of results obtained, this can be seen quite dramatically in the case of Digit Span above.

Performance on the Paired Associate Learning Test was impaired for these CFS participants as compared to controls, with anxiety and depression as significant covariates. These differences still remained when controlling for the effects of comorbid symptoms. Further analysis suggested that the performance was worse for hard pair performance, whilst differences between CFS and control groups were not significant for easy pairs. The deficits observed here support those observed in a number of studies (e.g. Krupp, Sliwinski, Masur, & Freidburg, 1994, Wearden & Appleby, 1997, Cope, Pernet, Kendall, & David, 1995, Grafman, 1993, McDonald, Cope. & David, 1993, Joyce, Blumenthal, & Wessely, 1996).

CFS performance on the logical memory test was worse than control performance. These differences were independent of depression and anxiety, and were in the main associated with differences in the ratings of physical fatigue. These results are consistent with some of the literature (Grafman, Schwartz, Dale, Scheffers, Houser, & Straus, 1993, Grafman, 1993, Riccio, Wilson, Thompson, Morgan, & Lant, 1992), but conflict with reports of impaired performance being attributable to depression (Krupp, Sliwinski, Masur, & Freidburg, 1994, Wearden & Appleby, 1997) and a number of studies which report no differences (De Luca, Johnson, Beldowicz, & Natelson, 1995, Krupp, Sliwinski, Masur, & Freidburg, 1994). Discrepancies between these results and the existing literature may have arisen as a result of differences in the methods used. In this study the effect of depression was considered by looking at symptoms incrementally, from non-depressed to extremely depressed, rather than considering clinical versus non clinical diagnosis as in (Wearden & Appleby, 1997). The different diagnoses as in (Krupp, Sliwinski, Masur, & Freidburg, 1994, De Luca, Johnson, Beldowicz, & Natelson, 1995), and as discussed in chapter one, may also have impacted on cognitive findings.

3.6. Summary

The group of patients that are investigated here performed similarly on standard neuro-psychological tests to those in other research samples and is comparable to other samples demographically. The results from the following studies are generalisable to the rest of the tested CFS population, though symptoms may be expected to be less severe in primary care samples. The next chapter will concentrate on illustrating differences in speed of processing, and the following chapters on describing the nature of such slowing. Tests of sufficient power are particularly important in this population, as is the inclusion of confounding variables such as depression and anxiety, which may account partially or totally for differences. These concerns will thus be addressed in the analysis of work presented in the following chapters.

Chapter

4

Information Processing: Graded Reactions.

4.1. Introduction

As discussed in section 3.5.4. the observed deficits of CFS patients on the WMS-R sub-tests, together with the deficits previously observed in this population (reviewed in chapter 2), are consistent with an explanation of slowed processing. In this chapter the expected slowing of performance in CFS patients will be investigated using tasks graded from perceptual to conceptual in their processing requirements.

The study of conceptual and perceptual processing has a long pedigree, but is embodied in the work of Craik and Lockhart (1972) who defined a 'levels of processing' continuum. They suggested that there were a number of different depths ranging from a low level perceptual processing of the stimulus to a higher level more conceptual or semantic evaluation; depth essentially referring to a '*greater degree of semantic or cognitive analysis*' p.675 (Craik and Lockhart, 1972). Perceptual processing can be considered as that relating to the physical attributes of the stimulus, such as counting vowels, where as conceptual processing involves the analysis of meaning[1].

This depth of processing approach has generally been applied to the study of memory and its time course. Research on the time course suggests that conceptual processes take longer. Weldon (1993) studied the availability of perceptual and conceptual information during a word priming task. Words were exposed for durations of 500 ms to 12 seconds. The greater the exposure time the better the subsequent unintentional recall. Since visual word primes were better primes than pictures it was suggested that

word primes may result in the fast recruitment of perceptual processes. The second study manipulated the depth of the encoding task using a surface processing task (rating graphic or acoustic quality) and a deeper processing task of rating pleasantness. This work suggested that the time course for the activation of perceptual processes is faster and earlier than for conceptual processes in word fragment completion, though both may be involved in the task. Additionally those processes which take longer are better remembered (Craik & Tulving, 1975); in other words those with a high conceptual encoding content. Eysenck (1980) demonstrated that semantic or deeper processing of information was slower than phonemic or shallow level processing (see also Weldon, 1993). Here participants were required to read words or produce an adjective typically used to modify the noun. This unintentional learning paradigm was followed by intentional retrieval. Again both recall and recognition were better in the semantic condition.

The notion of depth of processing has been widely debated in implicit and explicit memory[2] (see Roediger, 1990a & 1990b for further discussion). Here much of the work on perceptual processing has been in implicit memory and on conceptual processing in explicit memory. However, since such levels of processing have been studied in memory their understanding is inextricably linked with the types of retrieval strategies used. It has been demonstrated that the extent to which the test processes overlap with those of encoding is a crucial determinant of the proportion of studied information subsequently retrieved (Morris, Bransford, & Franks, 1977). This is known as Transfer Appropriate Processing. Early studies of implicit memory were typically perceptually based. Hence in these studies the absence of an enhancement in implicit recall from more conceptual processing can be attributed to a mismatching of the processing at encoding and retrieval. Following this transfer appropriate processing approach, in both implicit and explicit memory conceptual processing at encoding when matched with a perceptual retrieval task should be worse than when matched with a conceptual retrieval task.

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[1] These may also be referred to as data driven and conceptually driven tests, as by Blaxton (1989).

2 In this thesis explicit memory is defined as intentional retrieval of a previously to be remembered event, where as facilitation of performance at test as a result of prior exposure to 'study' items reveals implicit memory, here learning is not intentional.

More recently in attempting to define implicit and explicit memory a distinction between perceptual and conceptual tests has been made. Here an integration of the levels of processing approach and the transfer appropriate processing approach is apparent. Essentially memory performance is enhanced when it may benefit from both levels of processing manipulations at study and an overlap with processes of retrieval. In other words memory for conceptually encoded information should be better on conceptual retrieval tasks, than memory for perceptual information with perceptual retrieval tasks[3].

Lately the idea of a processing continuum across both implicit and explicit memory has seemed probable, as benefits to implicit memory as well as explicit memory have been observed for encoding involving conceptual processing (Shimamura, 1986). In a study by Pitarque (1992) a lower level 'read' study condition was compared to a more semantically or conceptually processed 'generate' the study word. Here there was a clear advantage of the more elaborative generate condition over the read condition. Challis and Brodbeck (1992) reported clear levels of processing effects in a perceptual implicit memory test. However these studies have compared simply conceptual with perceptual processing. In a study by Blaxton (1989) three types of encoding tasks were used moving along the perceptual conceptual continuum: 'no context' where XXX was presented before the to-be-remembered (TBR) item; 'context' where a semantically related word preceded the TBR item; and 'generate' where participants produced a TBR item from a semantically related cue. In all conceptually driven tests there was a clear levels of processing effect moving from no context to generate conditions. The reverse pattern was apparent for perceptual tests where recall was enhanced by perceptually driven encoding tasks Whilst these latter results suggest a transfer appropriate processing explanation, there is still a continuum of processing from perceptual to conceptual encoding which overlaps with the extent of perceptual or conceptual processing at study.

A more recent report Challis,Velichkovsky and Craik. (1996) show a levels continuum using a number of conditions. Here five encoding tasks are employed: letter counting, syllable counting, deciding whether or not the item was living, the encoding of self referent information, and intentional learning. These are reported to be of increasing

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[3] Since further detail is beyond the scope of the chapter this represents somewhat of an over simplification, (see Brown & Mitchell, 1994 for review).

depth from letter counting to intentional learning on a continuum of processing. Again whilst the type of retrieval condition affected the proportion of recall, there were generally clear levels of processing effects, recall increasing from perceptual to conceptual study.

Examples of such depth of processing continuums have been demonstrated in a study of recognition of faces (Sporer, 1991). Here seven encoding strategies, varying in depth of processing, were used. Three encoding tasks were self generated: rating a distinctive physical feature, making a character judgement, and deciding the persons hobby. For the remaining four the participants were required to rate a given characteristic (e.g. one or three physical features, a personality trait, and a hobby). Self generated processes revealed increased memory performance as did increasing the processing depth.

Generally it is accepted that processing can be graded from perceptual to conceptual. More specifically, for example as generated from the above studies, a continuum from perceptual to conceptual processing might include the following ordered tasks:

- subliminal perception.
- automatic lexical perception, such as reading a word
- contextual judgement of physical features, such as number of letters
- more global physical features of the word, such as syllable counting
- semantic processing such as deciding if an item is living
- self referent tasks, such as deciding if you own an item.

The nature of the processing continuum provides the opportunity to assess the proposed slowed processing in CFS patients.

The previous research, discussed above would suggest that in healthy controls the expected response latencies would increase progressing from a perceptual to conceptual processing task. As was discussed in section 2.6 performance slowing may arise as a result of representational weakness. Here a difference between conceptual and perceptual processing might be seen. Perceptual processes would be expected to use fewer representations and require less processing than conceptual processes which require more active representations and processing; this is consistent with the demonstrated time differences. If representations are weakened those tasks requiring

more processing, and thus a longer time, may be subject to greater interference and thus a greater slowing, in other words more conceptual tasks.

It should thus be possible, by grading the response times obtained, to illustrate the possible effects of change in speed of information processing on decision making. Performance times should be slowed by an amount proportional to their complexity and number of representations likely to be used. Task difficulty should therefore be related to performance speed. It may be, however, that decision making times are slowed by the same absolute amount. Since in this scenario more complex conceptual processes are affected to the same extent as perceptual processes it might suggest that representational weakness is not solely responsible for slowing, factors such as large slowing of motor speed may create such an effect.

In summary, if cognitive representations are weakened in CFS patients, then their less conceptual judgements should show a smaller decrement in response latency than more conceptual judgements about an item. Such changes would be proportional to the response times typical for such processes, and should therefore represent a similar overall change in response speed.

4.2. Selection of items for the graded reaction test.

In order to exploit the possible differences present between control participants and CFS patients in performance speed, a continuum of processing was devised based on the research presented above.

It has been reported that though the perception of words is automatic and highly perceptual (Weldon, 1993), that there may be some contamination after a prolonged period of exposure by the recruitment of conceptual processes (Weldon, 1993). It was therefore decided to use a non-lexical stimulus, with no meaning, as the first level of the continuum. This represented a base line where conceptual processing of the items was not expected. Response times were expected to be fast and the difference between control participants and CFS patients thus to be minimal. The next level used was that of lexical processing, as stated above thought to be largely perceptual. Since exposure was not prolonged, conceptual processing was expected to be minimised. Physical

features of the word formed the next level, with processing focusing on the number of vowels present. The remaining levels were semantically based, participants deciding if items could be found in the countryside and whether or not items were useful, thus introducing a self referential judgement. In these tasks processing theoretically is more complex, involves more representations and should take longer and it is thus here that the difference between the two groups of participants would be expected to be greatest.

Thus, test and practice items requiring judgement were both symbols and words, a total of 14 words and 6 symbols for each participant (see table 4.2.a.). There were five types of question graded from perceptual to highly conceptual in their processing requirement. Each of these was presented 4 times, thus making a total of 20 experimental trials. Five practice trials were also included, in order that participants became familiar with the response format.

Table 4.2.a. Statement and response items for graded reaction time test

LOP	statement screens	test items
1 *(perceptual*	The following item is a symbol	4 *
2	The following item is a word	2 *, 2 words
3	The following item has more than 2 vowels	4 words
4	The following item could be found in the countryside	4 words
5 *conceptual)*	The following item is useful	4 words

each statement was randomly presented 4 times.

For each of the 20 trials, participants were required to read the statement and then they proceeded to the item to be judged. For this task they had a maximum time of 10 seconds, and could spend as much or as little of this time reading the question, initiating the test item when ready. This ensured that all readers would have sufficient time to read the statements yet did not have to wait for the item screen to be presented. It prevented the potential consideration of related category concepts, which may have speeded up response times in particular categories of statement by the provision of conceptual links (discussed further in section 5.1.)~ in effect a self generated priming.

Questions were worded so that the responses available for each item were uniform and could be compared across levels of processing and so the duration of Yes/No response on truth or falsity could be recorded. The list of response items was devised in order

that the correct response did not become predictable; thus a mixture of both false and true statement-item pairs were used.

Since response latencies to particular words may differ as a result of word frequency, orthographic structure and phonetic spellings (Massardo & Cohen, 1994), two controlling factors were implemented. Firstly, words were randomly cycled through the possible levels of processing judgement positions. This was done by pairing statement screens with item screens, word item screens were randomly cycled through word positions for each new trial, of the 20 presented trials. Thus each word could appear as a possible item to be judged for each level of processing[4].

It was also important that the same proportions of word could be judged correctly and incorrectly for each level of processing, since it could potentially appear as a response to each question and a balance of potential affirmative and negative responses were required. Words were thus selected so that there was an even number of correct and incorrect responses for each possible trial type, thus responses did not become predictable and differences as a result of response type were minimised. A list of 16 words was devised from which 14 were randomly used for each participant. These were then presented randomly with statements screens requiring word positions, as detailed on table 4.2.a. Of the 16 words, given overlap between categories, 7 could be considered useful, 7 had more than two vowels and 7 could be found in the countryside (see appendix 4.1.).

These sixteen concrete nouns (appendix 4.1.) were taken from Eaton (1940) based on their frequency of usage in British, rather than American English. This corpus consists of 20 000 words compiled from a frequency count of 956500 words from 279 written sources. The 16 nouns used were from concepts 4627 to 4939. This indicates for example that concept 4627 was the four thousand six hundred and twenty-seventh most frequently used of the 20 000. Using the Brown Corpus of American English (Kucera & Francis, 1982) this corresponds to an average usage frequency of 10.99 per million. Thus all items selected were of approximately the same frequency use in the population tested, and any potential difference in the response times obtained would not be attributable to differences in word familiarity. Furthermore, words did not duplicate with those used in other parts of the overall testing schedule.

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[4] this excludes the 'symbols' level (1 , table 4.2.a.), since words were not included as test items.

4.3. Graded reaction Test

4.3.1. Method

4.3.1.1 Participants

68 CFS patients as described by the OCC (Sharpe, Archard, Banatvala, et al., 1991) were matched with 63 control patients, as described in section 3.2.1.

4.3.1.2. Design and Materials

4.3.1.2.1. Graded reaction Test

Instructions and items were presented on a Toshiba 1900 portable p.c. programmed in C, in order that accurate measures of response latency could be made. The task was to decide whether or not the statement screen was a true description of the presented item. Participants first read the instruction screen (appendix 4.1). Five practice items were presented, thus enabling participants to become familiar with the tasks. This was immediately followed by the presentation of the 20 test stimuli. Their presentation order was randomly generated, items appearing once, thus controlling for order effects. Presentation of these stimuli was interspersed with a 'get ready' screen, which was presented for 1.5 seconds This 'get ready' screen was used in order that participants knew when the next item was to be presented, thus minimising response delays as a result of inattentiveness. In order to move from the 'get ready' screen to the next item, participants were required to press the **H** key. Responses were made via the keys **Y** and **N**, where **Y** corresponded to 'yes' and **N** to 'no'. The **H** key was used to initiate the presentation of the next stimulus in order that the distances required for yes and no responses did not differ. This arrangement of the **H** key to initiate item presentation, also enabled participants to pause when motor repetition became painful or tiring. Reaction time was electronically recorded, in seconds, from the end of each 'get ready' signal to **Y/N** key pressing to 3 decimal places. If a participant did not make a response, after ten seconds the next item was automatically presented. The program recorded the reaction times, corresponding statement screen, participants response and participants participant number.

4.3.1.2.2. Additional Measures

As stated in chapter 3 (section 3.2.2.), participants also completed in a counterbalanced order: the Profile for Fatigue Related Symptoms (Ray, Weir, Phillips, & Cullen, 1992)

(PFRS); a scheduled interview to assess background details; The Fatigue Scale (Chalder, Berlowitz, Pawlikowska, et al., 1993); the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983); a computerised test of semantic relations and lexical decision (considered in the following chapter); subtests from the WMS-R; and tests of implicit and explicit memory.

4.3.1.3. Procedure

Participants were recruited as described in section 3.2.3. As described in section 3.2.4., participants read an information sheet, were able to discuss the study, and then gave written consent. The testing session followed, the order in which tests were presented to each participant being determined by the counter balance schedule (appendix 3.4.). At the end of testing participants were given a debrief sheet and any questions were answered.

4.3.2. Results

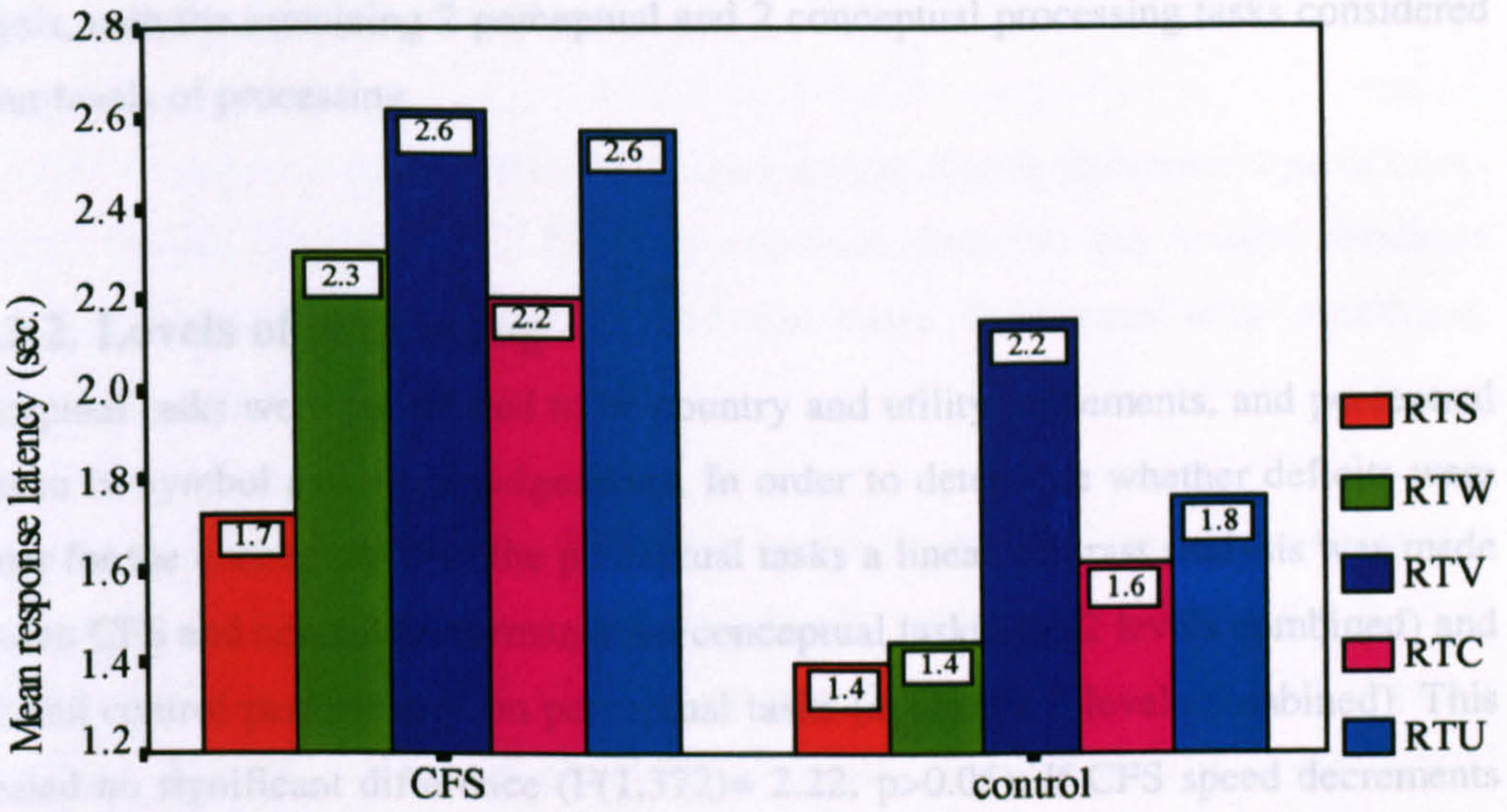
Data was available for 126 participants, 63 healthy controls and 63 patients with chronic fatigue syndrome.

4.3.2.1. The processing continuum

As can be seen from the descriptive statistics (table 4.3.2.a.) CFS patients were slower than controls on all levels of processing. However what could be described as an anomaly appears in both groups for the reaction times for vowels. These do not appear to fit into the continuum of processing as it relates to time or speed, as discussed in section 4.1. and hypothetically proposed. In healthy controls the gradual increment in response latency from perceptual to conceptual processing levels is interrupted by an unexpectedly high latency for the determination of the number of vowels in a word.

This pattern is also apparent in those participants with CFS, though the magnitude of slowing appears to be lower than would be expected for the vowel condition (discussed further in section 5.3.3.) given the slowing apparent in the other tasks. Here a possible explanation for such a discrepancy is discussed prior to the full analysis.

Figure 4.3.2.1. Mean response times for questions graded in processing requirements



where RT is reaction time and S is the symbols condition, W the words condition, V the vowels condition, C the countryside condition and U the useful condition (see appendix 4.2 for standard errors)

The proposed continuum of increased processing and time may also be reflective of task complexity rather than a continuum of perceptual to conceptual processing. Generally the continuum of complexity would be expected to map to a continuum of perceptual to conceptual processing. More conceptual decisions should involve more representations and evaluation whereas perceptual tasks should be less complex, and require fewer active representations. Sometimes however a discontinuity may arise, a complex perceptual task being more 'difficult' than a simple conceptual task. This may result in an apparent anomaly on a perceptual-conceptual processing continuum. In hindsight, this suggestion is not unreasonable. For the remaining processing levels decisions must be made on the basis of information either already obtained in semantic memory, or stored lexically, where as for the vowels condition a search task is required. Determining the number of vowels may require more than verification or activation of existing representations, it probably requires the systematic counting of the vowels present. This is supported by research on visual search tasks which suggests that the larger the possible number of positions for target items, the greater the search times (Saarinen, 1997). It has also been demonstrated that visual search utilises serial, rather than parallel processing (Saarinen, 1997).

The vowel level of the continuum will thus be considered separately in the subsequent analysis, with the remaining 2 perceptual and 2 conceptual processing tasks considered as four levels of processing.

4.3.2.2. Levels of processing

Conceptual tasks were considered to be country and utility judgements, and perceptual items to be symbol and word judgements. In order to determine whether deficits were greater for the conceptual than the perceptual tasks a linear contrast analysis was made between CFS and control performance on conceptual tasks (the 2 levels combined) and CFS and control performance on perceptual tasks (again the 2 levels combined). This revealed no significant difference ($F(1,372)= 2.22$, $p>0.05$). If CFS speed decrements had been larger in the conceptual condition (or indeed in the perceptual condition) it would have been expected that this contrast analysis would have been significant.

A 2 (CFS, control) by 4(symbol, word, countryside, useful) mixed anova showed that there was a significant main effect of participant group, ($F(1,124)=26.70$, $p<0.001$). This was such that CFS participants were slower than controls, as can be seen in table 4.3.2.2.a below.

Table 4.3.2.2.a. Mean time (sec.) for participants on the levels of processing task.

	Symbols	word	countryside	useful
CFS	1.73 (1.05)	2.30 (1.29)	2.21 (0.96)	2.58 (1.18)
Controls	1.40 (0.76)	1.49 (0.56)	1.62 (0.55)	1.76 (0.64)
mean difference	0.33	0.81	0.59	0.82

There was also a significant main effect of levels of processing ($F(3,372)=17.11$, $p<0.001$) such that participants were slower for more conceptual tasks. There was a significant interaction of participant group by levels of processing, ($F(3,372)= 4.08$, $p=0.007$). Newman Keuls analysis showed that there was a significant difference between CFS and control groups for all conditions except the symbols condition, $p<0.01$. For the control group it can be seen that the response times increased from symbol to useful. For the CFS group it appears that this incremental pattern differed. In the control population performance significantly differed between the countryside and word conditions ($t(63)=2.07$, $p=0.04$), whereas for the CFS group this difference was

not significant (t(63)=-0.58, p=0.56). Anxiety and depression, as measured by the HAD scale were not significant covariates, and when entered into the analysis the significance of results did not differ.

Descriptive statistics suggested that CFS patients were slower than control participants by 0.47 seconds (2.6224 vs. 2.1526) in response times to the vowels levels of processing. An independent t-test showed that these differences were significant, (t(124)=2.46, p=0.015).

An inspection of the anxiety and depression scores in the CFS patients revealed that there was no significant correlation of depression and anxiety, as measured by the HAD scale, with the response times on all of the presented statement types, $p>0.005$ to adjust for multiple comparisons, though all probability values obtained were in excess of 0.08.

An independent t-test showed that there were no significant differences in response times between CFS patients who were taking antidepressants, and those who were medication free, $p>0.01$. Further there were significant differences between medication free CFS patients and controls on RT for the word, country and useful statements $p<0.01$, though that for symbols was not significant, (t(78) =0.31, p=0.41). Patient illness duration did not significantly correlate with speed of performance any of the 5 conditions (symbol, word, vowel, countryside or useful), $p<0.01$. A stepwise linear regression analysis (for full analysis see appendix 4.2.) showed that patients' subjective ratings of cognitive fatigue were the most important predictors of reaction times for response times for symbols country and useful processing levels $p<0.001$, but both ratings of physical and cognitive fatigue and anxiety were entered into the equation on reaction time for the word level of processing, $p<0.016$.

4.3.3. Interpretation

The descriptive statistics showed that as was expected the controls generally showed an incremental processing time with an increase in the conceptual demands of the task. CFS patients were significantly slower than controls in all but the symbol level of processing condition, the differences ranging from 0.59 to 0.82 seconds. The planned contrast analysis revealed that there were no differences between performance time decrements in perceptual and conceptual processing for the CFS patients, suggesting

that though there was slowing, all tasks were affected by approximately the same number of seconds.

However conceptual processing should require the utilisation of a greater number of representations according to that hypothesised in chapter 2. Unless the activation of all representations involved in processing occurs 'pseudo-simultaneously' (i.e. so quickly that detection of differences is not possible), extra slowing would be expected in the conceptual condition. A possible explanation for the uniformity in slowing relates to confounding by a more peripheral process slowing, e.g. a slowing to motor processing. All tasks may have appeared to be affected to the same extent if this peripheral slowing was greater than cognitive process slowing. Though evidence is conflicting it has been previously reported that CFS patients show motor slowing on some tasks (Smith, Behan, Bell, Millar et al., 1993, Smith, Pollock, Thomas, & Llewelyn, 1996). Comparatively large motor slowing could mask differences in processing times as a result of task. From the descriptive statistics the slowing on RTS is less than that for RTU, 26.6% as compared to 46.6%. It appears that there may be a change in performance times with the decrement decreasing with more perceptual processing. However the differences between the CFS and the control group are not significant for the symbols task. Here the slowing to the cognitive element of the task may be insufficiently small, even with motor slowing, to be statistically detectable.

Analysis also demonstrated that reaction time for words was not significantly different from reaction time for the countryside condition in CFS patients. There are two possible explanations for this result. This may be the result of a further slowed performance in the word condition as compared to the countryside, symbol and useful conditions. Support for this suggestion is found in the lexical decision times for presentations of words and non-words (section 5.3.2.). The pure lexical decision task is much faster for both groups than mixing the lexical with the symbolic stimuli as was presented here. In the symbol versus word lexical decision task the CFS are 54.6% slower than controls, where as on the pure lexical decision task they are 26.0% slower (see section 5.3.2.). These differences are probably attributable to task demands.

Alternatively, for some reason reaction time for country may be more greatly impaired in the CFS group. The provision of the country statement may provide a context for

priming of country related stimuli in the control population (despite partial control for this variable as discussed in section 4.2.). This task is in fact the only one where such a conceptual priming link is probable; the list of useful items is probably too encompassing for such effects. A possible mechanism for accentuated slowing is the loss of facilitation by context provision for the country related stimuli. Controls are 0.3 sec faster on lexical stimuli found in the country (yes responses) as compared to 1.23 times as fast as stimuli not found in the country, suggesting evidence for such a priming mechanism. The CFS patients perform similarly for those items found in the country and those not found in the country, thus suggesting a failure to benefit from the context provided in the statement.

This interaction of word and country response times may thus be explained as a result of slowing compounded by the lack of benefit which appears to be present for the control group for the country affirmative answers. A lack of benefit to CFS patients on measures of recall in conditions of cue/context provision has been previously reported (Sandman, 1992, Grafman, Schwartz, Dale, Scheffers, Houser, & Straus, 1993). This effect on processing times should therefore not be entirely unexpected. If this interaction of country by word does represent a lack of benefit from cueing, then cue provision may be considered to decrease processing time as well as increase recall. In CFS perhaps this slowing is related to extra time required for the activation of associated representations, or for the activation of the existing weak representations which do not have the benefit of being strengthened by priming. This proposal should be possible to investigate by looking at the effect of cues on performance and will be investigated further in a matched versus mismatched processing retrieval paradigm (see chapter 6 for further work).

That RT vowels took the longest for the CFS group but was proportionally less slowed may give some further insight into the processes involved. Here speculations on the cognitive processes involved in determining whether or not a word has more than 2 vowels may be useful. The decision is likely to involve the fast automatic lexical activation of the word, representational activations of the vowels and a match and count process mediated by higher order activity. It has been reported that as word length increases visual search time increases, suggesting that the count and match process has a temporal element. In this study words were of approximately the same length and randomly cycled through the levels of processing, such word dependent changes in

times should therefore not be apparent. In the vowels condition though CFS patients are slowed, slowing is less than would be expected given the task performance time and the decrements reported in the other conditions. This may suggest that the search time is relatively unimpaired and that a percentage change to processing speed is unlikely to be contributing to a large proportion of slowing. A peripheral slowing such as motor activity may explain the differences obtained.

Given the high psychiatric comorbidity of these patients it could be suggested that performance decrements were related to anxiety or depression. Bivariate Pearsons correlations of times for processing levels with anxiety and depression scores revealed that slowing was not related to comorbidity of psychiatric symptoms. As a result of the psychiatric comorbidity of the population 57.7% of patients were taking prescribed medications (see section 3.3.1). There was thus the possibility that sedative effects of medication resulting may have resulted in slowing. Since the majority of those patients taking medication were using antidepressants the numbers of patients taking other drugs were too small for stratification for analysis (see also section 5.3.2.2.). Analyses of the differences between CFS patients on antidepressants, those who were medication free and control participants were thus conducted. These revealed that CFS patients who were medication free were significantly different from the control participants on RTW, RTU and RTC, but not on RTS. There was no difference between the performance of CFS patients taking antidepressants and those who were medication free. Psychiatric symptomatology, sedation, or other side effects of medication are thus unlikely to account for the slowing demonstrated in the CFS population.

4.4. Conclusions

CFS patients are slower than control participants in all levels of the graded reaction test, except the symbols condition, and in performance time for vowels. In all conditions, excluding reaction time for the words task, anxiety and depression were not associated with change in performance. Given that neither a percentage slowing or an absolute change in performance time were observed here, whether there is representational weakness is undetermined. It does however seem likely that there is a slowing to performance resulting from a combination of cognitive and peripheral slowing. This supports the initially speculated performance slowing in CFS and

Chapter

5

Information Processing: Semantic Relations

5.1. Introduction

As was demonstrated in the previous chapter, CFS patients were significantly slower than controls on tests of graded processing. However it was not clear if this slowing resulted from representational weakness, or was as a result of more peripheral processes, such as motor tasks. A number of investigations into speed of processing have utilised hierarchical semantic memory networks, this has been particularly apparent in work on Alzheimers Disease (Nebes & Brady 1990, Rohrer et al., 1995). As will be discussed below these semantic networks are potentially useful in describing the nature of slowing.

There are many theories on the ways in which items are semantically connected in memory and consequently on how to access these relations. The earliest idea was probably that of Collins and Quillian (1969) who suggested that items are organised in a categorical hierarchical network. Each item is represented only once in memory and is connected directly only to those items immediately above and below it. For example bird is a superordinate of its subordinate canary which has attributes of *yellow* and *sings*, plus the attributes of birds *feathers* etc. They also suggested that the proportion of time taken to make semantic judgements is directly related to the number of steps away from each other that the test items are (Collins & Quillian, 1969). For example deciding that a canary can fly takes proportionally longer than deciding whether a canary is yellow. This was thought to arise because in the former, it must be decided that canary is a bird and then whether a bird can fly, where as yellow is stored with canary rather than the superordinate bird. The closer the association between items the less time is taken to make semantic judgements (Collins & Quillian, 1969).

Network models of semantic memory suggest that where there is less association between 2 items the longer the processing time (Collins & Quillian, 1969, Miller & Fellbaum, 1991). Whilst this hierarchical proposal for the organisation of the mental lexicon has the advantage of information being stored only once in memory there are several problems with the model. Firstly the model deals only with the representation of concrete nouns. Secondly, all of the attributes are given equal weight. It has been shown that certain attributes may be more important than others, for instance that salmon is pink is more important than that it has fins (Conrad 1972). Finally the theory does not account for the relatively quicker speed with which the decision that *a robin is a bird* is reached by comparison with *an ostrich is a bird.*

Rosch (1975) attempted to overcome this problem, she suggested that within the categories there was an ideal example 'a prototype' to which 'to be judged items' were compared. For instance robin is more typical of the category bird than a penguin. However this model also has limitations; it gives no explanation for the relatedness of more abstract associations, such as crawling and walking vs. running and singing. Nor does it account for the differential effect of context. For example, *walking* if paired with *running* could be considered to be a sport more closely associated with *jogging*, alternatively if paired with *trekking* could be considered to be an outdoor activity associated with mountains.

Semantic priming has been shown for category co-ordinates like, *oranges* and *lemons*, *cat* and *dog*, antonyms such as *hot* and *cold*, *black* and *white* as well as the functional relations like *hammer* and *nail* or *knife* and *bread* (Moss, Ostrin, Tyler, & Marslen-Wilson, 1995). It is not clear however to what extent the priming between these words can be attributed to semantic relations or to associative strength (Fischler 1977) For example, if *hammer* and *tong* or *cat* and *dog* are frequently processed together the 'link' between them is facilitated. Hence the words become 'related' despite not necessarily being reflective of semantic, functional, antonymic or hierarchical orders. A number of studies have reported that the associative strength between two words is correlated with the extent of co-occurring usage (Rapp & Wetler, 1991, Spence & Owens, 1990).

It seems probable that hierarchical nets hold for storing information about the particular concepts, and that these may be related either directly or indirectly to most others in 'web', connectivity being determined by a variety of factors. The theory of a semantic

web is consistent with more recent connectionist models of semantic memory, for example as described in Joordens & Becker. (1997). In such models, information is represented over a number of 'neurone like' units. Processing depends on both co-operative and competitive processing between units on the basis of 'weights' or 'attractor states' between them. As information is assimilated these weights are adjusted; the network 'automatically learns'.

Miller & Fellbaum (1991) have suggested that the mental lexicon is organised by semantic relations between both forms and meaning. There are a number of ways in which words may be related. For example, synonymy exists where the words have semantic similarity (e.g. glasses & spectacles); hyponymy where one item is a superordinate of another. The hyponym has features of its superordinate and additional features which distinguish it from the other hyponyms (e.g. vehicle & bus). These relational structures differ for different semantic categories, verbs nouns, adjectives (Miller & Fellbaum, 1991).

The idea that lexical representations are stored in a related way is supported by a considerable amount of evidence. Word association studies illustrate that subjects always select items from the same semantic field (Keppel & Strand, 1970). Semantic priming experiments (Moss, Ostrin, Tyler, & Marslen-Wilson, 1995) have also illustrated that the activation of one item facilitates the activation of other related items in a spreading of activation through the semantic network. Whilst there is evidence to support this theory, it is a theory of the extent of relation between 2 items and indicates little about the associative strength between lexicons. For instance word association studies illustrate that the order in which presentation occurs determines the strength with which its pair is elicited. If the word *easier* is given, primary response is *harder* (associative strength 44.9%), however if the word *harder* is given the primary response is *softer*, its associative strength with easier being only 34% (Keppel & Strand, 1970). In other words the strength of relationship between words is not symmetrical. Additionally as mentioned previously the extent of semantic relation is not necessarily reflective of the strength of the association, and co-occurrence of usage may play an important role.

An early test of speed of processing utilising the organisation of memory was devised by Baddeley (1981). Subjects were required to verify the truth of statements of differing relational strength, for example a canary is a bird, a penguin has wings. The

number of units per the time taken to process these units (differing in relational strength) was measured. This was considered to be an index of speed of processing from semantic memory. It is however possible to exploit these relationships from a slightly different perspective. As has been previously noted (section 2.6.) as the strength of association between two items increases so does performance speed and a decrease in speed is associated with a decrease in the strength of association between two items/representations. Repeated presentation of an item is associated with increased strength of the item and better recall.

By investigating CFS and control participant performance on relational judgement tasks with pairs of differing associational strength it should therefore be possible to demonstrate differences in the speed of performance. If we accept as a proposition that in CFS there is a slowing in processing speed, then as discussed in section 2.6., representational weakness may be manifesting as slowing. A study of the time to judge whether or not pairs differing in relational strength (proposed to affect speed of retrieval) are related, serves as a method to test this hypothesis.

Intuitively it would be expected that if there is a global slowing of performance, CFS patients should be slower than controls on all levels of association. Since this slowing will impact across all relational strengths and times for access, these absolute change in speed would be greater where items were weakly related and processing times were slow, than for closely related items. The overall pattern of speed and its association to relationship strength will change. There should therefore be differences in the pattern of speed and relationship strength, with interactions between CFS and control participants on performance of weakly to strongly related item pairs. However, these semantic pairs already exist in memory, they are non-novel. In Chapter 3, the difference between novel and non-novel stimuli was discussed. The results suggested that recall was more difficult for unrelated novel word pairs and unimpaired for associations which already exist. It was proposed that these representations may be too weak for retrieval but that existing representations are sufficiently strong for activation to take place. Whilst this recall may be unimpaired, it may be that the process still takes longer. If there is a general reduction in activity or representational weakening, it should impact on all these existing representations to a similar, if not the same, extent. The time taken to activate these representations would be uniform across all conditions of associational strength. There should be no differences in the pattern of slowing and

no interaction between CFS and controls on performance of weakly to strongly related item pairs.

Though much of the CFS research has concentrated on verbal processes, a number of studies in non-verbal memory have been completed (see chapter 2). Research looking at the association of pictures using priming has shown that pictures and words are dealt with differently by healthy populations. Categorisation speeds of pictures are reported to be faster than those for words (Glaser & Dungelhoff, 1984). A recent explanation for this has been that words automatically activate lexical information, before activating associated semantic/conceptual meanings (Seifert, 1997). Pictures are thought to have direct access to categorical (but not non-categorical) semantic memory and thus picture categorisation is faster than word categorisation. Assuming that pictures have this privileged access to semantic memory, words automatically activating lexical processing before semantic associations, then according to the model as proposed in section 2.6. lexical processes should be affected to a greater extent, there being more stages (active representations) or a greater length of time for speed deficits to manifest. If the representations are weakened then the impact of slowing on lexical pairs should be greater than on picture word pairs (since more representations are required to be active), with both taking longer in CFS patients. Again, the pattern of speed with strength should remain the same, as the extra processing is required for all lexical pairs.

As discussed above, evidence has suggested that the initially simply proposed hierarchical stores of semantic memory may not be as simple as was first thought. In summary, semantic models of memory suggest a complex network of interrelations and associations. Items may be associated in a number of ways, for example as part of a hierarchy of information about an object, or conceptually with other items. It is probably the case that a number of types of relatedness exist for one item, and that a number of items are related in all of these ways. Therefore whilst the strength of relation may be proportional to reaction time, this is not necessarily indicated by the general lexical organisation of memory. The strength of association between two words will depend upon the particular stimuli presented, namely: part of speech; type of semantic relation; context; order of presentation; how typical the lexica is of its category, hyponimic 'distance' and the extent to which items commonly co-occur. With such a multi-factorial determination of the strength of a particular relationship prediction becomes difficult. Since it is an exploitation of this relational strength which is required for the proposed assessment of speed, it is necessary to approximate the

strength of association between specific item pairs. Pilot studies are thus necessary for a determination of relational strength of item pairs (word -word pairs and picture-word pairs).

The aim of the semantic pairs test is to manipulate relational strength of items, and look at the effect of this on speed to make a binary decision on relatedness. However, in responding to a presentation of two items it is not just the more central processes which are involved in deciding if pairs are related. There will also be visual input and motor output activity, as well as automatic activation of lexical representations. Although these factors will be present across all conditions, whether they account for all or part of slowing is important to determine. In order to obtain a better approximation of this central processing speed, a measure which is composed mainly of such processes would be useful. Such a measure could be used to determine whether any slowing which may manifest is more likely to be attributable to central processes involved in making semantic relatedness judgements, or is more peripheral, such as motor slowing. A lexical decision task will therefore be employed.

In this chapter, the presentation of two pilot studies used to determine the strength of item pairs will be described first. These studies yielded the stimuli for the semantic pairs computerised test, and the lexical part of the computerised lexical decision test. The design of the computerised tests will then be presented, followed by their procedure, result and interpretation.

5.2. Selection of items for the Semantic Relations Test

This test was composed of two parts, a lexical decision task and a judgement of relatedness of pairs test. Two studies were completed initially to devise the stimuli for these tests.

5.2.1. Study One

This study aimed to establish the degree of relation of particular word-word pairs.

5.2.1.1. Questionnaire design

Since nouns are thought to be organised in hyponimic trees, hyponimic trees were generated using the words: fruit, tool, fluid, system, furniture, planet, tree, animal,

buildings[1], using a similar paradigm to that employed by Miller and Fellbaum (1991). As it is thought that information about concepts is usually stored hierarchically and this is indicative of association, it should generally be the rule that those words 'closer' together in the hyponimic tree, would have more association and thus be more strongly related than those further apart in the hyponimic tree. Those pairs crossing hyponimic trees should be the least related. Seventy-two word pairs were generated from these hyponimic trees. They represented a range of five strengths, judged on the basis of their hyponimic distance, from closely to strongly related (see appendix 5.1.) ensuring that they did not duplicate the stimuli used for other tests. These were used as the stimuli for verification judgements of relationship strength.

These word pairs were presented to participants in the form of a self rated forced choice questionnaire. Since interest was in the strength of relationship of word pairs, subjects were required to first decide if the words were related, then if they were, to decide how strong that relationship was. Ratings of strength were on a 3 point scale of slightly related, moderately related and strongly related. To prevent systematic bias in relationship judgements arising as a result of proximity to other particular word pairs and order of presentation, two forms of the questionnaire were generated. Test word pairs were arranged randomly into 3 different groups of 24 word pairs for each form of the questionnaire. The forms were then partially counterbalanced, so that each set of randomised 24 words was presented first, second and last, giving a total of 6 forms of the questionnaire (example in Appendix 5.2.).

5.2.1.2. Subjects

A convenience sample of 59 participants, age range 20 to 60 years, median age range 30 to 35 years were tested from the following occupational groups: civil servants, cleaners, clerical, computer scientists, environmental health officers, postgraduates, managers, nurses, students, travel consultants and teachers.

5.2.1.3. Procedure

Ninety Questionnaires were given out, using the snowballing technique, to the above groups, and returned personally or by internal mail. Participants were required to state their occupation and age and complete the questionnaire, as described by the instructions (see sample questionnaire in Appendix 5.2.).

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[1] thus categorical semantic memory structures were used.

5.2.1.4. Results

Of the questionnaires distributed, 59 were returned giving a response rate 65.6%. Questionnaire responses were coded in the following way: unrelated: zero, slightly related: one, moderately related: two, strongly related: three. Measures of central tendency, skew, variance were calculated and frequency distributions were graphed. The following seven pairs were discarded on the basis of small numbers of response or large variance: [clay, dust]; [bat, club], [bitter, lager], [hen, owl], [person, public], [tree, oaktree], [beech tree, oak tree]. Words were then grouped according to central tendencies and distributions. This resulted in 6 categories, as described below, in Table 5.2.1.4.

Table 5.2.1.4. Relationship categories

Relation	Mean	Mode	sd.	No. of Pairs
no relation	0.03<x<0.3	0	0.00<x<0.68	12
no relation to slight relation:	0.47<x<0.93	0-1	0.47<x<0.93	11
slight relation	0.8<x<0.91	1-2	0.7<x<0.91	11
moderately related	1.6<x<1.9	2	0.73<x<0.87	11
moderate to strong relation	2.1<x<2.6	2-3	0.73<x<0.89	10
Strongly related	x>2.6	3	x <0.07	12

There were thus 67 word pairs suitable for use, with only small variances in the ratings of their relationship strength. These words were used in pilot study two, in order to determine whether or not the relationship strengths were retained for picture-word presentations.

For pragmatic reasons it was decided to have 4 word pairs in each condition of word-word and picture-word pair for each of 4 categories of relational strength in the final semantic pairs test. Categories of none, slight, moderate and strong were chosen, since these were distinct categories of strength (4 of the original 6), and were approximately 'relationally equidistant' in terms of the scale used in study one. There were thus to be a total of 32 pairs for presentation in the final computerised test, 16 word-word pairs and 16 picture-word pairs. This would thus result in a test that was of a reasonable length for a sick population, allowed some flexibility for the discarding of non-category

representative picture-word pairs in the test design; with sufficient items in each category for comparisons not to be dependent upon a particular association.

5.2.2. Study Two

It was possible that pictorial representations may have resulted in differences in subjective ratings of relationship values, for example by restricting the semantic associations available. It was therefore important to determine that the values for word picture relations were no different from word-word relations for the test items used. This study therefore aimed to determine relationship strengths for word-picture pairs, and to match these with corresponding groups of word-word pairs.

5.2.2.1 Questionnaire Design

Since an equivalent pictorial form of the questionnaire was required for comparison with the lexical form, pairs where one item could be represented as a standardised picture were chosen from the available study one pairs. Thirty items of the 67 possible were chosen as these could be represented as standardised pictures, 25 of these were taken from Snodgrass & Vanderwart. (1980), the remainder were selected from Power Point and Harvard Graphics Packages, and modified for use in black and white form. A further questionnaire using these 30 word pair pictures was then constructed. Again two forms of the questionnaire were devised. Pairs were randomly assigned to 2 groups of 15. As above these pairs were then counterbalanced with each group appearing first and second; a total of four forms were used.

5.2.2.2. Subjects

An opportunity sample of 58 volunteers, who had not taken part in study one, age range was 16 to 65 years, median age range 30 to 35 years were tested. They included postgraduates, researchers, clerical staff, students, cleaners, teachers, accountant, single mothers, sales representatives, and the retired.

5.2.2.3. Procedure

Eighty questionnaires were distributed, using the snowballing technique 4 months after the first pilot questionnaire. Again participants were required to state their age, occupation and to complete the questionnaire as per the included instructions (see sample questionnaire in Appendix 5.2.).

5.2.2.4. Results

Fifty-eight of the eighty questionnaires were returned giving a response rate of 72.5%. Questionnaires were coded as before (see section 5.2.1.4.). Eight test item pairs were selected from each category of relational strength, 4 picture-word pairs and 4 word-word pairs. These pairs had similar distributions and were representative of the categories reported in study one, according to median, mean and variance. Pairs were excluded on the basis of low or high mean strengths or high standard deviations, relative to the remainder of the category. Further, independent t-tests (see appendix 5.3) showed that the picture forms included did not significantly differ in relational strength from the original word forms. The final pairs and the means and standard deviations of relative strength are presented in table 5.2.2.4.

Table 5.2.2.4. Final Test Items for Semantic Pairs Test

Relation	Word-word	Mean Relation (sd)	Picture word	Mean Relation(Sd)
none	Cowboy step-child Stomach Jupiter island asteroid card mug	0.20 (0.56) 0.03 (0.18) 0.30 (0.58) 0.10 (0.22)	paper ***racket*** tape ***glass*** ***key*** pen water ***watch***	0.02 (0.13) 0.04 (0.19) 0.07 (0.32) 0.14 (0.35)
slight	Church-pew arm-chair Lawnmower spade Gondola train Cement slate	1.0 (0.87) 1.4 (0.81) 0.8 (0.72) 1.1 (0.77)	***penguin*** nightingale helicopter ***car*** ***hotair-balloon*** glider ***bookcase*** sideboard	1.2 (0.90) 1.1 (0.75) 1.6 (0.89) 1.6 (0.82)
moderate	Garage shed moth fly speedboat cruiser cot bunkbed	1.9 (0.83) 1.8 (0.87) 1.9 (0.74) 1.8 (0.73)	***apple*** lime ***yacht*** canoe car ***truck*** jeep ***sports car***	1.7 (0.84) 1.9 (0.75) 2.3 (0.67) 2.0 (0.69)
strong	mud soil carpet rug hazelnut almond conifer pine	2.7 (0.65) 2.6 (0.64) 2.7 (0.57) 2.7 (0.60)	***mouse*** rat ***orange*** satsuma sun ***star*** glasses ***spectacles***	2.7 (0.71) 2.9 (0.53) 2.4 (0.85) 2.8 (0.56)

Items in ***italics*** were presented in picture form, mean relation corresponds to the initial scale: 0 represents no relationship; 1 represents slight relationship; 2 represents moderate relationship; and 3 represents a strong relationship

As discussed in section 5.1 there may also be other components contributing to slowing when assessing semantic relatedness. A lexical decision task was therefore employed to

assess slowing in a simple rather than more complex central process. The stimuli (see appendix 5.4.) for this were twenty four pronounceable non-words either created, or adapted from (Rajaram & Roediger, 1993) to a natural English spelling. These were combined with the forty-eight words established for use in the semantic pairs test, as described above.

The final tests were thus a 72 item lexical decision task, with 3 practice items, and a thirty two item semantic judgement task, again with three practice items. For both tests a yes/no judgement was required; in the semantic pairs test whether or not items were related, and in the lexical decision task whether or not items were a word. In the lexical decision task there were twenty-four pronounceable non-words and forty eight words duplicating those used as the lexical items in the semantic pairs presentation. The semantic judgement task randomly presented subjects with 16 word-word pairs and 16 picture word pairs; these were from four groups of relationship strength, as depicted in table 5.2.2.4. above.

5.3. Semantic Relation Test.

As discussed in section 5.1. in proposing that speed of performance is slowed as a by product of representational weakness, the overall pattern or response times should remain unchanged, with equal decrements for each strength of association.

5.3.1. Method

5.3.1.1. Subjects

68 tertiary care patients with CFS, as defined by the OCC (Sharpe, Archard, Banatvala, et al., 1991) were matched with 62 controls, as described in section 3.2.1.

5.3.1.2. Materials and Design

5.3.1.2.1. Lexical Decision task

This was a simple 72 item lexical decision task, with 48 words and 24 pronounceable non-words, and three practice items. The task to was decide whether or not the presented item was a word. This was presented prior to the semantic pairs part of the test. Instructions and items were presented in a computerised form on a Toshiba 1900

laptop computer, programmed in C. An initial presentation of an Instruction Screen was made (see appendix 5.5). Three practice stimuli were then presented thus enabling participants to become familiar with the tasks, fewer than in the tests described in the previous chapter since the response format was slightly less difficult. Presentation of the test stimuli then followed immediately. Their presentation order was randomly generated, all items appearing once, thus controlling for order effects. Presentation of these stimuli was interspersed with a 'get ready' screen, which was presented for 1.5 seconds. In order to move to the next item subjects were required to press the **H** key. Responses were made via the keys **Y** and **N**, where **Y** corresponded to 'yes' and **N** to 'no'. The **H** key was used to initiate the presentation of the next stimulus in order that the distances in finger movement required for yes and no responses did not differ. This arrangement of the **H** key to initiate item presentation, also enabled subjects to pause when motor repetition became painful or tiring. The 'get ready' screen was used in order that participants knew when the next item was to be presented. It also facilitated a more accurate recording of reaction time, since at the end of the signal subjects were ready to respond, and had completed the previous activity. Reaction time was electronically recorded, in seconds, from the end of each 'get ready' signal to **Y/N** key pressing to 3 decimal places. If no response was made, after ten seconds the next item was automatically presented. The program recorded the reaction times, corresponding item pair, subject's response and subject's participant number. The purpose of this test was to illustrate the differences present as a result of peripheral slowing, such as motor slowing, and weakened representation of a unitary stimulus.

5.3.1.2.2. Semantic Pairs

This was a 32 paired item computerised test, with a 2 by 2 by 4 design. The two groups of participants were tested, CFS and controls. Half the presentations were picture word pairs and half were word-word pairs. These were subdivided into 4 categories of relatedness (not related, slightly related, moderately related and strongly related). Participants were required to make a judgement as to whether or not the two simultaneously presented items were related. Relatedness was not defined to subjects, in keeping with the initial design study, however examples were given at the start of the test. This test was presented in a computerised form. Participants first read an instruction screen (appendix 5.4.). Three practice items were then presented followed immediately by a random presentation of 32 non-practice items (as in table 5.2.2.4.).

The computerised presentation and response format was as described in section 5.3.1.2.1. above.

5.3.1.2.3. Additional Measures

As stated in chapter 3 (section 3.2.2.) subjects also completed, in a counterbalanced order, the Profile for Fatigue Related Symptoms (Ray, Weir, Phillips, & Cullen, 1992) (PFRS); a scheduled interview to assess background details; The Fatigue Scale (Chalder, Berlowitz, Pawlikowska, et al., 1993); the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983); a computerised test of graded reaction time (considered in the following chapter); subtests from the WMS-R; and tests of implicit and explicit memory.

5.3.1.2. Procedure

Participants were recruited as described in section 3.2.3. As described in section 3.2.4. Participants read an information sheet, were able to discuss the study, and then gave written consent. The testing session followed, the order in which tests were presented to each subject being determined by the counter balance schedule (appendix 3.4.).

5.3.2. Semantic Relations Test: Results

Data was available for 63 control participants and 65 CFS participants for the lexical decision test, and 63 control participants and 64 CFS participants for the semantic pairs test. Mean response times for each condition are presented in table 5.3.2.a. below.

Table 5.3.2.a Mean response times (sec.) for relational and lexical judgement tasks

	word-word pair				picture- word pair				single word
relation	NO	SL	MD	SG	NO	SL	MD	SG	
CFS	2.09 (0.67)	2.29 (0.80)	1.80 (0.72)	1.53 (0.52)	2.04 (0.67)	2.28 (0.80)	2.00 (0.82)	1.80 (0.58)	1.23 (0.40)
controls	1.66 (0.49)	1.80 (0.58)	1.35 (0.39)	1.24 (0.47)	1.71 (0.66)	1.72 (0.45)	1.44 (0.50)	1.40 (0.56)	0.91 (0.36)

where NO represents no relation, SL represents slight relation, MD represents moderate relation and SG represents strong relation.

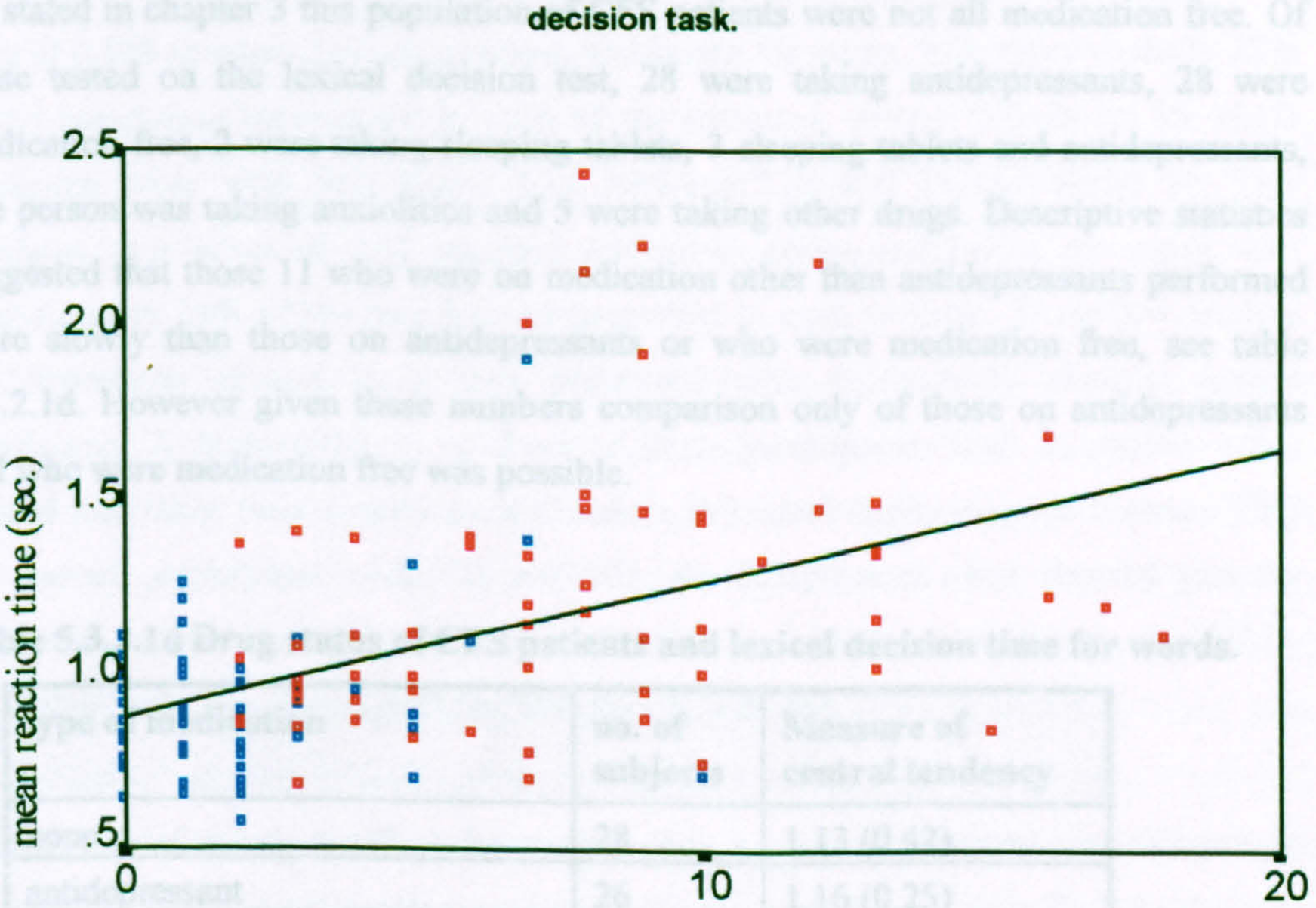
5.3.2.1. Lexical Decision Test

Descriptive Statistics suggested that there were differences between CFS and control participants, see table 5.3.2.a, with CFS patients taking longer to decide that the stimulus was a word in the lexical decision task. A Mann-Whitney test showed that there were significant differences in mean lexical decision time for single words between control and CFS participants, $z=-5.52$, $p<0.0001$. As can be seen in table 5.3.2.1.a. this was such that CFS patients were slower than control participants.

However though there were significant differences between CFS and control participants it may be that these differences were a result of comorbidity or medication, rather than a slowing caused by a factor such as representational weakness. Further analysis was therefore done to investigate the relationship of lexical decision time to depression, anxiety and medication.

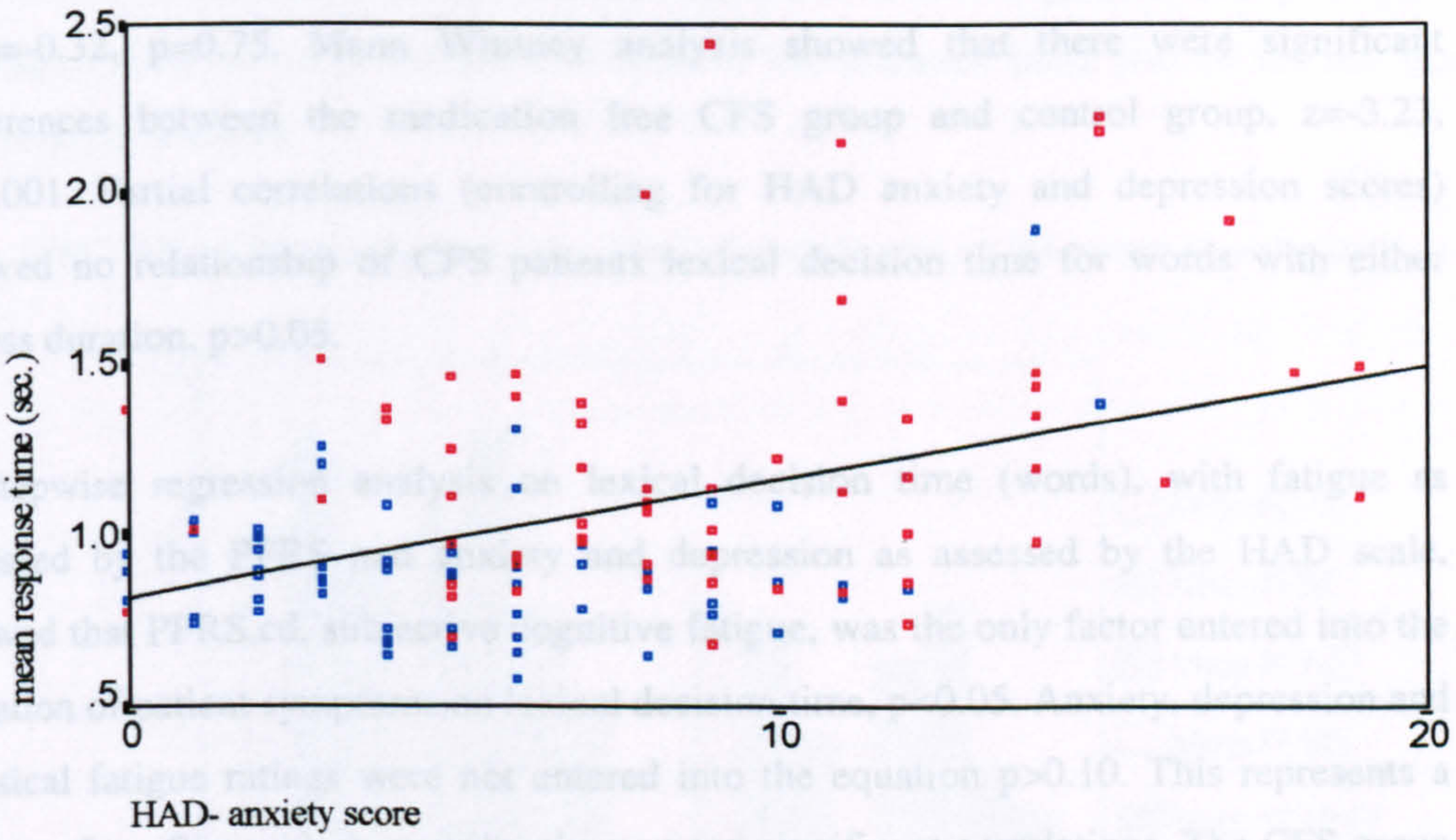
Mean response time to single words on the lexical decision task was significantly correlated with ratings of anxiety ($r(125)=0.42$, $p<0.001$) and depression ($r(125)=0.49$, $p<0.001$), as depicted in figures 5.3.2.1.a and 5.3.2.1.b.

Fig 5.3.2.1.a. Depression symptoms by mean response time for words in the lexical decision task.



Where □ represents control participants and □ represents CFS participants.

Fig 5.3.2.1.b. Anxiety symptoms by mean response time for words in the lexical decision task.



Where □ represents control participants and □ represents CFS participants.

As stated in chapter 3 this population of CFS patients were not all medication free. Of those tested on the lexical decision test, 28 were taking antidepressants, 28 were medication free, 2 were taking sleeping tablets, 3 sleeping tablets and antidepressants, one person was taking anxiolitics and 5 were taking other drugs. Descriptive statistics suggested that those 11 who were on medication other than antidepressants performed more slowly than those on antidepressants or who were medication free, see table 5.3.2.1d. However given these numbers comparison only of those on antidepressants and who were medication free was possible.

Table 5.3.2.1d Drug status of CFS patients and lexical decision time for words.

type of medication	no. of subjects	Measure of central tendency
none	28	1.13 (0.42)
antidepressant	26	1.16 (0.25)
anxiolitics	1	2.15
sleeping tablets	2	1.85
sleeping tablets & antidepressants	3	1.47
other	5	1.36

A post hoc independent t-test showed that there were no significant differences between the medication free CFS group and the CFS group taking antidepressants $t(52)=-0.32$, $p=0.75$. Mann Whitney analysis showed that there were significant differences between the medication free CFS group and control group, $z=-3.23$, $p=0.001$. Partial correlations (controlling for HAD anxiety and depression scores) showed no relationship of CFS patients lexical decision time for words with either illness duration, $p>0.05$.

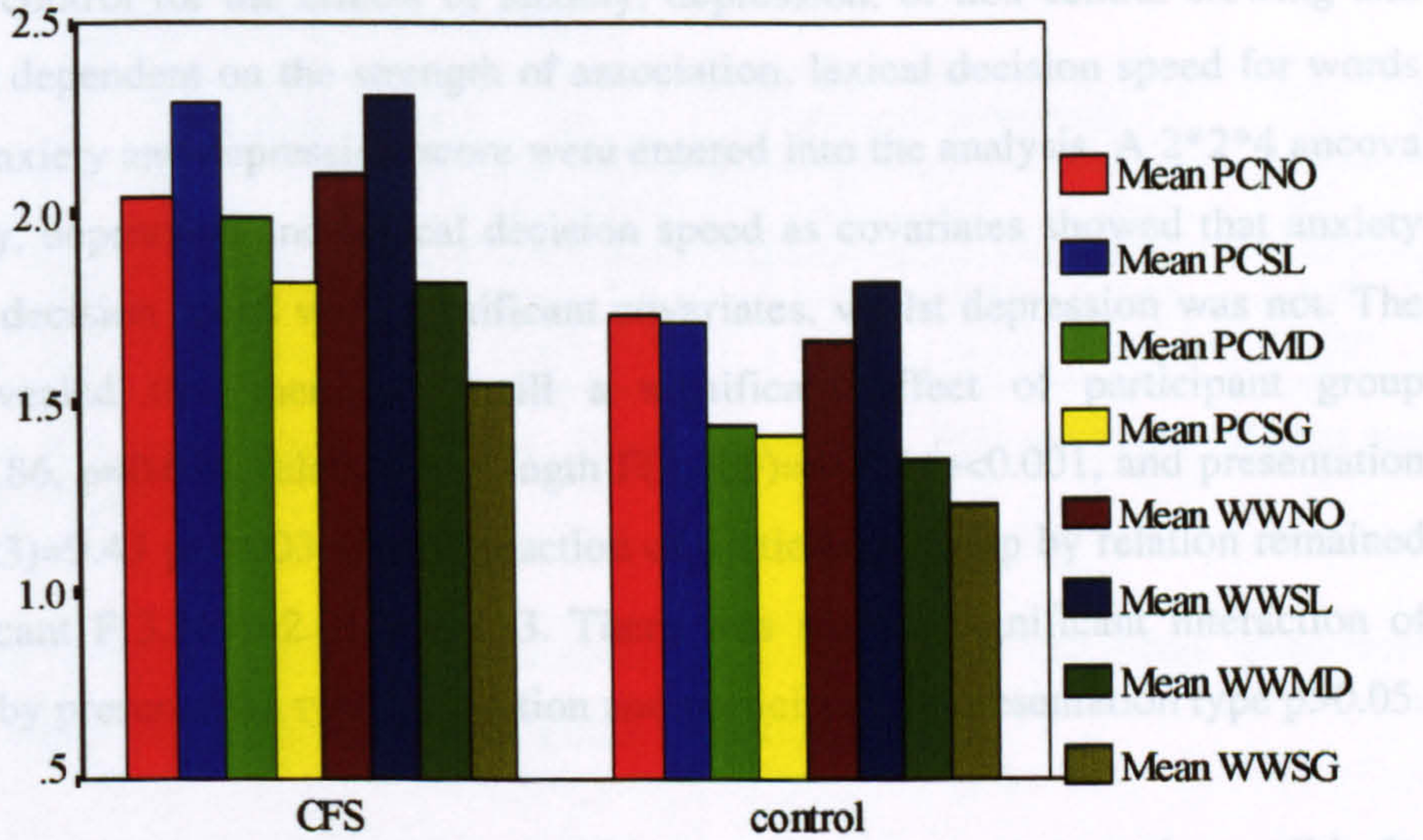
A stepwise regression analysis on lexical decision time (words), with fatigue as assessed by the PFRS and anxiety and depression as assessed by the HAD scale, showed that PFRS.cd, subjective cognitive fatigue, was the only factor entered into the equation of patient symptoms on lexical decision time, $p<0.05$. Anxiety, depression and physical fatigue ratings were not entered into the equation $p>0.10$. This represents a degree of conflict with the previously reported significant correlations. The CFS group was therefore divided into 3 groups, as designated by the accepted clinical cut off value of 11. Group boundaries for anxiety were thus below 5.36 for low anxiety, between 5.36 and 11 for moderate anxiety, and above 11 for clinical anxiety. This translated to a value of 0.658 standard deviations above and below the mean, with approximately 25% of this population represented in each of the extremes. Group boundaries for HAD depression score were thus below 7.34, between 7.34 and 11, and above 11. This translated to a value of 0.41 standard deviations above and below the mean with approximately 34% of the population represented in each extreme. These low anxiety and depression groups were then compared with equivalently scoring control participants. A Mann-Whitney analysis of those participants 'low' in anxiety score showed that there were significant differences in lexical decision speed between CFS and control participants $z=-2.700$, $p=0.007$. An independent t-test showed that the difference between control and CFS patients who had 'low' scores on the HAD-depression scale was also significant $t(91)=3.06$, $p=0.003$.

Partial correlations (controlling for anxiety and depression), showed that this lexical decision time was significantly correlated with the performance time for all relational levels of word-word pair judgements and picture word judgements, $p<0.001$ (see appendix 5.5 for full results).

5.3.2.2. Semantic Pairs Test:

Descriptive Statistics suggested that there were differences between CFS and control participants, see table 5.3.2.a and figure 5.3.2.2.a with CFS patients taking longer to respond to all levels of semantic relation in the semantic pairs part of the test than control participants.

Fig 5.3.2.2.a Mean response time (sec.) of participants on the semantic pairs task



Where PC indicates a picture-word pair, WW indicated a word-word pair, NO indicates no relation, SL a slight relation, MD a moderate relation and SG a strong relation. Means and standard deviations are quoted in table 5.3.2.a.

A 2(CFS, control) by 4(no relation, slight relation, moderate relation, strong relation) by 2(word pair, picture-word pair) anova illustrated that there was a significant main effect of participant group, $F(1,125)=25.91$, $p<0.001$. As can be seen in table 5.3.2.a this was such that CFS patients were slower than control participants. There was a significant main effect of relation $F(1,125)=71.26$, $p<0.001$, the interaction of relation by group was not significant $F(3,375)=2.31$, $p=0.08$. There was a significant main effect of type of presentation (word-word pair vs. picture-word pair), $F(1,125)=10.10$, $p=0.002$ word-word pairs being faster than picture-word pairs. There was no significant interaction of type of presentation by type of participant, $F(1,125)=0.87$, $p=0.354$, nor of relation by type of participant by type of presentation, $F(3,375)= 1.10$, $p=0.349$. There was a significant interaction of relation by presentation type $F(3,375)=7.18$, $p<0.001$. Newman Keuls analysis revealed that this was such that there was a

significant decrease in response times from slight to strong relational strength judgements with word-word pair judgements faster than picture-word judgements $p<0.001$, with the picture-word strong condition not significantly differing from the word-word moderate condition, $p>0.05$. It additionally revealed that there was no difference in the judgement speeds of word-word pairs and picture-word pairs in the unrelated condition, $p>0.05$.

In order to control for the effects of anxiety, depression, of non central slowing and slowing not dependent on the strength of association, lexical decision speed for words and HAD anxiety and depression score were entered into the analysis. A 2*2*4 ancova with anxiety, depression and lexical decision speed as covariates showed that anxiety and lexical decision speed were significant covariates, whilst depression was not. The Ancova revealed that there was still a significant effect of participant group $F(1,121)=4.86$, $p=0.026$, relational strength $F(3,369)=68.79$, $p<0.001$, and presentation type $F(1,123)=9.43$ $p=0.003$. The interaction of participant group by relation remained non significant $F(3,369)=2.01$ $p=0.113$. There was still no significant interaction of participant by presentation type by relation and participant by presentation type $p>0.05$.

Post hoc analysis on the effects of medication on performance were again possible for those patients on antidepressants and those who were medication free. A 2(antidepressant medication, no medication) by 4(no relation, slight relation, moderate relation, strong relation) mixed analysis of variance was used on word-word pairs and picture-word pairs. The main between subjects factor of medication was not significant for either the picture-word analysis $F(1,51)<1$, $p=0.60$, or the word-word analysis $F(1,51)<1$, $p=0.98$. The effect of relational strength was significant for word-word pairs, $F(3,153)=11.33$,$p<0.001$ and picture-words pairs, $F(3,153)=36.41$, $p<0.001$. There was no significant interaction of medication by relation, $p<0.05$, for either analysis. Depression and anxiety, as measured by the HAD scale, were not significant covariates in either analysis and the results remained the same when these were entered into the analyses. There were no significant correlations of all levels of relation for picture-word pairs or word-word pairs with either depression or anxiety, $p>0.032$ (see appendix 5.5.) supporting the results reported in the anova.

The association of the remaining of the measured illness variables with speed judgements were calculated using Pearson's Product Moment Correlation Coefficient.

Duration of illness was significantly positively correlated with subjective perception of fatigue as measured by the PFRS.cd, r=0.250, p=0.04. Using a significance value of p £0.00625 to adjust for multiple comparisons, correlations of illness duration with both moderate and strong pairs of picture-word pairs and word-word pairs, were significant, p<0.006, see table 5.3.2.2.a.

Table 5.3.2.2.a Correlations of semantic pair response times (sec.) with illness duration and treatment times

	word-word pair				picture- word pair			
relation	NO	SL	MD	SG	NO	SL	MD	SG
duration of illness n=64	0.18 0.150	0.20 0.117	0.36 0.003	0.40 0.001	0.19 0.129	0.13 0.320	0.43 <0.001	0.37 0.003

where NO represents no relation, SL slight relation, MD moderate relation and SG strong relation.

Correlations of illness duration with no association and slightly associated word-word pairs and picture word pairs were not significant p>0.006.

5.3.3. Interpretation

As was seen in section 5.3.2.1. chronically fatigued patients were significantly slower than controls in deciding correctly that a presented item was a word, by a mean of 0.32 seconds. This slowing of response time was correlated positively and significantly with psychiatric comorbidity; those patients with high depression or anxiety scores being slowest. This suggested that comorbidity may play a role in the manifest slowing. An analysis of the effects of drugs on this lexical response time suggested that antidepressants had little effect, those on antidepressants performing no more slowly than those who were medication free. It was not clear whether this arose from the effective treatment of depressive symptoms known to correlate with fatigue, or whether these drugs simply had no sedative side effects. As discussed in section 1.5.4. studies have reported that the newer SSRIs have few sedative side effects whilst it is generally accepted that older generation drugs have a sedative potential. Pertinently, one study (Vercoulen, Swanink, Zitman, et al., 1996) also reported that 20mg of fluoxetine had no impact on depressive symptoms or speed of information processing. What is clear is

that the slowed performance remained in CFS patients on antidepressants suggesting that whilst such drugs may assist in mood, they provide little benefit in the alleviation of cognitive symptoms that may or may not be mediated by mood. Those few patients who were prescribed sleeping tablets, anxiolitics, sleeping tablets with antidepressants, at a descriptive level seemed to be slower than control participants. This is to be expected given the well documented sedative side effects of such drugs (Unrug, vanLuijtelaar, Coles, & Coenen, 1997, Coldwell, Milgrom, Getz, & Ramsay, 1997).

A stepwise linear regression analysis illustrated that the variance of lexical decision time for words was strongly related to the patients subjective perception of cognitive fatigue; whilst physical fatigue, anxiety and depression were not significantly associated with the variance. Deciding whether or not an item is a word represents a fairy shallow level or automatic level of processing. It has been postulated that an automatic activation of lexical representations follows on presentation of a word before the activation of associated semantic meanings (Seifert, 1997). This notion is supported by studies of visual, auditory and picture primes, which suggest that the word perceptual information is accessed at a faster speed and earlier than semantic information, which becomes available later (Weldon, 1993). Thus what has been demonstrated here is a slowing in performance at a relatively low level of processing, with potential confounds such as motor slowing. Previous work on motor performance in this population has not been conclusive (Fiedler, Howard, De Luca, Kelly-McNeil, & Natelson, 1997, Krupp, Sliwinski, Masur, & Freidburg, 1994, Marshall, Forstot, Callies, Peterson, & Schenck, 1997), though it has been reported that performance does not appear to be related to depression (Michiels, Cluydts, Fischler, Hoffman, LeBonner, & De Mierlier, 1996). In this study it seems possible that there is a contribution of motor slowing to performance. It is also possible that there is cognitive slowing of which there is subjective awareness.

The regression analysis suggests that anxiety and depression do not account for a significant proportion of the variance in lexical decision response time, however this is not supported by the significant correlation coefficients. A further analysis of groups low in depression and anxiety suggest that there are still differences between control and CFS participants in lexical decision speed for words. It thus seems likely that firstly there is a slowing in CFS, then that this may be compounded by the effects of comorbidity of symptoms.

The processing involved in the lexical decision task, is also required in the recognition of words prior to their conceptual judgement, and in implementing a motor response. It was therefore not unexpected that when depression and anxiety were considered, using partial correlation, the time to make lexical decisions for words correlated with the time to make relational judgements on word based stimuli. This factor was included in the analysis for semantic pairs to control for the slowing which may be present as a result of slowing of processes such as motor response, and that arising as a result of weakening of representations of the unitary stimuli.

In the first 2(participant group) by 2(presentation type) by 4(relational strength) anova there was a significant effect of participant, this was such that CFS patients were slower than controls for all levels of the semantic pairs test. Though there was no significant interaction of relational strength by participant type, there was a trend to significance. This might suggest that the amount of slowing differed across relational strengths, but that the effect size was too small to detect with this population. Indeed this type of relationship can be largely seen at the descriptive level of statistics, with the difference between CFS and control participants being greater on slight and moderate pairs which take longer, than on strong pairs. These figures suggest a slowing of between 21.67% and 33.33% in CFS patients. However when the effects of anxiety (depression was not a significant covariate) and lexical decision speed are factored into there is no trend to significance, the interaction of type by relational strength is not significant. CFS patients are still slower with the main effect of participant group remaining significant, but it would appear that the slowing does not differently affect the distinct levels of relational strength.

The uniform slowing across conditions in the CFS patients may be associated with a general reduction in activity. For the non-novel representations and associations, there is, in effect, sufficient representation for recall of the association and semantic judgement. However, the decrement in all levels of associational strength supports the notion that there may be a general reduction in cortical activity, it taking longer to activate these representations.

The 2 by 2 by 4 Ancova (controlling for lexical decision speed for words and anxiety) also showed that there was a significant effect of presentation type, relational strength and a significant interaction of relational strength by presentation type. There was no interaction of participant group suggesting that these effects were present in both CFS and control participants. That there is a main effect of presentation is consistent with previous literature on CFS. Weldon (1993) reports an advantage of word performance speeds over picture performance speeds. Further it has been reported that the presentation of pictures with associated words (from the same category) results in a slowing of naming (Seifert, 1997), presumably as a result of interference (Rosinski, 1977). Additionally, if words and pictures are presented together for categorisation then word categorisation is slowed (Smith & Magee, 1980). This "*picture-word interference (is reported) to be semantically based*" pg. 643, (Rosinski, 1977). Such an interference effect may explain the sudden drop in speed for both CFS and controls for strong picture-word associations, thus accounting for the interaction.

There was a significant main effect of relational strength, as would be expected. As was discussed in section 5.1. previous research has shown that the time to make judgements based on relational strength, decreases as relational strength increases. This was precisely the relationship found in this population as can be seen in Fig 5.3.2.2.a. both groups performed in the expected fashion for each level of relational strength.

There were no significant effects of antidepressants on the CFS patients' performance of the semantic pairs test, those patients on antidepressants performing no worse than those who were medication free. That HAD depression and anxiety scores did not correlate with the semantic pairs variables may suggest that these variables have little effect on processes which require more central and effortful processing. The significant covariance of anxiety score in the 2 by 2 by 4 anova on relational strengths, is probably attributable to the addition of lexical decision times as a covariate since anxiety correlated with this variable.

There was a significant association of illness duration, or chronicity, on performance of some levels of the semantic pairs. For both the picture-word pairs and word-word pairs, those of moderate or strong relation were positively and significantly correlated with chronicity. Only one study has looked at the effects of chronicity or length of illness on cognitive performance (Cope, Pernet, Kendall, & David, 1995). Illness duration was

reported to be weakly correlated with performance on digit span (r=-0.28, p=0.05) (Cope, Pernet, Kendall, & David, 1995). However an inclusion criteria cut off of four years duration has been arbitrarily used by another research group to avoid symptoms associated with the '*psychosocial consequences of long term illness*' pg. 85 (De Luca, Johnson, Ellis, & Natelson, 1997). In the current study it is on those semantic pairs which are more closely and conceptually related slowing of response latency is exacerbated. Duration of illness has no significant association with either lexical decision performance or unrelated or slightly related semantic pair performance. Duration of fatigue has been demonstrated to be no different between hospital and tertiary care sample, whilst fatigue severity is worse in tertiary care sample (Grafman, 1993). This might suggest that the affects of the relationship of illness duration with slowing pertain to the affects of long term illness.

In this population illness duration and severity of cognitive symptoms are weakly correlated. Therefore the relation of duration with these more strongly associated pairs may alternatively suggest a possible index for chronicity associated with severity. Where fatigue, which may manifest as slowing, is more severely affected, representations that are more closely associated are impaired; despite the fact that these are the generally faster reaction times. This suggests further support that in central slowing speed is not the problem since if this were so, difficulties would be more apparent on those pairs which require longer for processing. A possible mechanism relates to interference of closely associated representations. This is reminiscent of the effect of interference between representations from the same category in priming experiments (Blaxton & Neely, 1983). They report that the activation and retrieval of several items/representations in a category of words, inhibits the subsequent retrieval of other members of the category. Where fatigue is more severe, a greater slowing of latencies would be expected. It may be that a greater representational weakness results in interference between two representations which are active and indistinct, the more closely associated such representations the greater is the likely extent of interference between them. This explanation is consistent with the framework that chronicity is associated with increased severity and increased representational weakness. This data and explanation are also consistent with the lack of benefit to recall from increasing the overlap in retrieval context (Sandman, 1992, Grafman, Schwartz, Dale, Scheffers, Houser, & Straus, 1993). Previous investigations suggesting a lack of association of illness duration and the association with severity have used combined assessments of

fatigue. The association of duration with fatigue fundamentally becomes a question of what is meant by fatigue severity, and whether or not differences in the cause of symptoms of fatigue and slowing result in differences in how that slowing is produced and perceived.

It is therefore perhaps the processes which are more central, less automatic and involve greater activation of conceptual representations and their associated representations which are central to CFS. These difficulties are unrelated to cognitive perception of fatigue as measured by the PFRS scale and seem to be unobserved by the patient. This together with the relation of subjective cognitive fatigue with the more perceptual and automatic lexical decision performance, suggest that peripheral processes may have more to do with the conscious perception of cognitive problems than more central conceptual processes. In the light of our models of consciousness this perhaps seems counterintuitive. However it is important to remember that this awareness may not be conscious and may be directly influencing the subjective awareness of fatigue without a knowledge of its origin. Given the type of problems reported by patients such as poor memory (Komaroff, Fagioli, Geiger, et al., 1996), and the number of reports suggesting that these problems do not correlate with subjective fatigue (Cope, Pernet, Kendall, & David, 1995, Altay, Toner, Brooker, Abbey, Salit, & Garfinkel, 1990, Ray, 1993, Grafman, Schwartz, Dale, Scheffers, Houser, & Straus, 1993, McDonald, Cope, & David, 1993), this seems an entirely likely scenario. Alternatively these processes may be consciously monitored for fatigue. Here deficits in tasks thought to be simple may be of greater psychological significance than difficulties with tasks which are thought to be more difficult. It is important to remember that the PFRS measures the perception of cognitive fatigue therefore we should not be surprised if it correlates better with some types of processing than others.

5.4. Conclusions

As can be seen in the descriptive statistics and the main effects in the analyses of variance, those participants with chronic fatigue syndrome were significantly slower than controls in making lexical decisions and relational association judgements. Since the slowing observed may have been the result of a peripheral slowing, such as caused by muscle wastage, the mean time for lexical decision was entered into the anova on relational strength as a covariate. This suggested that performance on the semantic

relations task was associated with a change on all relational strengths to the same value, once these possible peripheral problems were controlled for. There was thus support for a general reduction in activity in the CFS patients with existing representations taking longer to activate. A further interesting result suggested that patients who were more chronic showed a greater impairment on the faster more related pair judgements. This opposes what would be expected in a framework where slowing time is proportional to processing time. It is possible that in the more chronic cases there is representational interference amongst more closely associated weakened representations, thus contributing further to slowing. As has been noted a lack of benefit to recall by context provision is consistent with this impairment where representations are close. This will be discussed in the following chapter where the effects of matching (highly similar study and retrieval representations) and mismatching of encoding and retrieval cues on implicit and explicit memory performance are investigated.

Chapter

6

Implicit and Explicit Memory

6.1. Introduction

Implicit and explicit memory were discussed briefly in chapter 4 where the focus was on the development of a processing continuum. In this chapter I recapitulate and expand upon some of the literature discussed previously. Here, the emphasis will be on the theories currently available to explain the dissociation between explicit and implicit memory, as well as consideration of the factors affecting recall performance. The possible effects of representational weakness on memory performance will then be proposed, before the presentation of theoretically associated empirical work.

6.2. Implicit and Explicit Memory

Memory for past events can be revealed in two different ways: either consciously, as in explicit memory; or unconsciously as in implicit memory tasks. Cognitive researchers have long demonstrated a dissociation between explicit and implicit memory performance, for example: as stated above, explicit recall seems to be conscious and intentional, whereas implicit recall is unconscious and is revealed by facilitation of performance. It has also been reported that amnesiacs show impairment on tests of explicit memory, but have intact performance on tests of implicit memory (Warrington & Weiskrantz, 1970, Mayes & Meudall, 1981). Dissociations have been demonstrated on tasks with prolonged study-test intervals where explicit memory shows deterioration but implicit memory is preserved (Jacoby, 1983). Some researchers have also noted that conceptual benefits to memory have been observed in explicit though not in implicit memory (e.g. Roediger, Weldon, Stadler & Riegler, 1992).

There are currently three main competing theories available to account for this dissociation between implicit and explicit memory performance: the systems account (Schacter, 1987, Tulving & Schacter, 1990, Squire, 1978); the processing account (Roediger, 1990); and the component processing account (Moscovitch & Umilta, 1991, Moscovitch, Vriezen & Goshen-Gottstien, 1993), as discussed in chapter 2. These will each be reviewed briefly since a full review is beyond the scope of this thesis.

6.2.1. Systems account

The systems account proposes that the dissociations observed between priming and explicit recall are evidence for distinct subsystems (e.g. Squire, 1986). In a recent review of the systems approach Tulving and Schacter (1990) suggest that these dissociations represent evidence for what they refer to as a perceptual representation system (PRS).

This PRS is responsible for the processing of perceptual information on an automatic unconscious level. It involves automatic lexical processing and the processing of pre-semantic information and also interacts with other memory systems. The processing of meaning and conscious processes are thought to involve the semantic memory system. It is suggested that this is evidence for stochastic independence[1] and thus multiple memory systems, rather than a unitary system (Tulving & Schacter, 1990). Firstly, it is noted that in priming prior access to a target item from a cue is independent of successive recall of the target item by a different cue, whereas in explicit memory there is moderate interdependence. Secondly, the absence of priming effects with non-possible 3D visual objects suggests that the PRS "*perform(s) only ecologically valid computations*" p303 (Tulving & Schacter, 1990). Thirdly, they suggest that differences in the neuropsychology of memory are also best accounted for by separate systems.

There are problems with such an account, for example in a study on imagery enhancements to recall, implicit test performance on images was adversely affected by elaboration at study (McCauley & Moscovitch 1996), even though the PRS is defined as pre-semantic.

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[1] Stochastic independence is demonstrated where the probability of successful retrieval of target on implicit memory is independent of the probability of success on explicit memory, and vice versa.

6.2.2. Processing account

Proponents of the processing approach have suggested that this dissociation in performance of implicit from explicit memory can be largely explained from a transfer appropriate processing perspective, rather than as product of two separate systems.

The transfer appropriate processing theory was first illustrated by Morris, Bransford, & Franks (1977). Participants were given either rhyming cues for recall (bail, hail) or semantic cues for recall (sleet, hail). In the semantic cue condition retrieval was higher when items had been semantically encoded; whereas in the rhyming condition retrieval was greater if the item had been encoded phonetically. In other words the retrieval was facilitated more in perceptual or conceptual matched conditions rather than in mismatched conditions. This suggested a 'transfer appropriate processing' theory; recall being improved to the extent that the processing engaged at retrieval matched that of encoding (Morris, Bransford, & Franks, 1977). It has also been demonstrated that the type of processing at encoding may have an impact on subsequent retrieval, as discussed in chapter 4. Memory is improved for items that have been more elaborately or conceptually processed. For instance the consideration of meaning has been reported to facilitate recall as compared to encoding with a more perceptual focus (Craik & Lockhart, 1972, Challis Velichkovsky & Craik, 1996).

The contemporary study of implicit memory has typically relied on priming where exposure to the stimulus facilitates its subsequent retrieval. The retrieval tests have characteristically implemented degraded perceptual stimuli as cues, such as word stem completion or word fragment completion. For example, the completion of the word fragment *_ r _ n _ e*, would be facilitated by prior exposure to the stimulus *orange.* Implicit tests have thus generally relied on perceptual paradigms. This contrasts with the typically semantic/conceptually driven tasks used in explicit memory, such as free recall and recognition (see Brown & Mitchell 1994, for review of the encoding and retrieval paradigms used). Since implicit and explicit memory tests have historically employed different processes it has been proposed that such a dissociation is easily obtained (see Blaxton, 1989 and Roediger, 1990) and is insufficient to suggest that implicit and explicit memory represent two different systems. Further support for this notion is provided by the recent reports of conceptual encoding benefits in implicit memory, described below.

Earlier work on elaborative or conceptually driven processing effects in implicit memory suggested that there was little effect on performance, e.g. Jacoby & Witherspoon (1982). However, as mentioned previously most early implicit memory tests were dependent on primarily perceptual tests such as word stem completion, word fragment completion or priming. Thus, there was a mismatch between processing at encoding and retrieval, and benefits to retrieval as a result of conceptual processing were compromised by the processing mismatch present between study and encoding. However, beneficial effects have now been reported when items are encoded and retrieved in both perceptual and conceptual matched conditions in implicit as well as explicit memory (Blaxton, 1989, Challis & Brodbeck, 1992). Though more recent work suggests that with conceptual and perceptual cues 'held constant' (Weldon, Roediger, Beitel, & Johnstone, 1995, p268), explicit tests may require more conceptual processing than implicit tests (Weldon, Roediger, Beitel, & Johnstone, 1995, Weldon & Massaro, 1997). Such a proposal is not entirely consistent with the processing approach. The transfer appropriate processing account also has difficulty in explaining why priming still occurs where stimuli are conceptually encoded and perceptually retrieved, and why priming is observed in tasks of semantic encoding and perceptual retrieval but not the reverse scenario (Vriezen, Moscovitch, & Bellos, 1995).

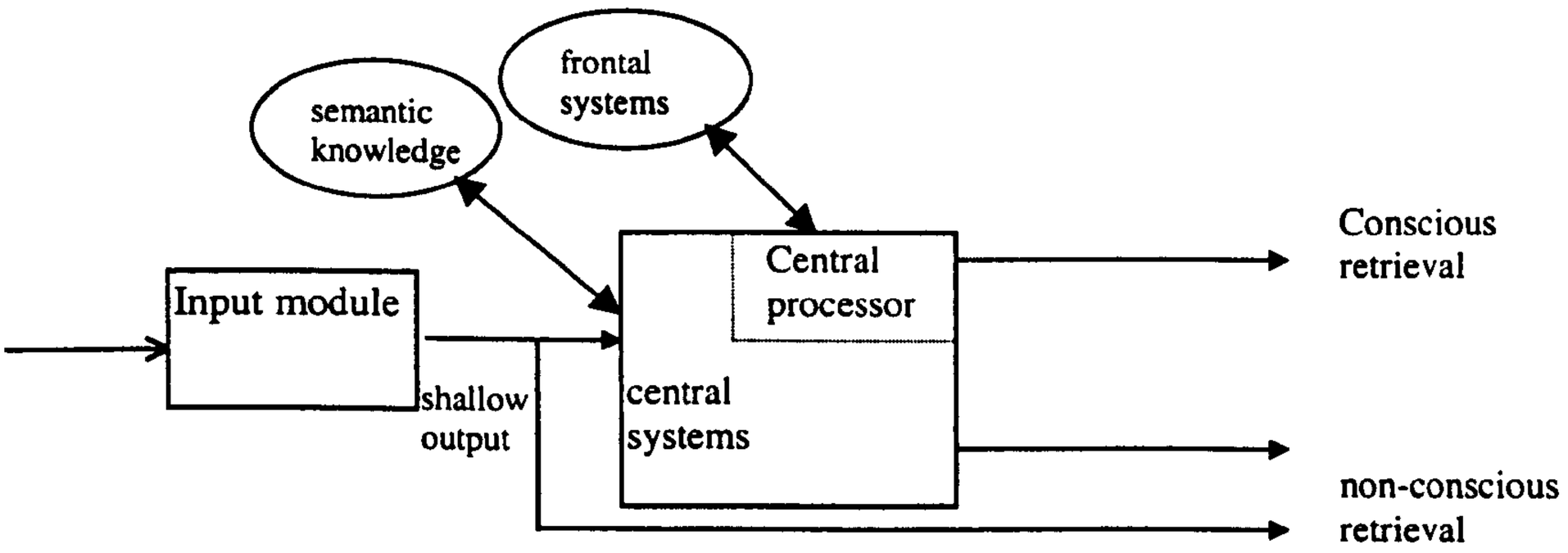
Additionally, studies of amnesiacs and control populations have suggested that different structures mediate implicit and explicit memory. Moscovitch (1991) demonstrated that amnesiacs engaging on dual tasks are more impaired on tests of frontal lobe function, but not on tests sensitive to hippocampal damage. It is suggested that consciously controlled tasks are frontally mediated. This is compatible with the work on the neuro-anatomy of memory proposed by Petri and Mishkin (1994) who suggest that explicit memory involves forebrain and limbic structures, whereas implicit memory involves basal ganglia and substantia nigra. It has also been suggested (Rugg, Mark, Walla, et al., 1998) that the neural circuits involved in implicit and explicit memory may qualitatively differ. This represents a problem for the processing approach which suggests that dissociations in performance are purely the results of processing demands at study and retrieval.

6.2.3 Component processing account.

The component processing account (Moscovitch & Umilta, 1991, Moscovitch, Vriezen & Goshen-Gottstien, 1993) attempts to combine the processing and systems account. It

accommodates findings such as dissociations between semantic and perceptual priming with recourse to processing explanations. It also advocates a position compatible with the neuro-anatomical evidence that different pathways are involved in explicit and implicit memory. This model was described in chapter 2, the following summary and figure 6.2.3. therefore serve as a brief reminder. The model is composed of separate sub-systems or component processes, where memory will be demonstrated according to the extent that these component processes overlap between study and retrieval.

Figure 6.2.3. Summary of Moscovitch & Umilta's (1991) Model of Memory[2]



Conscious processes are assumed to be associated with explicit memory, whereas implicit memory processes are unconscious. Consciousness is thought to be mediated centrally by a subsystem called the central processor, this relies on frontally mediated processes. Central systems may be activated without consciousness and mediate semantic processing, such as in conceptual implicit memory tasks.

6.3. Memory and weak representations

Initially research into explicit and implicit memory was proposed to look at possible differences between conscious and unconscious processing tasks. Though there are several definitions of consciousness (Natsoulas 1978), in this thesis conscious processes are considered to be those where there is an awareness of the input and output of the process, and unconscious processes to be those where there is no awareness. This dissociation is characterised in implicit and explicit memory, implicit being that of which we are unaware, and explicit that of which we are conscious.

[2] note that this figure was presented in chapter 2, and is included here for the ease of the reader.

Deficits in explicit memory performance with intact implicit performance have been long been observed in clinical populations reporting memory difficulties (Korsakoff 1889, Warrington & Weiskrantz 1968). Such amnesiac syndromes are perhaps best characterised as an impairment in the ability to "*consciously retrieve recently acquired information*" (Moscovitch and Umilta, 1991, p231). As Schacter (1991) notes there are two plausible explanations for such a dissociation in impairment. The first is that the outputs from memory processes fail to input into systems responsible for the activation of consciousness. If all memory processes are unable to activate such systems all conscious retrieval processes would be affected. However cases of more specific failure such as 'blind sight' and prosopagnosia have been observed. Here it is noted that there may be a "selective disconnection" (Schacter, 1991, p194) of processing types, or of memory modules.

This notion of failure to activate consciousness is also compatible with deficits reported in control populations over long retention periods. As is summarised by Shimamura (Shimamura, 1986) amnesiacs have been reported to have intact cued recall performance with impaired recognition and free recall performance (Warrington and Weiskrantz 1982). A similar pattern of performance has been documented in healthy control populations when the time elapsed between study and test is long (Meyes & Muedall 1981, Squire, Wetzel, & Slater 1978). It is possible that this dissociation represents a "*weak memory*" p 621 (Shimamura, 1986); performance on cued recall being preserved as a result of activation of pre-existing representations being facilitated by the cue provision (Warrington & Weiskrantz, 1982, Diamond & Rozin, 1984) but without conscious memory of the input episode.

This notion of reduced activation and weakness of memory relates well to the more neuro-anatomical accounts of impaired memory as discussed by Petri and Mishkin (1994). In this paper they propose that lesions to groups of ascending serotonergic and adrenergic fibres, responsible for the maintenance of consciousness, may ultimately result in the disruption of higher order processes such as memory. These fibres are thought to be more fundamental for explicit memory performance. Again, as proposed by Schacter (1991), the notion of an activation of consciousness is implicated in the performance of recall with consciousness or awareness.

Taking the hypothesis that CFS patients are slowed as a result of possible representational weakness, there is the potential for a difference in the performance on implicit and explicit memory measures. At input there will be conscious awareness even though representations are weakened as the external representation of the stimulus will provide sufficient activity to activate consciousness. However, in the absence of external stimulus provision at retrieval the representations may be too weak to activate the ascending systems responsible for conscious processing. This reduced representational activity may be simply insufficient to support the cortical activation and conscious processing required for explicit memory. As has been earlier stated the extent to which the processes used at retrieval overlap with those used at encoding has also been implicated in retrieval performance (Morris, Bransford, & Franks, 1977). With insufficient activity the weak representations are insufficient to invoke conscious retrieval and for an overlap in processing to be apparent. The extent to which representations may overlap to aid in retrieval thus becomes redundant.

Investigations into the differences between perceptual and conceptual processing were also initially planned. It was expected that there would be differences in recall performance of items which were perceptually and conceptually processed. Those involving the greater conceptual processing being impaired to a greater extent than the more perceptual by virtue of the increased processing and representations presumed to be required. Investigations into this possible dissociation are now additionally pertinent since the manipulations of processing levels (discussed in chapter 4) failed to yield unequivocal evidence regarding the effects of processing type. Additionally the provision of encoding and retrieval involving increased elaborations and context has become important. In previous chapters it was noted that context provision may not be beneficial to the performance of CFS patients contrary to observations in healthy controls. It was also hypothesised, in Chapter 5, that there may be interference between strongly associated representations. Previous research into cue provision (section 2.3.2.4.) illustrated that where the cue overlapped to a greater extent with the studied item CFS performance was impaired as compared to controls. Again in another study (Grafman, Schwartz, Dale, et al., 1993), similar effects were observed; here performance on cued recall tasks was worse than on free recall tasks, the reverse of expected. Here in this thesis we have observed in section 4.3.3. that performance on the country task may be worse in CFS than in control participants. This is the only condition of this test where the initial statement screen may act as a prime thus aiding

performance. A similar effect was also observed with respect to chronicity of illness in the performance of patients on the semantic pairs test (section 5.3.3.). In this instance task times on the more associated pairs were more impaired in the more chronic patients. It would be expected that increasing the available cues at retrieval may result in a lower recall performance in the CFS group as compared to the control group. The effect of perceptual versus conceptual retrieval cues on explicit recall was therefore also investigated.

Thus in this chapter the effects of CFS on memory, processing level and transfer appropriate processing were investigated in a verbal retrieval paradigm.

6.4. Method

6.4.1. Participants

68 CFS patients as described by the OCC (Sharpe, Archard, Banatvala, et al., 1991) were matched with 63 control participants, as described in section 3.2.1.

6.4.2. Materials and Design

A 2 by 2 by 2 by 2 mixed design was implemented with study condition (perceptual, conceptual), retrieval condition (perceptual, conceptual), and memory (implicit, explicit)[3] as within subject variables and with participant group (CFS, control) as a between subjects condition. Thus eight forms (appendix 3.1) of the two study and retrieval lists were devised, see figure 6.4.2.. The study and test lists were devised so that each target item appeared in all eight conditions, thereby controlling for systematic errors which may have arisen as a result of specific words being associated with each condition.

Stimuli and conceptual test items used were those used in experiment two of Parker, Gellatly & Waterman (1998), materials originally from Rajaram & Roediger (1993), using the norms of Snodgrass & Vanderwart (1980). Forty items were taken from the original list of 80. These were divided into two parallel lists of 20 study items in order to control for possible facilitation of performance as a result of recent prior exposure to the stimuli (e.g. magazines in the hospital waiting room).

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[3] Implicit and explicit memory are considered as 2 levels of 1 independent variable in order to look at interaction effects.

Table 6.4.2. Design of implicit and explicit memory tests

	STUDY		RECALL	TEST	abbr.
(2 parallel lists of 20 words)	intentional learning/recall	Perceptually Studied	perceptual	explicit perceptual matched	emp
			conceptual	explicit perceptual mismatched	emmp
		conceptually studied	perceptual	explicit conceptual mismatched	emmc
			conceptual	explicit conceptual matched	emc
	unintentional learning/recall	perceptually studied	perceptual	implicit perceptual matched	imp
			conceptual	implicit conceptual mismatched	immc
		conceptually studied	perceptual	implicit perceptual mismatched	immp
			conceptual	implicit conceptual matched	imc

The encoding and retrieval questionnaires were manipulated in a 2 by 2 design so that encoding and retrieval style for an item was either perceptual or conceptual; hence retrieval or encoding conditions could be either matched or mismatched, see table 6.4.2.. For each parallel list the twenty items were randomly divided into 2 groups of ten words for conceptual and perceptual encoding manipulations as outlined in table 6.4.2.. As stated above each target word appeared in all possible conditions. These 4 conditions were presented in a random order within in each of the forms of the study lists, thus controlling for potential within test order effects.

In order that performance on explicit memory tasks could be compared with that on implicit memory tasks, tests were constructed which allowed the same study and retrieval lists to be used, with the only difference being in the instructions given to participants. The explicit and implicit tests thus differed only in participants intentionality to learn and remember target items.

As was noted in chapter 4, perceptual processing is considered to focus on the physical characteristics of the word whereas conceptual encoding relates to the meaning. For the implicit perceptual study task subjects were required to count the number of vowels in the word. For the implicit conceptual study task they were required to rate words for usefulness on a five point Likert scale. These tasks were presented as the object of the

implicit study task. For the explicit study phase subjects were told that they would later be tested on the words presented, and that they should therefore try to remember them as they progressed through the conceptual and perceptual study tasks.

For the test phases perceptual cueing was via word stem completion and conceptual cueing was via crossword style clues. The two test phases differed only in that participants were required to add letters to word stems to create a word, or to solve a cross word style clue, under the guise of testing how well they could 'think up words' in the implicit condition, and to use them as clues to retrieval in the explicit condition.

It has been noted that implicit memory performance may be contaminated by explicit processes (Srinivas & Roediger 1990); therefore to maximise subject naiveté regarding the purpose of the task the implicit form always preceded the explicit form. The digit span task from the WMS-R, the results of which were reported in section 3.4.2. was used as a filler task between study and test phases in both the explicit and implicit memory tasks. The use of a filler task was principally to ensure that participants were less aware of the purpose of the implicit memory test.

It was reported in previous chapters that CFS patients are slower than controls on some cognitive tasks. There is therefore a danger that CFS patients retrieval scores may be lower than controls purely as a function of time on test. Therefore on both retrieval tests participants were given as much time as they required to complete the task.

The implicit-explicit memory test (implicit, digit span & explicit) was counter-balanced with tests presented in previous chapters, thereby controlling for order effects, as described in section 3.2.2.8. (appendix 3.3).

6.4.2.1. Additional Measures

As stated in chapter 3 (section 3.2.2.) subjects also completed, in a counterbalanced order, the Profile for Fatigue Related Symptoms (Ray, Weir, Phillips, & Cullen, 1992); a scheduled interview to assess back ground details; the Fatigue Scale (Chalder, Berlowitz, Pawlikowska, et al., 1993); the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983); a computerised test of semantic relations and lexical decision, considered in the previous chapter; a computerised task graded in processing

requirements, considered in chapter 4; and subtests from the WMS-R reported in chapter 3.

6.4.3. Procedure

Participants were recruited as described in section 3.2.3. As described in section 3.2.4. participants read an information sheet, were able to discuss the study, and then gave written consent. The testing session followed, the order in which tests were presented to each subject being determined by the counter balance schedule (appendix 3.4.). At the end of testing participants were given a debrief sheet and any questions were answered.

6.5 Results

Data was available for 66 CFS patients and 62 control participants for the implicit conditions, and 65 CFS patients and 62 controls for the explicit conditions. The number of correct responses was summated for each of the eight tests outlined in figure 6.4.2..[4] Mean recall performance scores are displayed in Table 6.5.a. below.

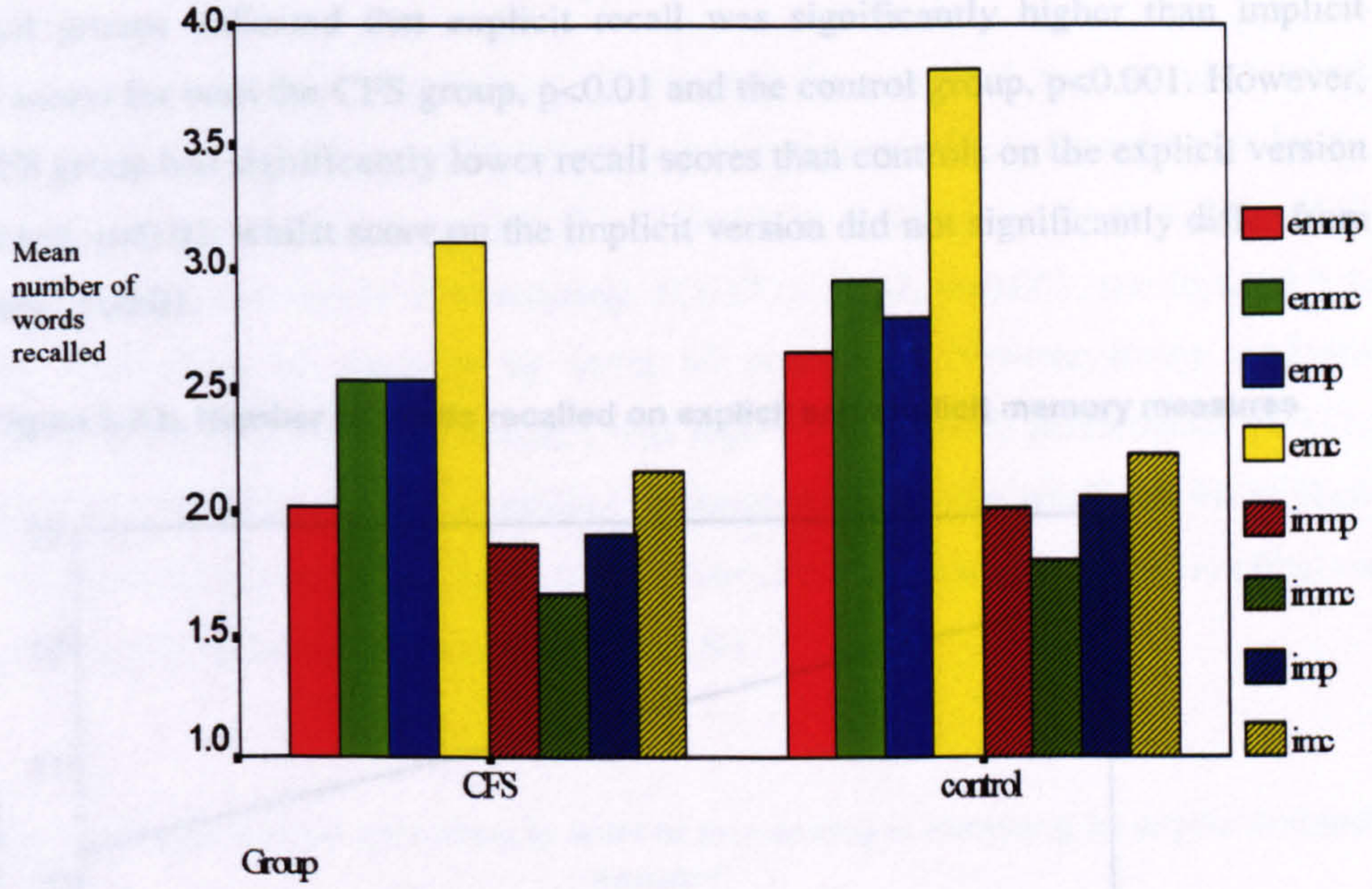
Table 6.5.a Mean recall score for explicit & implicit tests

participant	emp	emc	emmp	emmc	imp	imc	immp	immc
CFS	2.54 (1.17)	3.11 (1.08)	2.03 (1.17)	2.54 (1.26)	1.91 (1.16)	2.18 (1.09)	1.88 (1.00)	1.65 (0.97)
control	2.84 (1.26)	3.84 (1.13)	2.66 (1.19)	2.95 (1.12)	2.06 (1.07)	2.24 (0.97)	1.98 (0.97)	1.82 (1.03)

As can be seen from these descriptive statistics and figure 6.5.a., CFS patients recall scores appear to be lower than scores for controls, particularly for explicit recall performance

[4] note that implicit recall performance for controls was above baseline, suggesting that recall performance was facilitated as a result of study, see appendix 6.1.

Figure 6.5.a. Recall scores for explicit and implicit memory



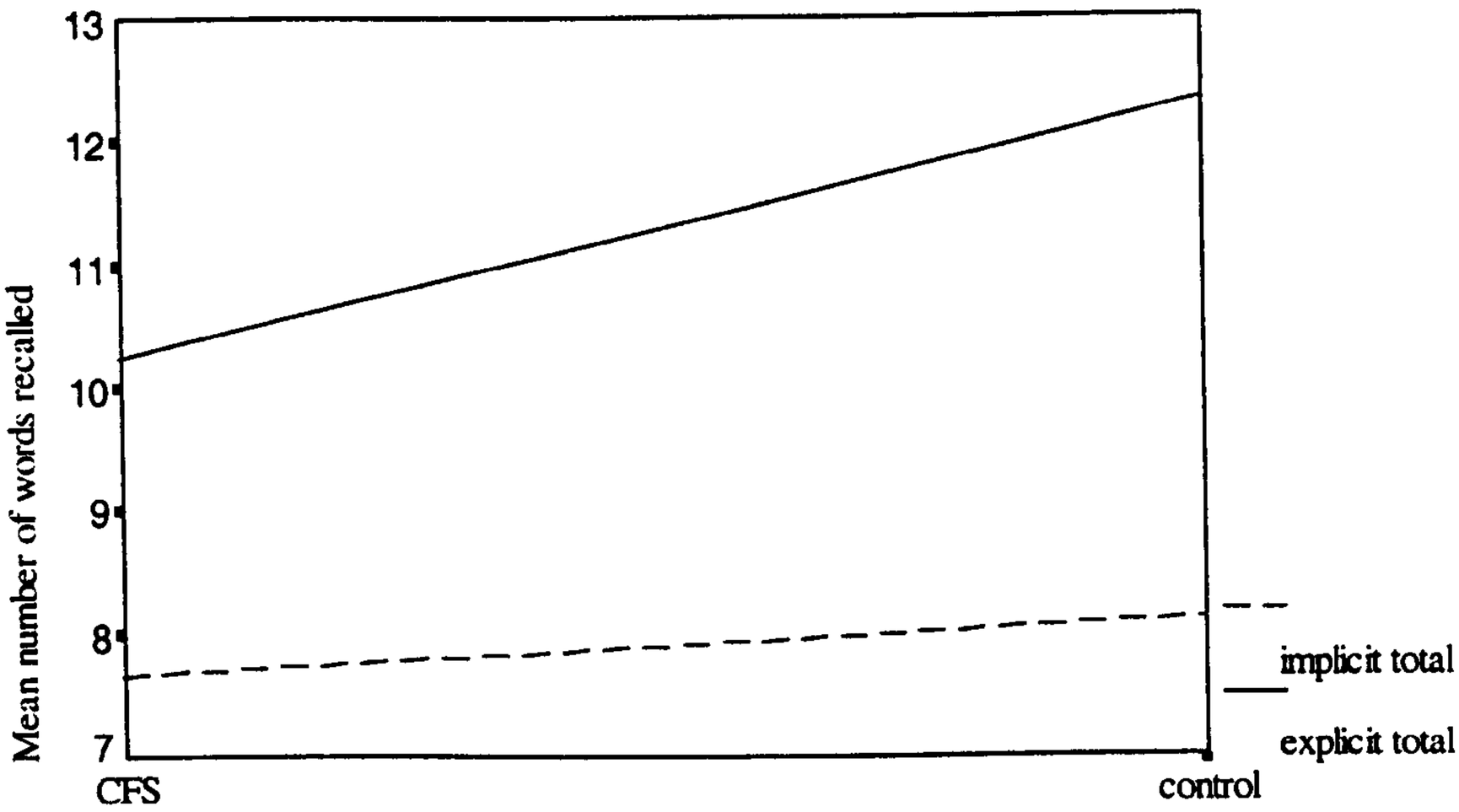
Pearson Product Moment correlation coefficients illustrated that the 8 memory measures were not significantly correlated with anxiety or depression scores in CFS patients, $p>0.0625$ to control for multiple comparisons. CFS patients perception of cognitive fatigue as measured by the PFRS was correlated significantly with overall explicit memory score, $r(65)= -0.40$, $p<0.001$, but not with implicit memory performance $r(66)= -0.14$, $p=0.25$.

Though depression and anxiety did not significantly correlate with memory performance, it was possible that they may have been significant covariates for the ancova, as a result of systematic differences of anxiety and depression between the CFS and control group. Depression and anxiety were therefore considered as covariates for the main analysis. Depression was a significant covariate, $p=0.041$, and was thus entered into the ancova model. Anxiety was not a significant covariate and results remained unchanged if this variable was entered into the analysis. The 2 (matched, mismatched encoding and retrieval paradigms) by 2 (perceptual and conceptual encoding) by 2 (implicit, explicit memory) by 2 (CFS, control) ancova revealed that there was no significant effect of participant group $F(1,120)=0.92$, $p=0.34$. However,

there was a significant interaction of participant group by memory, F(1,121)= 6.15, p=0.015, as can be seen in figure 6.5.b.

Newman-Keuls analyses, using the Games & Howell procedure[5] (1976) to adjust for unequal groups indicated that explicit recall was significantly higher than implicit recall scores for both the CFS group, p<0.01 and the control group, p<0.001. However, the CFS group had significantly lower recall scores than controls on the explicit version of the test, p<0.01, whilst score on the implicit version did not significantly differ from controls, p>0.01.

Figure 6.5.b. Number of words recalled on explicit and implicit memory measures



There was a significant main effect of memory F(1,121)=143.67, p<0.001. This was such that explicit recall scores were higher than implicit recall scores, (mean recall score of 7.70 versus 11.31, t(122)=11.90, p<0.001 and see table 6.5.a.).

There was a significant main effect of matched versus mis-matched encoding and retrieval conditions F(1,121)=32.0, p<0.001. This was such that number of words recalled was higher in matched conditions (mean of 5.15 versus 4.37, t(122)= 5.94, p<0.001. There was a significant main effect of level of processing at encoding

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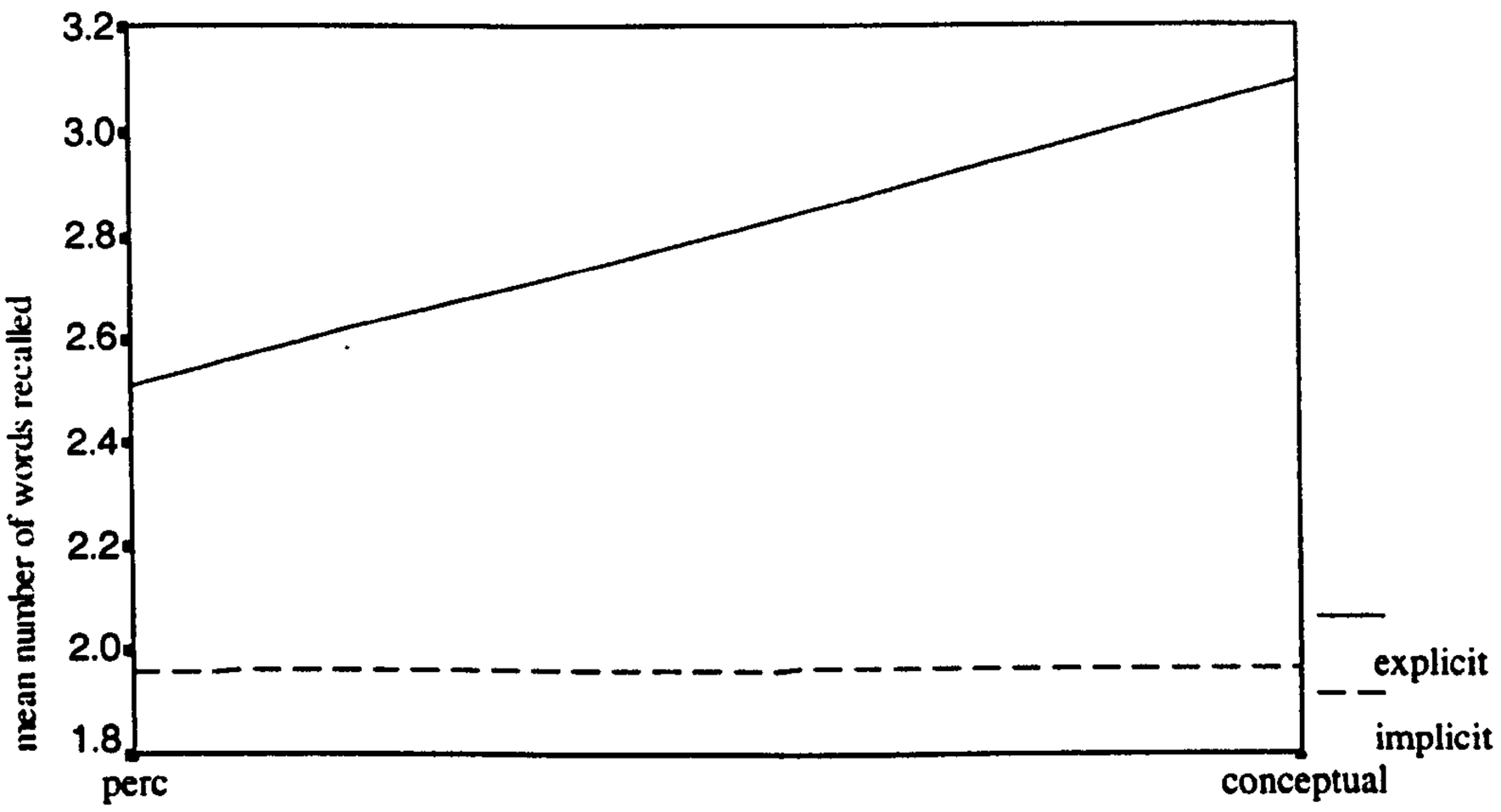
[5] note for this procedure critical values and degrees of freedom for each comparison are calculated with reference to the standard deviations, critical values for W therefore differed from those which would be calculated using published norm tables.

(perceptual, conceptual) F(1,121)=20.94, p<0.001. This was such that more words were recalled in conceptual encoding conditions (mean of 2.53 versus 2.24, t(122)=4.59, p<0.001).

There was no significant interaction of memory by matched versus mismatched conditions, F(1,121)=3.74, p=0.056. There was a significant effect of memory by levels of processing (perceptual, conceptual) F(1,121)=17.25, p<0.001 see figure 6.5.c. and of matched condition by levels of processing, F(1,121)=11.32, p=0.001, see figure 6.5.d. For the interaction of memory by level of processing Newman-Keuls analyses indicated that explicit recall performance was higher than implicit performance p<0.01. Specifically conceptual encoding resulted in significantly higher recall for the explicit tasks than did perceptual encoding, p<0.01, whereas the encoding style had no effect on the recall scores in the implicit condition, p<0.01.

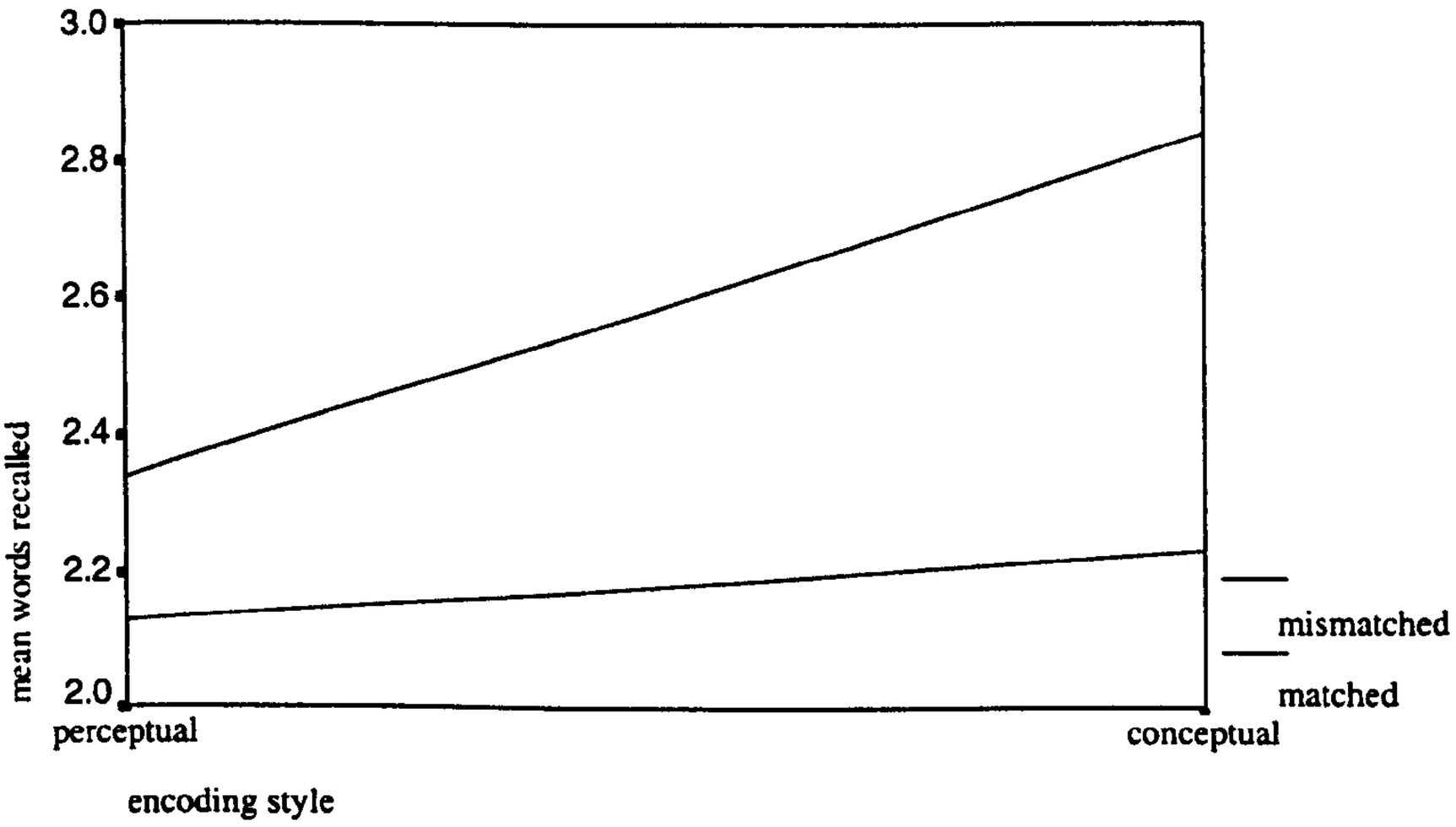
Figure 6.5.c Recall scores according to level of processing at encoding by explicit/implicit memory



For the interaction of levels of processing by match/mismatch (see figure 6.5.d.), Newman-Keuls analyses indicated that in conditions where encoding and retrieval conditions were matched recall was significantly higher than in conditions where encoding and retrieval were mismatched, p<0.01. Specifically, conceptually encoded

and tested recall scores (matched) were higher than conceptually encoded and perceptually tested recall scores (mismatched), $p<0.01$, and higher than perceptually encoded and conceptually tested recall scores (mismatched), $p=0.68$. Recall scores for perceptually encoded and tested targets were greater than scores for perceptually encoded and conceptually tested targets $p=0.018$. However whilst conceptual encoding resulted in a significantly higher recall scores for the matched conditions, there was no benefit to recall scores as compared to perceptual encoding in the mismatched condition, $p>0.05$.

Figures 6.5.d. Recall scores according to level of processing at encoding by match mismatched condition



Regarding the transfer appropriate processing effects there were no significant interactions of participant group by matched versus mismatched encoding, $F(1,121)=0.01$, $p=0.92$, nor of memory by matched versus mismatched conditions by participant group $F(1,121)<1$, $p=0.96$. Concerning levels of processing effects there was no significant interaction of level of processing at encoding by participant group $F(1,121)=0.10$, $p=0.75$, or of memory by levels of processing (perceptual conceptual) by participant group $F(1,121)=0.72$, $p=0.40$. There were no further significant second or third order interactions $F(1,121)=0.08$ to 2.69, $p>0.05$.

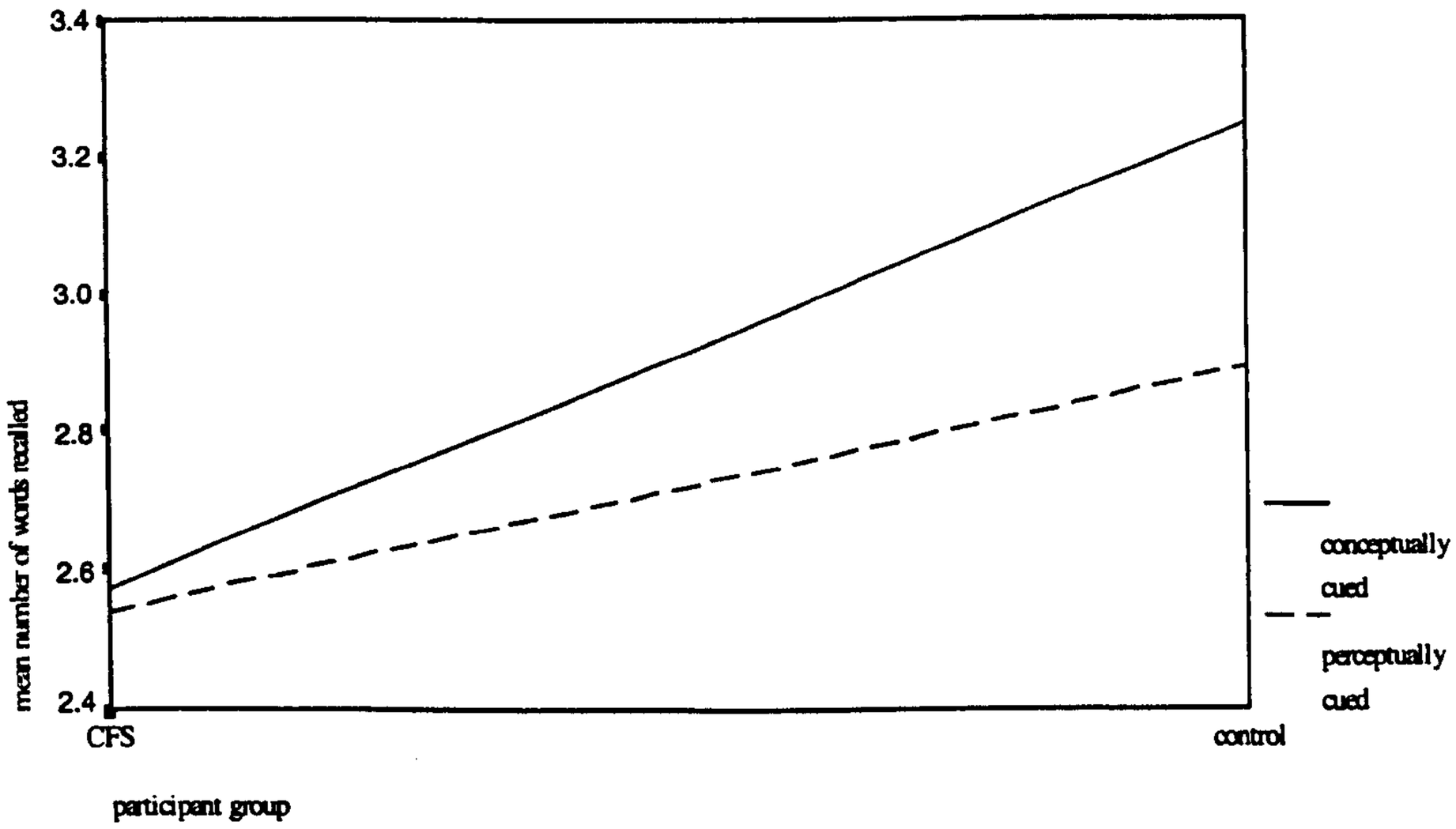
Bivariate regression analysis indicated that subjective cognitive ratings of fatigue, PFRS.cd, accounted for 16% of the variance in total explicit recall score, $F(1,63)=$

11.8, p=0.001, depression for 13% of the variance, F(1,60)= 9.11, p=0.004. Anxiety and physical ratings of fatigue were not significantly associated with a change in the variance of explicit total recall performance, p>0.05.

As stated previously (section 5.3.2.1.) not all CFS patients were medication free and analysis of performance variables by medication was only possible for data relating to antidepressants or medication free patients. An independent t-test showed that there were significant differences between control participants and CFS patients who were medication free on tests of explicit memory, t(78)=-2.69, p=0.009. This was such that CFS patients recalled fewer words than control participants (10.96 versus 12.64). There was no difference between CFS patients who were medication free and those on antidepressants on explicit memory measures, t(53)=1.38, p= 0.17.

Descriptive statistics suggested that there were differences in the mean recall scores of CFS patients and controls related to the type of cues provided at encoding, see figure 6.5.e.

Figure 6.5.e. Number of words recalled as a function of patient group and retrieval cue



A 2 way (conceptual retrieval, perceptual retrieval cue) by 2 (CFS, control) repeated measures ancova (controlling for the significant covariate of depression, p<0.05) on the

number of words recalled explicitly, suggested that this difference was not significant $F(1,122)=3.13$, $p=0.079$.

Given the duration effects noted in chapter 5, bivariate Pearson's Product Moment Correlation Coefficients were calculated between illness duration and performance scores in the explicit conditions for CFS patients. These correlations were not significant, $r(65)= -0.015$ to -0.21, $p>0.0625$, to control for multiple comparisons.

6.6. Interpretation

The fourway ancova revealed a significant main effect of memory, as would be expected. This was such that recall scores for implicit memory were lower than those for explicit memory. This is a well documented phenomenon and has been observed in many other studies, e.g. Jacoby & Dallas 1981, Schacter, 1987. Both groups of participants also showed the expected increase in recall as a result of conceptual encoding. As has been reported elsewhere in the thesis (see chapter 4), levels of processing are accepted to impact on memory performance. A number of researchers have demonstrated increased recall with increased conceptual processing at encoding in explicit memory (Craik & Lockart, 1976, Challis Velichkovsky & Craik, 1996, and see Nave, Herer, Haimov, Shlitner, & Lavie, 1996 for a review). Though the findings are less consistent for conceptual encoding in implicit memory it is now generally accepted that conceptual processing may also facilitate implicit memory (see Brown and Mitchell, 1994 for review).

There was a significant main effect relating to whether the processes invoked at retrieval matched those employed at encoding. Again this is to be expected given the reported transfer appropriate processing effects mentioned previously, see Morris, Bransford, & Franks (1977) and Challis, Velichkovsky & Craik (1996) for discussion. This was also evident in the interaction of level of processing by match/mismatched condition. Following the classic pattern (Morris, Bransford, & Franks, 1977) conceptual retrieval was better for conceptually encoded information than perceptually encoded information; and perceptually retrieved information was greater after perceptual encoding than conceptual encoding.

The interaction of memory by levels of processing was significant (see figure 6.3.2.c). This was such that implicit recall performance for conceptually encoded targets was no better than for perceptually encoded targets, whereas conceptual processing resulted in an increased recall in explicit processing. Though initially this may seem to be further supporting evidence for a lack of conceptual encoding benefit in implicit memory (see Jacoby & Dallas, 1981 and Graf & Mandler, 1984 for further work reporting similar effects), it should be remembered that these recall scores are compiled from recall scores which are matched with the encoding conditions in only half of cases. For example, scores for the conceptually tested recall measures are a compilation of scores from perceptually and conceptually encoded tests. It has been documented that whilst implicit memory does show facilitation to performance as a result of conceptual processing, these effects are smaller than those typically observed in explicit memory (see Brown and Mitchell, 1994 for discussion). These weaker effects may thus be statistically 'cancelled out' when a mismatched retrieval paradigm is enforced in implicit memory, whereas for explicit memory where the effects are larger, mismatching of processing has less of an apparent effect.

Consistent with the pattern of deficits reported in amnesiac populations (Moscovitch & Umilta, 1991) the 2 by 2 by 2 by 2 ancova also indicated that the group of CFS patients were significantly worse than controls on tasks of explicit learning and retrieval, but were unimpaired on tasks of implicit learning and retrieval. This lower recall performance was correlated significantly with patients subjective ratings of mental fatigue, but not their subjective ratings physical fatigue, anxiety or depression. This suggested that patient co-morbidity was not related to the impaired performance on the explicit version of the test, an interpretation supported by the significant interaction of memory by participant group in the ancova, controlling for depression. The regression analyses further supported that this deficit in total explicit recall was related to the patients perception of cognitive fatigue, and not to physical fatigue, anxiety or depression. It should be noted that the patients perception of cognitive fatigue was related to performance on objective measures. Since implicit recall performance is unaffected but explicit recall is impaired sceptics might suggest this is evidence of patients feigning deficits. It should be remembered that such performance is typical of other noted amnesiac populations, and that deficits have been noted in this thesis in processing times, logical memory and paired associate learning, though not digit span.

Given the high medication use of the group tested it was possible that decrements in performance may have been associated with medication use. Several studies have reported that antidepressant medication may result in impaired memory performance (Hindmarsh, 1998) (Clayton, Harvey, & Betts, 1997). An analysis of the medication effects on explicit memory indicated that there was no significant difference in recall performance of those CFS patients who were taking medication and those who were medication free. Further, there were significant differences in total explicit recall performance between control participants and CFS patients who were medication free. Combined, these results suggested that there was no effect of antidepressant medication on total explicit recall performance in this population. This again suggests, as was noted in section 5.3.3., that whilst antidepressant medication may or may not alleviate the negative mood symptoms in this population, it does not reduce the cognitive symptoms present in CFS. This is consistent with the reported non-effects of antidepressant medication on cognitive function in CFS drug trials (Vercoulen, Swanink, Zitman, et al., 1996, Wearden, Morriss, Mullis, et al., 1998).

Thus in CFS patients it is probable that there is a decrement in explicit recall but not implicit recall. This relates well to the notion of weakness of representations in amnesia. As was discussed in section 6.3 the amnesiacs ability to unconsciously retrieve information that is inaccessible to conscious retrieval may arise from the failure to output to systems relevant to consciousness. Such an explanation is consistent with the deficits observed here, and in chapter 5. In this test all stimuli were assumed to be non-novel. A reduction in activity may mean that there is insufficient activity to output the relevant ascending systems and thus activate consciousness. Recall across all explicit conditions would be impaired.

Further investigations into the possible effects of weakened representations were made by the manipulations of transfer appropriate processing and cueing. It was initially proposed that if representations were sufficiently weakened then the extent of overlap would become redundant, in terms of effects on recall performance. However the CFS group did not differ from the control group with respect to the matched processing manipulation. Both groups demonstrated transfer appropriate processing.

This may be the result of the representations being weak, but not sufficiently weak for retrieval to be unfeasible. The test stimuli implemented here all occur with moderate

frequency (Snodgrass & Vanderwart, 1980) in the English language. It may be therefore that the representations are used sufficiently often for them to be only partially weakened. If the impairment in this test was the result of a representations being too weak for recall, we would expect that transfer appropriate processing would be affected.

The impairment seems dynamic, a combination of representational weakness and global reduction in activity. As was described in chapter 2, a global reduction in cortical activity may impact on conscious processing, and is thought to be more critical for explicit rather than implicit memory (Petri and Mishkin, 1994). For those representations which are novel, the reduction in activity may be critical in maintaining a weak representation and making acquisition of the novel stimulus difficult; whereas if representations are non-novel the reduction in activity impacts on all the existing representations to the same extent. Since the representations already exist, though they may be slightly weaker than in a person without CFS Transfer Appropriate Processing could still take place. The relationship between manipulations (matched mismatched) would thus be the same for CFS and control participants.

As stated in section 6.3. it has been demonstrated previously that CFS populations often fail to benefit from increasing the context available at retrieval (see Grafman, Schwartz, Dale, et al., 1993 and section 2.3.2.4.). In control populations such manipulations typically result in increased performance (for example Challis, Velichkovsky & Craik, 1996). In this thesis similar effects have been demonstrated with respect to time on task. In chapter 4 a possible exacerbation of slowing was observed in the condition where contextual priming was possible; and in chapter 5 illness chronicity showed a greater association with more closely related item pair judgements. Given this it was proposed that a distinction would be observed between perceptually and conceptually cued recall between CFS and control groups. Descriptive statistics supported this distinction suggesting that the CFS group failed to benefit from the provision of conceptual cues at encoding. However the 2 by 2 ancova revealed that this difference was not significant. Whilst cueing effects have been reported to have little benefit to recall in CFS population, research has typically employed a paradigm of comparing free recall with cued recall (Sandman, 1992, Wearden & Appleby, 1997). This is the first occasion where the type of information available for cued retrieval has been manipulated. Here conceptual cue provision is compared to perceptual cue

provision. It should be remembered that the absence of deficits between these conditions does not preclude cued versus free recall differences or that free recall may be spared as reported by (Sandman, 1992) for example.

There are 3 explanations possible for the observed absence of cueing effects in the CFS group. The first explanation centres on the notion that cueing impacts on performance, as consistent with the previous literature; the second is that there is a general reduction in activity, thus deficits observed are global. Finally, it may be that there is simply insufficient power to detect deficits of the size observed.

Firstly as stated in section 6.3. the number of cues available in the conceptually retrieved condition should be greater than in the perceptual condition. It would therefore be expected that greater interference would be present when there were a greater number of available cues. Previous studies have demonstrated failure to benefit from cue provision (see section 2.3.2.4.) and greater interference effects in recall performance have been previously noted in CFS populations (Sandman, 1992). However it may be that cue provision per se presents sufficient interference for a decrement in performance to be present across all cued conditions. If representations are weakened, and are therefore more indistinct they may be more susceptible to interference effects. The number of cues interfering may not be important, just that there is sufficient interference for representational activation to be sub-optimal. However as was reported above these representations do not appear to be sufficiently weak so as to result in transfer appropriate processing differences. This scenario is thus unlikely. Additionally, in the absence of free recall effects it is pure speculation that cueing affects performance rather than some other variable such failure to activate ascending systems responsible for consciousness.

As noted above though words selected for the list were all of a similar frequency of usage there was some degree of variability. For example the words *tortoise* and *snake* are generally less frequently used than *glass* and *football*. It may be that for some, but not all representations the weakness is low and retrieval is therefore not possible. Since words were varied across all conditions such a decrement would impact equally across these conditions. Additionally there may be a global reduction in activity imposed upon this resulting in disruption to explicit memory performance. This global activity

reduction should impact on both perceptual and conceptual conditions with no differences being apparent.

Previous studies have compared free versus cued recall performance in CFS. In all but one (Wearden & Appleby, 1997) a failure to benefit from increased cue provision was observed. As noted above the results here do not preclude that cue provision may provide no benefit to recall. They do however raise the problem of how such effects may be mediated. Previous research suggests that there is interference in conditions of increased context, both in retrieval paradigms (Sandman, 1992) and in processing times as reported in this thesis. The absence of effects of conceptual retrieval between groups precludes such an effect. However, it may be that there is insufficient power to detect the small effect size observed, 0.025. Given that the words used in this study were non-novel and frequent in use, the representational weakening may be small. A minimal exposure to a slightly weakened target may be sufficient to result in its successful retrieval, this may account for the small effect size. It is possible that the use of more novel or rare words would yield a larger effect size. Previous studies in paired associate learning with CFS groups have noted that novel pair recall is worse than recall of pairs which are already semantically associated (Joyce, Blumenthal, & Wessely, 1996, McDonald, Cope, & David, 1993 and see chapter 3). This is consistent with the notion that unrelated pairs (novel associations) are more weakly represented and thus more difficult to retrieve. In a novel or rare word learning scenario representational weakness may thus be expected to be greater, and thus the effects of interference be greater. In order to resolve this issue further studies are needed (see chapter 7).

6.7. Conclusions

There were significant differences between the CFS group and the control group on all measures of explicit memory whilst implicit memory showed no deficit. The effect of transfer appropriate processing and levels of processing manipulations on performance did not differ between groups. Both the CFS and control groups had higher recall scores where processing at encoding was conceptual and where the type of processing at encoding and retrieval was matched. The results suggested that the global effect of CFS on performance was not attributable to depression or anxiety, nor related to the side effects of mediation. It is proposed that by using words which occur frequently in

the native language of the participants, that representational weakness may be minimised and the effects of manipulating processing styles are thus difficult to demonstrate. The impairment in explicit memory in the absence of impairment to implicit performance suggested that there may be a global reduction in activity, impacting on conscious processing.

Chapter

7

Conclusions and Future Work

7.1. Introduction

The principal aim of this thesis was to characterise the cognitive problems described by patients with CFS. Specifically, it aimed to demonstrate that there was a slowing of cognitive performance in patients with CFS and to elucidate the nature of this slowing from an explanatory perspective. The role of psychiatric comorbidity was also considered. In this chapter I will give an overview of the CFS literature as discussed in Chapters 1 and 2. The results will then be summarised with respect to the original theory proposed. As discussion of the individual results has been presented previously this chapter aims to give an overview of the main findings and interpretations given.

What we currently refer to as CFS today has been around for at least 200 years being first referred to as Febricula in the 1700's. The nomenclature and specifics of definition for such malaise have been diverse over the years, and even currently there are 5 main definitions in use. Theories on aetiology have oscillated from organic to viral and vice versa, but as yet the cause remains unknown. Though there has been much work researching the causes, and defining the boundaries of the physical components of fatigue, there has been less work in the area of mental fatigue. This is despite the high prevalence of subjective cognitive symptomatology. It has been reported that 83% of patients experience concentration difficulties whilst 71% experience forgetfulness (Krupp et al., 1994). Prevalence rates vary, depending on the definitions used as for some criteria (e.g. OCC) mental fatigue is a prerequisite and for others it is simply another possible symptom (e.g. CDC).

This diversity in definition has presented problems for the comparability and consensus of research results. A number of factors contribute to this lack of agreement in particular: the use of multiple case criteria, definitions of fatigue used; the types of measurement scales used; the inherent sample heterogeneity; the methods employed to evaluate performance and the effects confounding variables (considered in chapter 2). Additional problems arise as a result of comorbidity. Anxiety and depression are known to be associated with impairments in cognitive performance, with comorbidity high in a CFS group separating symptoms of CFS from depression may become difficult. Though there has been no formal investigation into the impact of case definition on cognitive function these definitions have been reported to influence epidemiology and comorbidity estimates (Bates, Schmitt, Buchwald, et al., 1993). Cognitive deficits are more likely in samples for which mental fatigue is a prerequisite for inclusion, i.e. OCC and ME criteria. Similarly, a more extensive variety of psychiatric symptoms are likely in samples which used the earlier CDC criteria, where symptom definitions are broader than the recent criteria. In short, case definitions may have a major impact on research findings.

Further difficulties for comparability arise as a result of actually defining fatigue, a ubiquitous phenomenon with a highly subjective meaning. Depending on the definition used, prevalence rates may vary by as much as 38% (Wessley, 1995). There are further problems with respect to the medication state of patients as well as differences in their pre-morbid states and age. It is therefore no surprise that studies often produce conflicting results. This lack of comparability has been particularly evident in cognitive studies where discrepancies in reported effects of CFS may be a result of methodological differences, or the characteristics of the particular CFS group measured.

Despite the relative recency of neuropsychological investigations in CFS, there has been research into a wide range of cognitive functions. There have been studies in higher intellectual function, visual and verbal memory, attention and speed of information processing. Studies in higher intellectual function have measured tasks such as, time perception (e.g.Grafman, Schwartz, et al., 1993), planning reasoning and problem solving (e.g. De Luca, Johnson et al. 1995, Joyce, Blumenthal et al., 1996). As discussed in Chapter 2 and elsewhere (Tiersky, Johnson et al., 1997) there are few

differences reported in tasks of higher intellectual function. Where deficits are reported between CFS patients and healthy controls, it is possible that these may be accounted for by symptoms of comorbidity.

Investigations have also been conducted into verbal and non-verbal memory. With few exceptions, there have been no reported deficits in CFS recall for patterns (e.g Riccio, Wilson et al., 1992, Grafman, Schwartz et al., 1993, Joyce Blumenthal et al., 1996). Tests of verbal memory have relied on visual as well as auditory presentations of word stimuli. Results generally show that recognition memory for word lists is intact in CFS patients (e.g. Cope, Pernet et al., 1995). Several studies report that free recall performance is worse in CFS patients that in control groups (Smith Pollock et al., 1996, De Luca, Johnson et al., 1995), caution is however needed regarding the role of depression. It should also be considered that failure to retrieve may represent difficulties in learning rather than in recall.

CFS patients have shown impaired performance in the hard pairs condition of the paired associate learning task, though performance on easy pairs remained intact (Joyce, Blumenthall et al., 1996). They have also been reported to benefit less form the provision of cues at retrieval (Sandman, 1992). Initially it may appear that this lack of benefit from cueing conflicts with intact performance on word list recognition. It should, however, be considered that CFS patients demonstrate more susceptibility to interference at study, and may thus be worse for pairs of words rather than single words. Specifically the literature seems to suggest that CFS patients have problems with tasks of explicit memory, but that this performance decrement seems to be restricted to those tasks where the processing and formulation of new representations is required.

Measures of processing and attention have yielded some interesting results. CFS patients vary widely on these measures, with intact performance in tracking (e.g. De Luca, Johnson et al., 1996) and impaired performance on vigilance tests (e.g. Smith, Pollock et al., 1996. Cope & David, 1993). Deficits in tests of slowing have been particularly apparent. Performance has been slower as measured by ERPs (e.g Prasher Smith et al., 1990), all conditions of the Classic Stroop (e.g. Marshall, Forstot et al.,

1997, Ray, 1993), Digit Symbols subtests from the WAIS (e.g. Pepper, Krupp et al., 1993) and the PASAT (e.g. De Luca, Johnson et al., 1995).

The deficits observed in CFS are consistent with slowed speed of information processing. Slowed speed of information processing is not unique to CFS and has been approached and defined in a number of ways. More recent models are in the framework of connectionism and artificial intelligence. They postulate that information processing involves the transformation of representations by sets of structured rules (e.g. Fodor & Phlyshyn, 1988). Such models have representation, organisation and processing levels. Insight into such levels of description may be derived from traditional experiments in learning and memory. Such experiments (e.g. Anderson, 1981, Becker, Moscovitch et al., 1997) have demonstrated that the speed of retrieval is proportional to the amount of practice which in turn determines the strength of the representation. If in CFS there was a weakening of representations resulting in a diffuse reduction if processing speed, tasks less dependent on speed of processing may remain intact (e.g. planning). Tasks more reliant on speed (e.g. PASAT) should show deficits.

Tests of processing were therefore conducted to determine whether there were deficits in the speed at which CFS patients processed information as compared to matched control participants; and to determine whether such slowing could be attributed to representational weakness. Sixty-eight CFS patients were compared with 63 matched controls. They completed tests of paired associate learning, digit span and logical memory from the WMS~R; measures of comorbidity, specifically the Hospital Anxiety and Depression Scale, the Fatigue Scale, and the PFRS. The expected slowing of performance was investigated using a timed yes/no response to tasks that were graded from perceptual to conceptual in their processing requirements. The nature of this slowing was then investigated using a similar paradigm. This time the items for response were word or picture pairs, graded in their strength of association. As has been previously noted as the strength of association between two items increases speed of response increases. Since the word pairs already exist as representations, if there is a general reduction in activity or representational weakening, it should impact on all representations to a similar extent, independent of the association between word pairs. There should therefore be no differences in the pattern of slowing. Alternatively, if there is just general global slowing (e.g. 5%) pairs with higher associative strength

should show less absolute slowing than less closely associated pairs. It has been theorised that a reduction in representational activity may impact on consciousness and conscious retrieval (Moscovitch & Umilta, 1991). Therefore differences as a result of processing style, conscious/non-conscious and perceptual/conceptual, were investigated using implicit and explicit memory tests. The results of this thesis suggest a slightly more complex theory of cognition in CFS than that originally suggested in chapter 2. Rather than simply a weakening of representations, it would appear that there are two processes at work: a combination of representational weakness and global reduction in activity. The impairment produced appears to be dynamic and task dependent.

7.2 A cognitive theory of CFS and supporting evidence.

7.2.1. Cognitive Theory of CFS

As proposed in chapter 2, the slowed speed of processing observed in these patients may arise as a result of decreased representational strength, and manifest with some retrieval difficulties. The impact of this strength or weakening may critically depend upon the existing strength of the representation. Deficits may thus be found in tasks apparently similar to those where no performance decrements are observed. Representations which have been previously learned and exist in memory may be already strong enough for a small boost to strength during learning to enable subsequent retrieval. For a novel representation, such as a new word, new connection or idea, the newly created representation may be weak and require repeated presentations for subsequent recall. Retrieval for old information is thus probably less affected than for newly learned information.

Since representational weakness is associated with slowing, it follows that the formation of new representations will probably be slowed in CFS patients. This may create the potential for interference between information arriving almost simultaneously. An example may serve to illustrate. During reading, a number of consecutive propositions are read and processed for the extraction of meaning. If the

processing used for the extraction of meaning takes longer there is the potential for a large number of unprocessed or partially processed representations from which the gist has not been fully extracted. Extraction of meaning may be more difficult since there will now be a number of propositions to consider. In short the processing of a large number of representations may result in less distinct and weaker representations making recall more difficult. From a subjective perspective it is possible that this relates to the described feelings of there being too much information to take in.

It has been reported that in control populations the retrieval of one word increases its strength relative to those closely associated to it (Seifert, 1997, Rundus et al., 1973, Blaxton & Neely, 1983). Similar interference to that described above may arise if one representation increases its strength relative to other closely associated stored representations, as for example in the semantic pairs test. This may result in increased difficulties for the CFS patient since these associated representations are already weakened, and are now further weakened by comparison with the retrieved word. These words thus become more difficult to recall. Retrieval difficulties may increase over and above those reported in control populations.

Differences in the pattern of deficits may also manifest between tasks requiring conceptual and perceptual processing, more particularly for new information or representations. Since more conceptual processing of information takes longer (Craik & Tulving, 1975, Weldon, 1993) there may be a greater potential for interference here, rather than in perceptually processed tasks. Practically, this may mean the CFS patients exhibit difficulties with tasks such as reading or in conceptually enforced encoding and retrieval. For non-novel information, where the existing representations are intact interference effects may not be apparent between tasks requiring conceptual and perceptual processing.

Differences arising as a result of a global weakening of activity should affect conscious processes rather than non-conscious processes. Ascending neocortical projections from the basal brain to the forebrain together with projections from serotonergic fibres in the midbrain and noradrenergic fibres in the hindbrain are thought to impact on the maintenance of cortical activation and conscious processing (Petri & Mishkin, 1994)

for a similar theory in the neurobiology of CFS see section 7.2.4.. If the level of general activation is weakened, these representations may have insufficient activity to support conscious processing. It may therefore be expected that CFS patients would demonstrate less difficulty on subconscious tasks. For novel stimuli, this effect may not be apparent. Since the stimuli are new, acquisition and maintenance of representations may be difficult, and impairment may thus appear uniform across tasks differing in their conscious processing requirements. For stimuli which have existing representation, and consequently retrieval is possible, differences may be apparent between tasks.

7.2.2. Main supporting evidence

7.2.2.1. Slowed performance speed

A number of results in this thesis and in the literature have demonstrated a significant slowing in the performance of CFS patients when compared to control participants. Slowing has been demonstrated on the lexical decision, the graded reaction time task, as well as in performance for word pair relatedness decisions when controlling for lexical decision time. As an anecdotal point, it is of interest that testing sessions for control participants generally took about an hour whereas for CFS patients they commonly took an hour and a half.

In chapter 4 the performance of CFS patients was significantly slower than control participants on three of the four tasks, graded from perceptual to conceptual in their processing requirements. There were, however, no significant differences between performance time decrements in perceptual and conceptual slowing in the CFS patient. This suggests all tasks were slowed by approximately the same amount of time. Theoretically though, conceptual processing should take longer (Weldon, 1993), and hence extra slowing would be expected in these conditions. A possible explanation related to uniformity introduced by confounding variables such as motor speed (e.g. as reported by Smith, Behan et al. 1993), this may mask the smaller effects of uniform slowing arising from representational weakness. It was suggested that both peripheral and cognitive factors might have contributed towards the overall slowed performance.

This was supported by the results of the lexical decision task in chapter 5. The CFS patients took significantly longer to decide that a stimulus was a word in the lexical decision task by a mean of 0.32 seconds. It was shown that this was significantly related to the cognitive perception of fatigue. It has been suggested that lexical representations are automatically/non-consciously activated following word presentation and before the access of their semantic meaning (Seifert, 1997). Thus the effect demonstrated was slowing of performance at a relatively low level of processing. In effect a similar process to the generalised slowing seen across all conditions of the Classic Stroop (Ray, 1993, Marshall, Forstot et al., 1996), in star cancellation tests (McDonald, Cope et al., 1993), and in target detection (Smith, Behan et al., 1993).

However slowing was not restricted to simply peripheral or low-level tasks. Slowing has been reported previously in more complex tasks such as the PASAT (De Luca et al. 1995, 1997) and digit symbols subtest of the WAIS~R (Pepper, Krupp et al., 1993). Similarly in this thesis, slowing was demonstrated in the more complex conceptual; task of word pair relatedness decisions. Even when the role of peripheral factors, such as time to read the information and to make motor responses were considered, CFS patients were significantly slower than matched controls.

7.2.2.2 Representational weakness and cueing effects

As discussed above, and observed in chapter 5, slowing of performance in CFS was still observed when the more peripheral part of the task was controlled for. Performance decrements were uniform across all of the semantic pairs tasks in CFS patients. The results demonstrated a uniform slowing of performance whilst differences as a result of manipulations to word pair strength were maintained. This suggested that a weakening of the representations required for the task, had resulted in slowing of performance, independent of the strength of association between the presented word pairs. These semantic pairs already exist in memory and a global reduction in cortical activity with weakening of the representations should affect all pairs to the same extent.

The hypothesised representational weakness was also supported by the results of previous research and those obtained for the paired associate learning task presented in chapter 3. Retrieval for previously learned information is probably less affected than

retrieval for new information. Joyce, Blumenthal et al. (1996) showed that CFS performance on hard paired associates was worse than on easy pairs. Hard pairs are novel, the connections between them need to be formed and performance is worse. In support of previous research (Joyce et al., 1996, McDonald, Cope e al., 1993, Grafman, Schwartz et al., 1993, Riccio, Wilson et al., 1992), the results of this thesis showed that CFS patients were worse than matched controls in tasks of paired associate learning. This performance decrement was specific to the novel paired associates, whilst performance on easy pairs remained intact. Here the absence of deficits on non-novel word pairs suggested that the existing representations may acquire a sufficient boost to enable transfer appropriate processing and thus recall. For the novel word pairs the new representations are weak and there is insufficient overlap between recall and study states, performance is therefore worse.

Difficulties in performance associated with cue provision have been observed on a number of occasions. Increasing the amount of conceptual information at study, as in paragraph recall, and increasing the number of cues at retrieval are both reported to increase recall performance in 'healthy' controls (Shimamura 1992, Pitarque, 1992, Morris Bransford & Franks, 1997). CFS patients however have shown a lack of benefit to retrieval in tests using word pairs which increasingly overlapped with items given at study (Sandman, 1992). Similar effects were observed in this thesis.

In chapter 4 there was a significant interaction between the CFS patients and the control participant performance for reaction times in the countryside and word conditions. This suggested, either a worse performance on the word condition, or a failure to benefit from self generated cues in the country condition. Given performance times in the control group it seemed likely that CFS patients were failing to benefit from self generated priming. In Chapter 3 a lower recall performance was observed for the logical memory test (WMS~R). Recall of prose is considered to benefit from internally generated cues (Bransford & Johnson, 1972 and as discussed in section 2.3.2.2.). Poor logical memory performance is supportive of a lack of benefit from the provision of internal cues, possibly combined with interference difficulties where the representations are sufficiently weak and indistinct.

In chapter 5 similar results were obtained with respect to illness chronicity. It was found that illness duration was correlated with performance on more closely associated pairs, despite that these are generally the faster reaction times. This suggests further support for the hypothesis that in central processing in CFS it is not a global speed reduction that is responsible for the deficits, since if this were the cases difficulties would be apparent on those test pairs which require longer processing. A possible mechanism is related to the interference between more closely associated representations. This is reminiscent of the interference demonstrated in control groups where the activation and retrieval of items in a category of words inhibits the retrieval of other members of that category (Blaxton & Neely, 1993). In CFS, where response latencies are longer and fatigue is at the severe end of the spectrum, it may be that greater representational weakness results in interference between two representations. These representations are active, indistinct, and the more closely associated they are, the greater the interference between them.

These results also suggest that representational weakness was worse in those patients who had been ill longer, similar effects have been reported in tests of digit span (Cope, Pernet et al., 1995). These patients also reported a greater illness severity. It is possible that increase severity is associated with a greater weakening of representations, and is thereby associated with increased interference on more closely associated tasks.

7.2.2.3. Recall performance and consciousness

In chapter 6 decrements in performance were found in implicit rather than explicit memory tasks. The notion that slowing may arise as a result of representational weakness, or a global reduction, in cortical activity has implications for differences between performance on conscious and non-conscious tasks. This was investigated in this thesis using tasks of implicit (non-conscious memory) and tasks of conscious explicit memory. As was reviewed in chapter 2, ascending systems are thought to be responsible for the maintenance of conscious activity. Neuro-anatomical experiments have demonstrated that implicit and explicit memory probably use two different circuits. Memory is considered to be dependent upon the level of activation across the system. Projections form seroternergic fibres in the hind brain are thought to be implicated in the maintenance of cortical activation (Petri & Mishkin, 1994). This

enables the neocortical cells to function normally, rather than these circuits being responsible for memory or higher order functions per se. In the account of slowing with weak representations, the activation level of the representations may be insufficient to support the cortical activity required by conscious processing, though non-conscious recall would remain intact. With insufficient activity it is suggested that processes and their outputs do not achieve consciousness.

CFS patients showed no performance decrements in implicit memory as compared to controls, this is similar to the effects observed in other populations (e.g. Jacoby & Dallas, 1981, Moscovitch & Umilta, 1991), as well as in the CFS population (Cope, Pernet et al., 1995). This pattern of lower recall performance on explicit tasks and intact performance on implicit tasks relates well to the notion of weakened representations in amnesiac syndromes. As was discussed in section 6.3., the amnesiacs ability o unconsciously retrieve information which is inaccessible to conscious retrieval may arise from the failure to output to systems responsible for consciousness. A reduction in activity may mean that there is insufficient activity to activate relevant ascending systems and thus higher order processing. The absence of worse performance in CFS patients on the implicit task, together with lower recall performance on explicit tasks is consistent with this hypothesis.

7.2.3. Conflicting results

There were a number of results which appear to conflict with the proposed cognitive theory.

7.2.3.1. Perceptual versus conceptual tasks

In both chapters 4 and 6 the expected differences were not demonstrated between conceptual and perceptual cues. Since conceptual tasks require more representations and more complex processing it would be expected that conceptual tasks would show greater performance decrements. In a sense because the 2 processes of representational weakness and global slowing probably interact, the effect is dependent upon the task and stimuli used.

In chapter 4, it was noted that there were no differences between performance on tasks loading on perceptual processing and those loading on conceptual processing. As was considered previously there may be a possible confound by processes not central to the cognitive element of the task e.g. motor response or the mechanisms involved prior to input to sensory regions of the brain. Large slowing to peripheral processes such as these may mask smaller cognitive differences. Alternatively because the words used as stimuli were non-novel the representations may not be weak enough for such differences to be apparent. If the existing representation are non-novel they may be activated and processed similarly in both conceptual and perceptual conditions. It is the conceptual judgement required for all conditions which is likely to result in a uniform slowing as a result of a general lowering of cortical activity. In chapter 6, deviation from the expected results may have arisen as a result of differences in a similar way to that latterly described.

7.2.3.2. Cue Provision

CFS patients have been shown to fail to benefit from the provision of cues to recall. This 'failure to benefit' is supported by the poor performance on logical memory, interference in the country condition of the graded reaction task, an increase in deficits with more closely associated representations parallel to an increase in chronicity, and by previous research (e.g. Sandman, 1992). The notion that provision of cues did not aid performance was seemingly not supported by the results presented in chapter 6. These results illustrated that there were no differences in recall performance decrements between CFS patients and control participants according to whether information was cued by a matched or mismatched cue. This effect would be expected if the representations were too weak, transfer appropriate processing would not be beneficial. However it is noted that again non-novel stimuli were used in this study. The existing representations may be sufficiently strong for an overlap between study and recall representations and thus differences would not be apparent.

7.2.4. Relation to Neurobiology of CFS

As was considered in chapter 2 explicit neural circuitry is thought to involve mainly limbic structures with ascending projections to the hypothalamus and the neocortex. Memory is thought to be dependent upon the level of activation across the whole system. As Petri and Mishkin (1994) noted basal forebrain projections are thought to be responsible for the maintenance of this cortical activity. Though it is beyond the scope of the thesis to propose a possible neurobiological mechanism for the slowing seen in CFS, it is of interest to note reports of parallel changes in the reticular activation system (RAS). It has been suggested (Dickinson, 1997) that a central problem in CFS may be a lack of brain stem activation, specifically the RAS. The peribrachail area of the RAS contains cholinergic paths thought to project to the cortex via the basal forebrain, thalamus and hypothalamus. Lesions to the RAS are associated with reduced arousal, and it is generally accepted that the RAS is required for consciousness. Dickinson (1997) reports that such a reduction in activity may explain many symptoms reported by CFS patients, for example dizziness and sleep disturbances. It has been reported in this thesis that a reduced representational activity or representational weakness may explain many of the cognitive deficits reported in CFS. We might speculate given the common regions of the basal forebrain that similar mechanisms may be involved in reducing activational levels.

7.2.5. Specificity of Fatigue

Slowing has been reported in a number of other conditions, such as anxiety, depression ageing, MS and influenza (see section 2.6.), perhaps the mechanism of slowing could be generalised to other conditions. In this study, there were a few results which related to the specificity of the mechanism producing slowing.

Anxiety and depression appeared to show effects which were different from those of CFS. This is consistent with much of the reported research (e.g. Cope et al., 1995, Marshall et al.,1997). Dissociations between the cognitive characteristics of CFS and those of its accompanying symptoms have been noted CFS patients with sleep abnormalities (Smith et al., 1996). CFS patients with sleep abnormalities were reported to have impairments in free recall and sustained attention, and psychomotor slowing

was not influenced by sleep. Comparisons with other patient groups reporting similar symptoms have also been made. For example, Johnson et al. (1996), report differences between the processing impairments of CFS patients and MS patients in tests of processing.

In this thesis there is support for the notion that processing deficits associated CFS may differ from those associated with psychiatric comorbidity. When CFS patients were presented with word pairs varying in their strength of relationship (Chapter 5), initial inspection showed the amount of slowing differed across relational strength. The differences were such that CFS patients were much slower than controls on less related word pairs. The figures suggested a slowing of between 21.7% (closely related pairs) and 33.3% (slightly related pairs). This is supportive of the idea that there is a general slowing in processing speed. However, when the effects of anxiety as well as lexical decision times were removed, the effect is not significant; slowing does not differentially affect the distinct levels of relational strength in CFS. This may mean that the mechanisms for slowing in anxiety are related to more global slowing rather than representational weakness. However, this proposal should be considered with caution since effects of anxiety may also be masked by more peripheral elements of lexical decision performance. Depression was not a significant covariate on the lexical decision measure. However, depression was, for example, a significant covariate in the performance of digit span and paired associate learning. When depressive comorbidity symptoms were controlled for there were no differences between the CFS group and the control group on digit span. This suggests further evidence for a distinction between the cognitive deficits associated with CFS those of depression.

It is beyond the scope of the current thesis to complete the comprehensive literature review which would be required to suggest that the mechanisms of slowing proposed are generalisable to other illnesses. However, given some of the discrepancies reported it seems probable that there are qualitative differences between illness states.

It has been argued that fatigue is a non-specific response to stressors, such as sleep deprivation and illness (e.g. Alluisi, 1972). It is not implausible to suggest that the cognitive effects we see in CFS are cognitive responses to fatigue. It has been

suggested that sleep deprivation and time on task interact in determining the fatigue level and time at which fatigue is experienced (Craig & Cooper, 1992). In other words, the CFS group may represent the more severe end of a spectrum of mental fatigue.

In this thesis it has been reported (chapter 5) that the correlation of semantic response times with illness duration was stronger for more closely associated item pairs. Performance was worse on pairs which were more closely associated despite that these were the faster reaction times. In this population illness duration and severity of cognitive symptoms were weakly correlated. It may therefore be suggested that representational weakness becomes worse with increasing severity/chronicity. It may be that the greater representational weakness results in a greater capacity for interference between closely associated and less distinct representations. There is support for the notion that 'Fatigue' as considered in CFS may represent a continuum. The performance decrements reported in this thesis may represent part of a continuum where CFS is the chronic end of mental fatigue.

In summary, it would be premature at this stage to suggest the specific mechanisms behind slowing in CFS are generalisable to other conditions, but research into the area of less severe fatigue states may prove interesting.

7.3. Patient characteristics and potential confounds

7.3.1. Illness duration

As mentioned above, illness duration was correlated with illness severity suggesting that those patients who had been ill longest also experienced more subjective fatigue. Illness duration was not correlated with the majority of the variables measured, as has been reported in other studies (e.g. Cope, Pernet et al., 1995). However, for performance on more closely associated word pairs there was a positive correlation between duration and response time. In this study there were no extra inclusion criteria imposed relating to the duration of illness, though some researchers have used cut-offs of four years (e.g. DeLuca, Johnson et al., 1997). It is possible that these correlations are the result of the long-term effects of illness, given the lack of association with

cognitive variables. However, since cognitive performance did not correlate with any measure of the semantic pairs test this may be an area where objective and subjective symptom reports simply do not coincide. It is perhaps slowing/breakdown of performance on previously fast, or automatic tasks, that has more to do with the subjective perception of cognitive fatigue. It is possible that those patients experiencing both greater illness durations and thus more fatigue are more impaired on this task, greater fatigue being associated with greater slowing and representational weakness.

7.3.2. Subjective fatigue

This sample of CFS patients rated themselves as severely rather than moderately or extremely fatigued. This is in keeping with their attendance both at tertiary care clinic and testing sessions. It has long been speculated that those patients who are more severe may not be sampled. Within this sample there is evidence of such a bias, where several patients did not attend testing sessions because of the severity of their symptoms (see appendix 3.5.). Physical fatigue was a more common complaint than cognitive fatigue in the week prior to testing, with 69.1% of patients experiencing cognitive fatigue and 80.0% experiencing physical fatigue. In conflict with a number of existing reports suggesting subjective accounts of fatigue do not correlate with their objective measurement, a relationship between objective and subjective cognitive fatigue was found. Regression analyses suggested that subjective cognitive fatigue scores were the most important predictors of performance score in the graded reaction test, lexical decision performance and explicit recall. Subjective cognitive fatigue was, however, not related to recall performance in any conditions of the semantic pairs test. Perhaps, as mentioned above, the subjective awareness of fatigue is dependent on factors other than conceptual performance decrements. Patients reporting more symptoms of depression and anxiety were also likely to report greater cognitive fatigue, probably as a result of individual differences in reporting behaviour.

7.3.3. Anxiety and Depression

Depression levels in this group were lower than would be expected. Almost 25% percent of the sample experienced clinical depression, as compared to an expected

value of between 45% and 50%. Conversely the anxiety rates were higher than would be expected 36.9% as compared to between 23% and 31%. This variability in prevalence rates of CFS samples has been previously noted (Bates, Schmitt, Buchwald, et al., 1993) to be largely dependent upon the methods of measurement and the criteria used for diagnosis.

In this thesis subclinical levels of depression were thought to be relevant in the production of cognitive symptoms as well as on cognitive symptoms typical of depression. Thus rather than considering the effect of clinical depression the level of comorbid symptomatology was measured.

One major issue in CFS is attributing neuropsychological or cognitive performance to either CFS, depression or anxiety. As has been reported elsewhere (e.g. Krupp et al., 1994) apparent differences may be attenuated when comorbidity is considered. Further support for this was demonstrated in chapter 3. Initial inspection of the results showed significant differences between CFS and control participant performance, however, these differences were no longer significant when depression was considered. Depression scores were found to be significantly related to lower recall performance in the digit span and paired associate learning tasks. Anxiety was significantly related to performance on the paired associate learning task, though recall performance was still lower in CFS patients when comorbidity was considered. There was no correlation of comorbid symptoms with logical memory performance nor with either implicit or explicit recall performance, or with performance on any conditions of the graded reaction test or semantic pairs test. Comorbid symptomatology was not related to speed of performance in this group. It is thus unlikely that the deficits in speed reported here were attributable to depression or anxiety.

Given the high use of medication in this population (57.7%) investigation into the effect of drugs on performance was planned. Unfortunately given the wide variety of drugs used it was not possible to examine the effects of any particular medication. Comparisons were however possible between CFS patients taking antidepressants and those who were medication free. These showed consistently that there were no differences in cognitive performance between these two groups. It is not clear whether

drugs had no effect on performance, or whether there was an effective treatment of the depressive symptoms which impacted upon cognitive symptoms. What was clear was that whilst the treatment of symptoms with antidepressants may have alleviated symptoms caused by mood they probably had little benefit on symptoms particular to CFS.

7.3.4 Potential confounds.

Intelligence has been reported to vary with processing speed (Kane, Proctor et al., 1997, McGeorge, Crawford et al., 1996). In order to compare the cognitive performance of CFS patients with controls, estimates of premorbid intelligence were required. Traditionally, premorbid intelligence has been investigated using a variety of methods, from reading times, NART, WAIS~R subtests. For this population since the effects of CFS on these tests has not been longitudinally determined, the highest educational level attained was used as an estimate. Though both groups were matched on education, and the differences between the groups were not significant (p=0.06), it could be suggested that there was a trend to significance. There may therefore have been significant differences between CFS and controls as a result of systematic differences between groups. These would manifest as a decrement in CFS performance since this group has the lower educational level. Though not reported, since a strict criteria of significance was adopted (section 3.2.5.), these effects were still considered in all analyses. Even when education was a significant covariate, the direction of the effects remained unchanged.

Similarly it has been reported that age is significantly correlated with speed of performance; as age increases speed declines (Weckowicz, Nutter et al., 1972). The two groups were well matched on measures of age. CFS patients had a mean age of 40.7, versus a mean age in controls of 41.0 years, this difference was not significant (p=0.878). There were no effects of systematic differences as a result of age between the CFS and control groups on any performance measures.

Sceptics might suggest that systematic differences between groups in performance measures may have arisen as a result of differences in motivation. There are a number

of results which suggest this is probably not a likely explanation. Impaired explicit performance with intact implicit performance is typical of other amnesiac populations (e.g. Warrington & Weiskrantz, 1968). Deficits were noted, in this thesis, in processing times of lexical decision, graded reaction and semantic pairs tasks. Participants were not informed in advance that performance time was being measured. CFS patient performance was intact on both digit span and easy paired associates. It was also reported that cognitive performance did not correlate with any measure of the semantic pairs test. Additionally, tasks which are more open to conscious control and awareness appear to be less related to the subjective perception of fatigue.

7.5 Limitations and Future work

In testing any population with CFS certain limitations will necessarily be evident. A number of these have been discussed already but of particular note are the comorbid symptoms experienced by this group, and difficulties in measurement of symptoms.

Tests were completed in a single testing session spanning one to two hours per patient. The symptoms of CFS are considered to be vacillating and it is therefore probable that some patients who had experienced fatigue during the preceding week were actually relatively unimpaired on the test day. By the same argument the reverse pattern is also likely. This probably contributed towards the heterogeneity of the group, as is evident in the wide variance in performance on some measures.

Additional variation in the CFS group may have arisen as a result of time on test effects. In this study, test order was counter -balanced, a particular test could therefore be scheduled for any position during the testing period. If time on test is related to performance decrement in CFS patients (e.g. Vollmerconna et al., 1997) results for a particular test are likely to be more varied; for some participants the test will appear at the end of testing, whilst for others it will appear nearer the beginning. With hindsight it would have been possible to measure this time on test effect, looking at performance decrement over time as a systematic error; this variability source could then have been considered in the analysis. However, it may be that the tests are not similarly affected

by time on test, since some performance on some tests appears to be intact. Counterbalancing also ensured that effects arising as a result of preceding stimulus exposure were considered.

Further criticism could be levied at the form of the reaction time based tests of graded reaction time, semantic pairs and lexical decision tasks. Traditionally in cognitive psychology a larger number of practice items have been used to familiarise participants with the test. In this experiment, in order that the majority of CFS patients were able to complete the testing session, these tests were shorter than would be typically used. Though it was ensured that all participants understood *'what'* they had to do, it is acknowledged that this may have meant some were still less proficient at *'how'* to do the task. To some extent, this is the essence of some of the suggested differences between control populations and CFS patients; representations are weak, and take longer to acquire. It is probable that with increased practice on some measures global performance decrements, such as those observed in the lexical decision task may be attenuated.

As in other studies, the levels of fatigue severity were evaluated using self report questionnaires. Some participants may have scored highly simply as a result of individual differences in symptom perception. Of course when this is translated to an objective measurement discrepancies may be evident between objective and subjective measures. Despite this, performance on some objective measures was shown to be associated with subjective symptom reports. Though depression and anxiety symptoms were considered in the statistical evaluation it is possible that there was variability of symptom reporting with the self report scales. Further work is therefore needed, perhaps with clinically diagnosed populations to determine the robustness of these effects. One major difficulty in working with clinically ill populations is in recruiting sufficient patients to study. As has been noted in a number of studies the most severe patients are often not tested, this may result in difficulties remaining unidentified, and presents problems when attempting to generalise to the larger CFS population.

The group tested here were generally representative of the tertiary care populations previously researched. They performed similarly to previously studied groups on

neuropsychological tests, and were similar in demographic variables such as age, sex ratio, illness duration and illness severity. They were however more highly educated and of lower sociodemographic status. The results of this study are probably generalisable to tertiary care CFS populations which have been studied previously. In terms of demographic and symptom characteristics they are similar to previously studied tertiary care groups. With caution, regarding high educational level of this group, results may generalise to a primary care population. What is not clear is whether the pattern of performance would be similar in those patients with extreme fatigue. The results presented in chapter 5 suggest that there may be large differences in performance as a result of fatigue severity. Further work is needed with those representing the more severe end of the spectrum, though in practice this presents some difficulties.

A recurring issue throughout this thesis was the distinction of novel versus non-novel stimuli and representations. There was only one test where novel representations were required, in the association of previously unrelated items on the paired associate test. This resulted in ambiguity regarding whether deficits were unmeasured or absent with manipulations of perceptual versus conceptual processing distinctions and matched versus unmatched cueing. It should be possible to test this by presenting a series of stimuli, either verbal or pictorial, from a continuum of stimuli graded from novel to common. This would indicate whether recall performance was indeed affected by familiarity or practice, and perhaps determine what level of familiarity was critical for performance.

It was also proposed that increased exposure or practice of stimuli results in increased representational strength and recall. If CFS patients simply have weakened representations, it should be possible with repeated exposure to strengthen the stored representations until a level sufficient for later recall is reached. In effect CFS patients should ultimately perform similarly to controls, it may just take more practice sessions to achieve this level. This may generalise to the acquisition of new skills such as trailmaking or repeated subtraction, as well as to tasks involving more concrete representations such as list learning.

7.6. Conclusions

Whilst there are a number of possible interpretations for the individual results presented here, and perhaps for the overall picture, representational weakness combined with a global reduction in activity do seem to be possible causes and thus merit further investigation. Though the thesis provides evidence for the theory proposed there are still a number of areas that require investigation, in particular the differences between novel and non-novel stimuli. Obviously this thesis is not an answer to the problem of CFS, nor even to cognitive deficits in CFS. However it hopefully goes some way to characterising a possible cause for the cognitive problems reported.

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Appendices

Table of previous research

STUDY	SUBJECTS & METHOD	COGNITIVE TESTS	RESULTS	AUTHORS INTERPRETATION
DeLuca et al. 1995	26 CFS patients diagnosed in past 4 years, moderate severity, no history of psychiatric disorder, substance abuse in last 5 years, or of loss of consciousness for more than 5 min. 12 multiple sclerosis, 14 depressed, 20 healthy controls. Completed BDI and neuropsychological tests and the State Trait Anxiety Scale (STAI) 1 session about 150 min. Controls were age, sex and education matched.	Digit Span, PASAT, Trail making, Booklet Category Test, Rey Complex Figure Test, CVLT, logical memory, intellectual function sub-tests of the WAIS	No differences from controls on: digit span total, trail making A or B, Rey complex figure (delayed and immediate), logical memory (delayed and immediate), cued recall and immediate & delayed free recall, booklet category, intellectual function sub-tests of the WAIS. Differences from controls on: PASAT (not diff from depressed and high and low depressed groups did not differ), CVLT (sig. lower than all groups, particularly trials 1 and 5).	Attention and concentration as assessed by PASAT, trails A & B, suggest selective impairment of information processing on tasks of complex auditory material. No diff on trail making plus the PASAT differences suggests impairment of sustained selective processing of information. Generally not impaired on tests of memory relative to controls, exception was the CVLT, suggested acquisition deficit, rather than recall could be depression related. No deficits on tasks of higher intellectual functioning.
Ray et al., 1993	24 CFS patients, 20 controls, matched for gender and age who were friends or relatives of patients. Other measures PFRS. Sub-clinical depression was not controlled for.	Stroop Colour Word Interference Test, Embedded Figures Test (EFT).	Not significantly different on the EFT, significantly different from controls on colour naming and word reading, but accounting for this, not significantly different on the interference condition.	Both tests show ability to focus attention is not reduced.
Altay et al. 1990	21 post infectious neuro myasthenia patients, all 21 met CDC criteria, no controls (used normative data).	Digit Symbol and Similarities (abstract reasoning) subtest of the WAIS~R, Trails A and B, Shipley Institute of Living Scale (estimates currents and previous intellectual function).	Better than normative data on trails B and digit symbol, similarities test and Shipley test.	Use of a comparison group may have been useful, but there is no evidence of reduced function compared to normative data, however, experimental group had a high educational level.

STUDY	SUBJECTS & METHOD	COGNITIVE TESTS	RESULTS	AUTHORS INTERPRETATION
Krupp et al., 1994	20 CFS CDC patients who additionally reported cognitive problems. 20 case control, 20 MS, session about 4 hours (rest periods included). Information and Vocab sub-tests of the WAIS, and the reading sub-portion of the Wide-Range Achievement Test~Revised (done as premorbid ability assessment).	Object assembly and block design sub-tests of the WAIS~R, Stroop Colour Word Test, Digit Span, Trail Making A and B, Digit Symbols Subtest, Symbol Digit Modalities Test, Booklet Category Test, 6 Trial Version of Selective Reminding, Paired Associate Learning and Logical Memory, Benton Visual Retention, Controlled Oral Word Association, Finger Oscillation.	Different from controls on: digit symbol (depression controlled for). No different from controls on: Logical Memory, Long Term or Delayed Retrieval, Digit Span, Trail Making A or B, Controlled Oral Word Association, Booklet Category Test. Remainder not reported.	CFS reduced function, small magnitude of change, tends to be on tasks relying on concentration, reduced ability in visuomotor search demonstrated by digit symbols.
McDonald et al., 1993	65 general practice CFS, identified by score on questionnaire, no controls, 2*2 design, high and low fatigue with high and low depression	Serial 7s, Digit Span, Star Cancellation, Paired Associate Learning.	High and low fatigue groups did not significantly differ in performance, except on hard paired associates where non depressed high fatigue scored worse than non depressed low fatigue. Digit span forward and backwards correlated with fatigue.	Psychiatric morbidity strongly associated with performance on digit span backwards, depression correlated with performance on easy paired associates. Anxiety did not correlate with performance..
Scheffers et al. 1992	13 CFS, CDC , 13 controls, matched on sex, age, years of education. All patients were moderately to severely disabled at the time of testing. Medication was withheld for 2 weeks prior to testing. BDI and the modified Speilberger scores were within normal range.	WAIS~R, WMS~R, BDI, modified Speilberger, Attention Test, Odd Ball Paradigm, EEG	Differences from controls on: odd ball reaction time, *run 1 from 3* runs CFS significantly slower. Reaction times were not sig. slower, though 9 of the 13 CFS patients were slower than controls. No different from controls on: attention paradigm odd ball paradigm for occipital N1 P2 and frontal P3, and N2 and P300.	CFS can focus/allocate attention to process selectively relevant information and limit processing of extraneous variables to same degree as controls.

STUDY	SUBJECTS & METHOD	COGNITIVE TESTS	RESULTS	AUTHORS INTERPRETATION
Sandman et al. 1993	39 CFS, CDC criteria, 23 depressed and 129 healthy controls, age matched (N.B. not matched on education).	Mini- Mental State Exam, WMS~R, Wisconsin Card Sorting Test, Trail Making Test, Boston Naming Test, Visual Function Scale of the Luria Nebraska Neuropsychological Test Battery, meta-cognitive estimate, free recall, paired associates, recognition and letter priming sub-tests, proactive inhibition, item recognition, semantic memory test.	Sig. differences on tests of increasing context, paired associates & recognition where CFS patients made more errors than controls and depressed groups. On item recognition CFS had a significantly flatter retrieval slope, recall was worse on proactive inhibition test & mental scanning was delayed compared to depressed in the 'no condition' and controls in both 'yes and no condition'. No diff on semantic memory.	As CFS patients showed no benefit from priming or increasing the context in recall tests, were unable to retain a 3 item list with a 10 second distraction task between study and recall and showed delay in memory scanning with increased load, the authors deduce that CFS patients had deficits in memory consolidation, were susceptible to interference and were slow at decision making.
Smith et al. 1993	57 CFS , 19 matched controls (age and educational level), all subjects were drug free. majority were from social classes I and II. No psychiatric illness. Tests were counter balanced to control for fatigue effects. Completed questionnaires on depression anxiety and physical and cognitive symptoms.	Battery of computerised tests: variable fore-period simple RT; 5 Choice Serial Response; sustained attention, detection of repeated numbers; free recall (20 words); delayed recognition memory; logical reasoning task; semantic processing task; Stroop Colour Word Test; pattern sensitivity	Significantly slower on simple RT, 5 choice serial response task, interference condition on Stroop and the semantic processing task, increased pattern sensitivity, reduced target detection on cognitive vigilance tasks, CFS also detected fewer targets and made fewer false detections of distractors in the recognition task. No differences on digit span, free recall. Depressed and non depressed showed similar deficits.	CFS show psychomotor impairments, problems maintaining attention, visual sensitivity, slowing of retrieval from semantic memory and slowing on the logical reasoning task not accounted for by depression. Impairments are not global.
De Luca et al.	12 CFS , to excluding depression and anxiety, were age, education and estimated verbal intelligence matched with 11 MS patients and 11 healthy controls. Completed neuropsychological measures & BDI.	PASAT (processing speed, and efficiency), Digit Span, Similarities and Vocabulary Sub-tests of the WAIS~R.	CFS worse than controls on Digit Span, and PASAT (though rate of decline over trials did not differ). No differences on the similarities subtest.	Patients with CFS have reduced information processing efficiency (demonstrated by PASAT) and are worse at tests of attention and concentration. processing of complex auditory information that is the problem, not depression related as did not correlate with BDI scores. Cognitive deficits are not global.

STUDY	SUBJECTS & METHOD	COGNITIVE TESTS	RESULTS	AUTHORS INTERPRETATION
Cope et al. 1995	11 CFS depressed patients, 15 CFS non depressed. OCC criteria were modified on severity. 18 age matched controls and 13 age matched mildly depressed patients. Exclusion of previous head injury, epilepsy, substance abuse, hypertension or contraindications for MRI. Completed BDI and State Trait Anxiety Questionnaire and fatigue assessments.	NART, WAIS~R, WMS~R, Warrington Recognition Memory Test (RMT), self assessment of RMT and memory over last 4 weeks. Graded Naming Test (pictures), Word Stem Completion, Supra-Span (memory for a list of 15 household objects), Verbal Fluency, Speed of Information Processing (time taken to do mental control task, first 6 items of Block Design and first 3 items of Object Assembly Test), MRI scans.	Memory: no difference in memory or attention/ concentration scores from the WMS~R. No sig. differences in Verbal Memory, Paired Associates, or Supra Span Learning, Graded Naming or Visual Memory Scale of the WMS~R. As no deficits on explicit test no prospect of demonstrating and explicit implicit dissociation. CFS worse on RMT faces, not correlated with anxiety and depression. Speed of Information Processing: depressed were sig. longer than CFS and controls.	The CFS subjects who did not meet criteria were not sig. different from those who did not, except had better performance on verbal and general memory scores of the WAIS~R and the WMS~R. No evidence for a decline in function in the CFS group. As a subgroup of CFS improved at follow up test, 6 months later, indicated may have been performing sub optimally at initial test.
Grafman et al. 1993	20 CFS patients and 17 age and education matched controls. Rated mood and physical symptoms using BDI, Somotisation Scale, Neuro-behaviour rating scale and fatigue scale and completed neuropsychological tests.	WAIS~R Timing and Reaction Time Tasks: Simple Reaction Time, Serial Reaction Time, Time Wall, Time Clock. Problem Solving and Planning: Tower of London, Tower of Hanoi, 20 Questions. Memory: WMS~R, Experimental Paired Associate Test, Hasher Frequency Monitoring Task, Story Memory, Word Fluency.	CFS were more variable in performance on timing of taps in the Time Clock Test, made more errors and solved more problems than controls on the Tower of London task. CFS were worse than controls on the second Story Memory Task and recalled fewer words than controls in the cued recall condition of the Paired Associates task. Though CFS were worse than controls on the general memory index of the WMS~R, there were no sig. differences on specific memory sub-tests of the WMS~R or on general intellectual functioning.	Performance was not related to mood state, fatigue, age or education. CFS patients had selective memory deficits not correlated with mood and generally intact cognitive performance.

STUDY	SUBJECTS & METHOD	COGNITIVE TESTS	RESULTS	AUTHORS INTERPRETATION
Riccio et al. 1992	10 Patients fulfilling ME criteria, 9 controls matched for age, sex and premorbid intelligence (NART estimated). Assessed on the present state examination, HAD, state trait anxiety, POMS, illness behaviour questionnaire, Eysneck Personality Questionnaire and cognitive measures.	WAIS~R, Logical Memory, Paired Associate Learning And Visual Memory Sub-tests of WMS; Semantic Processing Test; Verbal Fluency; Grooved Peg Board Test; modified Wisconsin Card Sorting Test; Trail Making A and B;	CFS had lower scores on Immediate Logical Memory, and on Total Paired Associate Learning score. No significant differences were found on the remainder of the tests.	CFS were more depressed but did not differ on anxiety scores. Since depression scores were not pathological authors state that difference found cannot be solely attributed to depression.
Prasher et al. 1990	25 controls, 25 CFS (criteria used not specified) patients	Sensory potentials: brain stem potentials, visual potentials and somato-sensory potentials Cognitive potentials: auditory discrimination tasks of frequency discrimination and duration discrimination	CFS significantly different from controls in mean latencies of cognitive potentials N2 and P3 on the more difficult duration discrimination task, but not on the standard odd ball frequency discrimination task. Reaction time for duration and frequency tasks were sig. longer for the CFS group. No sig. differences between CFS and controls on sensory potential measures.	Endogenous event related potential P3 was absent or significantly delayed in 52% of patients, this is consistent with complaints of memory and concentration disturbances. The amplitude of the P3 indicates attentional capacity and latency indicates speed of target detection. Hence suggests 2 groups of CFS, one with slowed target detection/ speed of information processing and one with attention deficits. In depressed patients P3 latency is usually unchanged, reports of amplitude differences are varied.
Millon et al. 1989	24 CFS , no controls (so used normative data). Patients completed mood scales and psychiatric scheduled interview and WMS. Sub-scales of WMS were compared using a 1 way anova	WMS: Orientation; Mental Control; Logical Memory; Memory Span; Visual Reproduction and Associate Learning	Significant differences between CFS and normative data. CFS scored lower on Mental Control and Associate Learning and better than normative on Digit Span and Visual Reproduction.	Authors note that findings are inconclusive. Composite scores yield no differences, subtest patterns show deviations. Digit Span is elevated despite being adversely effected by depression, which is high in this group.

STUDY	SUBJECTS & METHOD	COGNITIVE TESTS	RESULTS	AUTHORS INTERPRETATION
Joyce et al. 1996	20 CFS patients and 20 controls matched for age, sex ratio, and IQ (NART estimated). Completed fatigue scale and HAD. Patients were not clinically depressed.	CANTAB: pattern recognition memory; spatial recognition memory; simultaneous and delayed matching to sample; paired associate learning; spatial span; spatial working memory task; planning; attention set shifting Paired associate learning subtest from the WMS~R, verbal fluency.	Sig. differences on delayed matching to sample, spatial span and strategy score on spatial working memory, verbal fluency and unrelated/hard paired associate learning subtest of the WMS~R. This profile differs from that of depressed patients on the CANTAB battery There were no correlations between performance and depression.	Spatial span and working memory scores combined with increased between search errors suggest CFS had a poor use of search strategy and impaired spatial span. This impairment is not global as there is normal performance on spatial recognition. CFS completed the attentional set shifting task but were slower and made more errors on the matching to sample task, suggesting attention problems are not global. Impairments on verbal fluency and hard paired associates suggest these are also found in verbal modality. The authors suggest that there is a reduction in attention capacity with tasks that require more effortful rather than automatic processing being more impaired.
Fiedler et al. 1996	18 CFS, 18 controls, 23 multiple chemical sensitivities and 13 chemical sensitivities. Groups were age, sex and education matched. 22% of CFS had axis 1 diagnosis (major depression and anxiety rates were significantly higher than in controls). SCID III~R and neuropsychological tests were administered on the same day. Subjects were not on drugs that would affect neuropsychological performance	Tests of concentration: simple RT (dominant and non dominant hand), Continuous Performance Test (RT), Stroop Colour Word Test. Visuomotor Skills: Digit Symbols Subtest, computerised Hand Eye co-ordination, Grooved Pegboard (dominant and non-dominant) Memory: CVLT, Continuous Visual Memory Test, Visual Reproduction I & II,	No sig. diff groups on number of false alarms except on the Continuous Visual Memory Test, where controls and CS are better than MCS but not CFS	Reported symptoms were not supported by objective evidence, somatic symptoms were sig. predictors of CVMT performance. Suggested that subjects with numerous unexplained symptoms have difficulties distinguishing relevant and irrelevant signals. *(NB on many measures CFS were slower, by a number of seconds or had worse scores. Small subject numbers and larger sds, may have resulted in type II error.)*

STUDY	SUBJECTS & METHOD	COGNITIVE TESTS	RESULTS	AUTHORS INTERPRETATION
Michiels et al. 1996	35 CFS patients, matched with 33 controls for age, gender, education and intelligence. Medication free for at least 2 weeks. Structured psychiatric interview (SCID-P) for screening within 5 days of the neuro-psychological testing. 5 CFS were depressed and 33 complained of cognitive impairment. *(hence not all met OCC criteria despite claims)* session 2 hours with a 15 min. break.	6 tests used to assess motor speed, memory and attention: Finger Tapping Test; Selective Reminding Test; Memory for Location Test; Trail Making Test; WAIS Digit Span; WAIS Digit Symbol. General intelligence assessed with the WAIS vocabulary & short form of the Standard Progressive Matrices.	Psychomotor: CFS were slower than controls on Finger Tapping. Memory: CFS performed worse on Memory for Location Test (immediate and delayed recall); total sum of trials on Selective Reminding Test (immediate and delayed recall). However no sig. differences were found on delayed recognition or short term retrieval. Attention: CFS were significantly slower on Trail Making A and B, worse on Digit Span forwards and backwards, significantly slower in matching digits and symbols on the Digit Symbols Test (however there was no difference in the number of errors). There was no relationship between score on the BDI (depression) and neuropsychological tests.	Results indicate that CFS have psychomotor slowing, verbal and visual memory deficits and attention problems. These do not appear to be related to depression. Verbal memory results showed that CFS patients remembered material at a lower rate than controls, this is probably due to impaired retrieval as delayed recognition showed no deficits.
Smith et al. 1996	67 CFS compared with 126 general population, the groups did not differ on intelligence (NART) or socio-economic status. Trait anxiety was significantly higher in the CFS group, as was emotional distress and subjective cognitive difficulty. Performance tests and questionnaires on sleep, anxiety and physical and cognitive symptoms.	Psychomotor speed in 5 choice serial response task, free recall, cognitive vigilance and Stroop colour word test.	Patients were slower than controls on 5 choice serial response task, recalled fewer words in free recall, detected fewer targets on the cognitive vigilance tests. Those patients with abnormal sleep were worse in the interference task of the Stroop. There were no impairments in free recall and sustained attention in CFS patients with no sleep abnormalities.	Psychomotor slowing and subjective ratings of fatigue were not influenced by sleep. Abnormal sleep patterns may be important in the pattern of deficits observed in CFS patients, though whether this is cause or effect remains undetermined.

STUDY	SUBJECTS & METHOD	COGNITIVE TESTS	RESULTS	AUTHORS INTERPRETATION
Vollmer-Conna et al. 1997	21 CFS , 21 healthy controls, 21 depressed patients, 21 patients with infections. 7 of the depressed patients were on low dose antidepressants. Groups were matched on gender, age, education, and scores on NART and Ravens Advanced Progressive Matrices. 3 to 4 hour testing session.	A modified computerised Rozelle Test Battery used to assess attention and concentration: auditory discrimination, pursuit tracking test; divided attention (first 2 tests concurrently); set shifting task; short term memory; arithmetical test; left right spatial discrimination test ; Mackworth Clock (vigilance task). POMS.	Subjects in the 3 patient groups performed significantly more slowly than controls on tests of auditory discrimination, short term memory, left right discrimination and sustained attention. Patients with CFS did not differ from those with depression, but were significantly slower and less accurate than in those with infective illness. Tracking performance in CFS and depressed was worse than in those with infections (easy and hard trackings). There were no significant differences between patient groups in subjective fatigue. Depressed patients had significantly higher ratings of subjective depression, and the CFS and infection group did not differ on any factor. Subjective complaints of cognitive difficulty were not related to mood.	Subjects in all conditions were impaired on cognitive tasks. Performance deficits thus appear to be general rather than specific. CFS did not differ from the depressed patients but were worse than controls and those with acute infection. Complaints of mood were not related to those of memory. Performance declined as a function of complexity and duration of the task in all groups, including control. CFS and depressed patients showed within subject fluctuations in performance; this variability in performance suggests a difficulty in maintaining attention. Such an attention deficit would could explain performance deficits within the remainder of the cognitive tests. Proposals of a specific deficit such as impaired attention or slowing are not inconsistent with these results.
Lakein et al. 1997	17 CFS , 17 controls. Groups did not differ in age, education or estimated IQ HAD, Shipley institute of living scale, Fatigue Severity Scale, and a symptom rating scale CFS group had significantly lower subjective fatigue than usual on the day of testing HAD scores were significantly higher in the CFS group, but anxiety sub-score was significantly higher in the control group.	Gave a trivia quiz. Subjects completed till had 20 bits of information that they were unable to recall from long term memory. Completed FOKs and multiple choice style recognition of answers (MCQ).	No diff between CFS and controls on confidence ratings of accuracy and inaccuracy of performance on MCQ test. CFS and controls did not differ on recall of trivia from long term memory, nor on the number of items subsequently recognised. Controls and CFS had similar RT. Confidence ratings were not correlated with reaction time. HAD anxiety and depression did not correlate with performance or perceived fatigue severity. There were no significant differences in between groups on accuracy of FOK response (correct response with low confidence or incorrect response with high confidence).	CFS perform no differently from controls on tasks of meta memory. There were no differences in recall of information from semantic memory. Groups did not differ in their predictions of performance of recognition. These same subjects (not reported in this paper) did not differ from controls on measures from the WAIS; it is suggested therefore that CFS do not have impairments in long term semantic or short term episodic memory. Possible that there were few symptoms to measure as CFS reported feeling less fatigued than usual

STUDY	SUBJECTS & METHOD	COGNITIVE TESTS	RESULTS	AUTHORS INTERPRETATION
Marcel et al. 1996	29 CFS and 25 healthy controls. The 2 groups did not differ in age, education, and scores from the vocabulary subtest of the WAIS~R. Used Hopkins SCL-90 as an index of global psychiatric severity	Attention: Digit Span Forward Language ability and fluency: Boston Naming Test and Benton Verbal Fluency Test. Memory: Russel version of the WMS~R, Word List Learning. Executive function: Stroop Colour Word Test, Proverb Interpretation, Figure Copying. Computerised battery: Continuous Performance Task, Associate Learning Task, Pattern Matching, Hand Eye co-ordination Test, Set Shifting/Switching Attention Task.	Manova was used to compare domains: there were significant differences from controls on test of language, memory, spatial ability and set shifting. ANCOVA with SCL-90 as a covariate showed sig. differences from controls on: category fluency (animals), but not category fluency (vegetables), on WMS-Memory Quotient, Immediate List Recall, learning total and Pattern Recognition, on Cube Copying, and 'monitoring'. There were no differences on: attention (Mental Control, Digit Span, simple RT and Continuous Performance); Boston Naming Test; Letter Fluency, Figure Copying, Pattern Matching; Hand Eye co-ordination; Proverb Interpretation; switching direction or Stroop.	Suggested that CFS have impairment of non verbal and verbal memory and learning. Also suggest that a marginal difference (not significant) supports the conclusion that executive function abilities are compromised and are partly responsible for problems with learning and memory. That CFS patients show impairment of memory on immediate tests but not delayed suggests that CFS have ineffective learning strategy, but that once developed they can learn effectively. CFS are not impaired on tests of attention.
Marcel et al. 1996	29 CFS criteria (with mixed reporting of cognitive deficits), 25 healthy controls. The two groups did not differ in age, education or scores on the vocab subtest of the WAIS~R. Hopkins symptoms check list showed CFS group had sig. more psychiatric symptomatology (anxiety and depression) Drug status was also measured (2/3 on psycho active medication)	**Computerised Test Battery**: continuous performance task (attention); associate learning test (verbal memory); pattern memory test (non-verbal memory); pattern matching (spatial ability); hand eye co-ordination set shifting task **Neuropsychological Tests:** Digit Span Forwards; Boston naming test & Benton verbal fluency (language ability); Russel version of the WMS, word list learning, Stroop interference test (to assess set shifting and conceptualisation), proverb interpretation, figure copying.	There were sig. diff on: category fluency-animals, WMS~R total, immediate list recall, learning total, pattern recognition, cube copying and monitoring. No sig. diff on : mental control, DSF, side RT, continuous performance, Boston naming, letter fluency or category fluency-vegetables, figure copying, WAIS pattern matching, hand eye co-ordination, proverbs, switching direction, Stroop. Power ranged from 65% for pattern matching to almost 0% for digit span. Sig. differences between drug free and medication CFS groups on DSF (drug group better) and computerised set switching (drug group worse).	Word list learning was worse in CFS group but this correlated with depression, though not anxiety. Impairments in category fluency and word monitoring were not the result of psychiatric comorbidity or drugs, though drugs did affect scores on the set switching and digit span. It is suggested that there are overall significant impairment in learning and memory

STUDY	SUBJECTS & METHOD	COGNITIVE TESTS	RESULTS	AUTHORS INTERPRETATION
Marshall et al. 1997	20 CFS , 20 healthy controls and 20 patients with affective disorder. CFS individually matched with controls and affective patient group on age, sex, level of education and intelligence (block design and vocab sub-tests of the WAIS). Prior to testing all subjects completed the Diagnostic Interview Schedule for affective disorder, somotisation and anxiety. Participants had no history of neurological problems, substance abuse or medication (antidepressants) that might have affected cognitive performance. Testing was at the same time of day to control for diurnal fluctuation in performance. Controls and CFS did the same test battery on 2 consecutive days. 8 CFS and their matched controls walked on a treadmill for 30 min. to increase fatigue. The verbal SAT was completed at a later testing date CFS had higher BDI scores than controls	Buschke Selective Reminding Tests: delayed recall and long term retrieval & storage. Continuous Performance Test-Identical Pairs Version, a test of sustained selective attention. Consisted of numbers with and without visual and auditory distraction. PASAT: measure of information processing speed, attention and working memory. Stroop Colour Word Test: measures information and motor speed and attention Reaction Time Tests: simple and choice. Salthouse Reading Span Test: answer questions about computer presented sentences. Tests working memory (storage and retrieval). Verbal Scholastic Aptitude Test	**Speed**: On Simple and Choice Reaction Time CFS were slower than controls but not slower than affective patients. On test of motor speed CFS were slower than both groups. CFS and affective disorder patients were slower than controls on colour naming, there was no interaction suggesting they were not significantly more slowed in the interference condition. **Working Memory:** CFS had lower recall than controls and affective patients, but were not differentially affected by increasing the speed of trials. On the Salthouse Reading Test CFS performed worse than controls, though not significantly worse than affective patients. On the Verbal SAT, CFS performed worse than controls in all conditions, there was no condition by group interaction. **Verbal Memory:** CFS did not differ from controls on the long term retrieval and storage of the Buschke Selective Reminding Test, but were significantly worse than controls (but not affective patients) on the delayed memory task. **Attention:** On the Continuous Performance Task CFS were not significantly different from controls or affective patients on hit reaction time, though they were biased to a more conservative response style. Depression score co-varied with performance on all tests, but did not fully account for changes in performance. Performance on consecutive days was not significantly different.	The results suggest that CFS have impaired motor and cognitive processing speed. They were worse on tests where speed was critical, including the verbal SAT, though significance was not quite reached on the PASAT. Since these differences are less than 1 sd. lower than controls they are not clinically significant *(Since several patients declined to participate in the study as they felt they would become too tired, these differences may be larger in groups reporting higher subjective fatigue)*

STUDY	SUBJECTS & METHOD	COGNITIVE TESTS	RESULTS	AUTHORS INTERPRETATION
Johnson et al. 1996	20 CFS , plus no loss of consciousness for more than 5 min, history of substance abuse or psychiatric problems. 20 MS patients. Age and education matched with 20 sedentary controls. 3*2 design . Half subjects in each group assigned to visual or auditory processing condition. also measured BDI	paced auditory serial addition test (PASAT), Paced visual serial addition test(PVSAT), Digit span. Paced serial addition test is a measure of complex information processing. Digit span is a measure of attention	No sig. effect of test (auditory or visual) overall. sig. effect of group by test interaction such that CFS were worse at PASAT, compared to PVSAT, and to controls. CFS did not differ from controls on Digit span. CFS had higher BDI scores, these did not correlate with performance measures	Auditory but not visual processing is impaired according to the serial addition test; hence the phonological loop of working memory is impaired. Digit span (an auditory task) is unimpaired since is not so complex and does not involve parallel processing. Visuo-spatial sketch-pad remains intact. alternatively, response & presentation modality differs for the PVSAT, presentation is, visual response auditory; for the PASAT both elements are auditory. There maybe interference between task and response for the auditory serial test, rather than it being an auditory processing deficit per se. MS and CFS differ in profile, suggesting the mechanism for information processing is differentially affected.
Christodoulou et al. 1998	53 CFS criteria plus additional inclusion criteria of moderate severity, duration less than 4 years, no history of loss of consciousness, psychiatric problems at least 5 years prior to CFS onset, or involvement in exercise program. 53 % had axis I diagnosis. The CFS group was matched with 32 healthy controls. CFS group was sig more depressed than control group (BDI).	Functional status questionnaire (daily and social activities, general inactivity). CVLT a verbal memory measure (total, trials 1-5, short and long delay free recall.), ROCFT (measure of immediate and delayed visual memory), PASAT (attention/concentration measure)	regressed patient scores with cognition and education, to give quotient indicating differences from controls unaccounted for by demographics. Separated the 3 groups on the basis of functional status. Group failing at least 2 tests reported a greater number of days of inactivity in the preceding month. Those who failed at least one verbal memory test scored sig. lower on the general activity subscale. There were no differences as a result of function for visual memory.	The differences remained when psychiatric symptomatology was considered. Patients with CFS who perform worse on neuro-psychological tests are more likely to have a greater functional disability.

STUDY	SUBJECTS & METHOD	COGNITIVE TESTS	RESULTS	AUTHORS INTERPRETATION
Schmaling et al. 1994	16 CFS patients (diagnosis not specified), 5 had pre-CFS axis I disorder, all subjects reported cognitive problems, 8 were on antidepressants. 23 major depressives , 4 on antidepressants. Groups did not differ in age education, or estimated verbal (composite of 4 WAIS-R measures used). There was no control group, therefore compared with normative data. Testing time 1 hour, tests not counter-balanced	Stroop, short category test (booklet form), CVLT, WMS~R (visual memory span & visual reproduction sub-tests), WAIS~R (vocab, block design, DS & digit symbol sub-tests),Wisconsin card sorting test, Trail making, Dot counting (measure of motivation) , Reys 15 item dissimulation.	No significant differences between CFS and depressed on Stroop, short category, WCST, CVLT, WMS~R (visual memory span or visual reproduction) or Trails A & B. Both CFS and depressed groups performed within normal range, except on the Stroop. CFS group did not differ from the depressed group on overall scores. The CFS psychiatric group were worse on Stroop than the non-psychiatric group, but both groups performed worse than standard estimates and controls. Lower CVLT scores were associated with more depressive symptomatology as measured by IDD (inventory to diagnose depression)	CFS demonstrated no cognitive problems their complaints were not attributable to depression. Hyper-vigilance or somatic focus may result in over reporting.
Johnson et al. 1994	**Study 1**: reported a duplicate of De Luca 1993 (reported above) **Study 2**: 22 CFS . 21 age and education matched controls. axis I diagnosis exclusion for all subjects.	CVLT (acquisition, retention and recognition of verbal material).	There were no differences between CFS and controls on any part of the CVLT.	Verbal memory is not impaired in CFS. Memory difficulties may be secondary to information processing difficulties. There is a need to focus future research on attention and concentration measures.
Polich et al. 1995	25 CFS, some patients were depressed. They were individually matched with 25 healthy controls (age, sex, education/ occupational level).	P3(00), N1, N2, P2 ERPs measured. An auditory tone discrimination paradigm was used with probability of target stimulus of 0.2, 0.5, 0.8. subjects completed all conditions. Probability conditions were counter-balanced across subjects.	No sig. differences in amplitude or latency of P3 between CFS and controls. CFS demonstrated longer latency on N1 target (however did not demonstrate longer N1 latency on non target, reported therefore that target data is not likely to be reliable)	No reliable differences between CFS and controls, contrary to other reported studies. Findings may reflect the discrepancies found in neuro-psychological studies. Cognitive difficulties reported in CFS are not likely to be the result of CNS dysfunction.

STUDY	SUBJECTS & METHOD	COGNITIVE TESTS	RESULTS	AUTHORS INTERPRETATION
Weardon & Appelby	50 CFS were divided into 2 groups; 24 depressed and 24 non depressed. 18 controls. Groups were matched on education age and NART (but were sig diff in age). Both CFS groups were more depressed than controls. The CFS non-depressed and control group did not differ in anxiety, subjective physical or cognitive fatigue, ratings of concentration effects; but rated these symptoms as significantly worse than controls. HAD, FS , Cognitive failures questionnaire, concentration questionnaire (mind blanking and mind wandering), rating of extent to which concentration had affected reading ability.	(presented on an IBM PC.) Paired associate learning task (6 easy, 6 hard involving free recall, paired-free recall, and cued paired recall), Text reading 13 short pieces presented at rate of 1 per 7.5 sec (re-reading keystrokes recorded), then free recall of story content.	Self evaluation of reading performance was significantly worse for depressed CFS, CFS depressed recalled significantly fewer story units under free recall conditions and cued recall than CFS non depressed and controls. On paired associate learning the ratio of cued to free recall was sig. higher in the CFS depressed than non-depressed group. For all subjects HAD correlated with performance on reading test (positively with ratings on cognitive failures and negatively with free recall questionnaire and performance evaluation). There was a correlation of mood with blanking and re-reading in CFS non depressed patients. Across all CFS groups strong correlation between retrospective evaluation of performance and recall of text; re-reading also correlated with poorer recall.	Only subjects with comorbid depression recalled fewer story units than controls, yet both reported more problems. Subjects evaluation of performance correlated with objective performance. Depressed mood affected only reading; this was perhaps because reading was more sensitive to change in performance than the paired associates test (more complex and requires greater duration of concentration). Depressed CFS recalled less on the free recall task relative to cued; the provision of cues did not appear to impair performance. Argues that CFS display heightened sensitivity to their performance.
Johnson et al. 1996	15 CFS criteria, with symptoms of less than 4 years duration and of moderate severity. Matched with 15 MS patients. 14 depressed. 15 sedentary healthy controls. Groups did not differ in mean age, years of education, estimated verbal IQ or digit span. also completed BDI and psychiatric interviews.	Repeated performance of the PASAT (complex information processing, processing of parallel events). PASAT was administered 4 times over a 3 hr period, with Ss rating subjective fatigue prior to each occasion.	CFS and depressed performed significantly worse than controls. PASAT performance did increase over repeated testing (trial 1-trial 3) and there were no differences between groups on practice effects. Subjective fatigue and depression were not related to objective performance.	Repeated testing does not negatively impact on performance. Worse performance on PASAT is unlikely to be a result of fatigue as subjective fatigue does not correlate with performance. PASAT did not decline in depressed group, contrary to previous research, possibly a result of the moderate severity of the group tested here.

STUDY	SUBJECTS & METHOD	COGNITIVE TESTS	RESULTS	AUTHORS INTERPRETATION
De Luca et al. 1997	36 CFS patients (criteria modified on current symptoms, onset duration, premorbid psychiatric history). 15 patients had concurrent DSM III-R axis I diagnosis, 21 were non cases. These latter groups did not differ in age sex or education. These were matched with a group of 31 non exercising healthy controls which did not differ in age, sex or years of education from the CFS group.	PASAT (assessing complex information processing efficiency). WAIS-R: Digit Span, arithmetic and vocabulary sub-tests (attention and intelligence measures). CVLT (verbal memory). Rey-Osterreith complex figures test (ROCFT) (visual memory and spatial construction)	CFS cases and non cases did not differ from each other but differed from controls in overall performance. Specifically the CFS non-case group performed worse than control and CFS case on immediate & delayed recall test of the ROCFT. The CFS non cases performed worse than controls on trials 1-5 short and long delayed free recall of the CVLT and worse than the CFS case group on short delayed free recall. There were no sig. diff between groups on digit span forwards, or block design, arithmetic, copying of ROCFT or the vocabulary sub-test of the WAIS-R. CFS non case group performed worse than controls and CFS case on digit span backwards and the PASAT.	CFS patients without comorbid axis 1 diagnosis were impaired compared to healthy controls on tests of cognitive function. Interestingly these differences were not present on each test in those patients who met criteria for psychiatric case. However CFS-case, did differ from controls in overall performance; the thus authors suggest that there are symptoms present, but that they are small.

Appendix 3.1. Implicit and Explicit Memory Tests (implicit test instructions)

Instructions.

You will be presented with a list of twenty words and a simple question about each word. There are 2 types of question.
The first is to say whether or not you agree that the item is useful using the scale below. This is just your opinion and there is no right or wrong answer.

Scale:
This item is useful
1 2 3 4 5
where
1 = strongly disagree
3 =neither agree nor disagree
5 =strongly agree

The second type of question is about how many number of vowels each word has (A E I O U),You need to count the number of number of vowels and enter it in the space provided.

Example 1

cleaver this item is useful **1 2 3 4** 5

If you agree that a cleaver is 'useful' mark the 4

cleaver this item is useful **1 2 3 (4) 5**

Example 2

house number of vowels [ ]

count the number of vowels and put the answer in the box

house number of vowels [3]

Appendix 3.1. Implicit and Explicit Memory Tests (example of implicit study task)

1) knife	number of vowels	☐
2) hammer	This item is useful	1 2 3 4 5
3) flower	This item is useful	1 2 3 4 5
4) pineapple	This item is useful	1 2 3 4 5
5) football	number of vowels	☐
6) ladder	number of vowels	☐
7) onion	number of vowels	☐
8) grapes	This item is useful	1 2 3 4 5
9) skunk	This item is useful	1 2 3 4 5
10)guitar	This item is useful	1 2 3 4 5
11)chair	number of vowels	☐
12)balloon	number of vowels	☐
13)accordion	This item is useful	1 2 3 4 5
14)peanut	number of vowels	☐
15)barrel	number of vowels	☐
16)ashtray	number of vowels	☐
17)basket	This item is useful	1 2 3 4 5
18)clock	This item is useful	1 2 3 4 5
19)spoon	This item is useful	1 2 3 4 5
20)envelope	number of vowels	☐

Word Generation

This task is to see how well you 'think up' words. There are 2 types of question. For the first type you need to add more letters to those given to make a word. The second type needs the solving of crossword type clues.

For example.

1) DRA 1)DRA*Polene*

2) swims in the sea 2)swims in the sea *dolphin*

In both cases please write down the ***first*** word that you think of

1) tropical fruit
2) played by buskers
3) GRA
4) found on stem
5) KNI
6) HAM
7) ASH
8) birds winter feast
9) CHA
10)brings tears to eyes
11)fruit container
12)LAD
13)for kicking
14)container for letters
15)BAR
16)for eating with
17)at childrens' parties
18)CLO
19)SKU
20)GUI

Instructions.

You will be presented with a list of twenty words and a simple question about each word. There are 2 types of question.
The first is to say whether or not you agree that the item is useful using the scale below. This is just your opinion and there is no right or wrong answer.

Scale:
This item is useful
1 2 3 4 5
where
1 = strongly disagree
3 =neither agree nor disagree
5 =strongly agree

The second type of question is about how many number of vowels each word has (A E I O U),You need to count the number of number of vowels and enter it in the space provided.

Later there will be a 'memory test ' , to see how many words you can remember from this list.

Example 1

cleaver this item is useful **1 2 3 4** 5

If you agree that a cleaver is 'useful' mark the 4

cleaver this item is useful **1 2 3** (**4**) **5**

Example 2

house number of vowels [ ]

count the number of vowels and put the answer in the box

house number of vowels [3]

1) candle	number of vowels	☐
2) monkey	number of vowels	☐
3) turtle	number of vowels	☐
4) bicycle	number of vowels	☐
5) wheel	number of vowels	☐
6) horse	number of vowels	☐
7) glass	This item is useful	1 2 3 4 5
8) carrot	This item is useful	1 2 3 4 5
9) glove	This item is useful	1 2 3 4 5
10)snake	This item is useful	1 2 3 4 5
11)kangaroo	number of vowels	☐
12)heart	number of vowels	☐
13)lobster	number of vowels	☐
14)mushroom	This item is useful	1 2 3 4 5
15)lemon	This item is useful	1 2 3 4 5
16)potato	This item is useful	1 2 3 4 5
17)doorknob	This item is useful	1 2 3 4 5
18)scissors	This item is useful	1 2 3 4 5
19)dress	This item is useful	1 2 3 4 5
20)mountain	number of vowels	☐

Now try to remember the list of words you answered questions about earlier. A list of clues to help you remember them is given below, they are either the starting letters of the words or cross word type clues.

For example.

1) DRA 1)DRA*Polene*

2) swims in the sea 2)swims in the sea *dolphin*

If you don't remember a word, please write down another word that solves the puzzle or would create a word

1) WHE

2) KAN

3) HEA

4) ladies clothing item

5) citrus fruit

6) BIC

7) MUS

8) HOR

9) CAR

10)POT

11)perhaps to climb

12)turn to open

13)burning bright

14)may live in trees

15)shears

16)shelled reptile

17)boa?

18)GLO

19) clawed crustacean

20)GLA

Appendix 3.1. Forms of the Implicit and Explicit Memory Tests

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FORM 1

Explicit list

word	study	test	test item
candle	vowels	puzzle	burning bright?
monkey	vowels	puzzle	May live in trees
turtle	vowels	puzzle	shelled reptile
bicycle	vowels	word stem	bic
wheel	vowels	word stem	whe
horse	vowels	word stem	hor
glass	utility	word stem	gla
carrot	utility	word stem	car
glove	utility	word stem	glo
snake	utility	puzzle	boa?
kangaroo	vowels	word stem	Kan
heart	vowels	word stem	hea
lobster	vowels	puzzle	clawed crustacean
mushroom	utility	word stem	mus
lemon	utility	puzzle	citrus fruit
potato	utility	word stem	pot
doorknob	utility	puzzle	turn to open
scissors	utility	puzzle	shears
dress	utility	puzzle	ladies clothing item
mountain	vowels	puzzle	perhaps to climb

implicit

word	study	test	test item
knife	vowels	word stem	kni
hammer	utility	wordstem	ham
flower	utility	puzzle	found on stem
pineapple	utility	puzzle	tropical fruit
football	vowels	puzzle	for kicking
ladder	vowels	word stem	lad
onion	vowels	puzzle	brings tears to eyes
grapes	utility	word stem	gra
skunk	utility	word stem	sku
guitar	utility	word stem	gui
chair	vowels	word stem	cha
balloon	vowels	puzzle	at children's parties
accordion	utility	puzzle	played by buskers
peanut	vowels	puzzle	bird's winter feast
barrel	vowels	word stem	BAR
ashtray	vowels	word stem	ash
basket	utility	puzzle	fruit container
clock	utility	word stem	clo
spoon	utility	puzzle	for eating with
envelope	vowels	puzzle	container for letters

Appendix 3.1. Forms of the Implicit and Explicit Memory Tests

FORM 3

explicit

word	study	test	test item
knife	vowels	word stem	kni
hammer	utility	wordstem	ham
flower	utility	puzzle	found on stem
pineapple	utility	puzzle	tropical fruit
football	vowels	puzzle	for kicking
ladder	vowels	word stem	lad
onion	vowels	puzzle	brings tears to eyes
grapes	utility	word stem	gra
skunk	utility	word stem	sku
guitar	utility	word stem	gui
chair	vowels	word stem	cha
balloon	vowels	puzzle	? at children's parties
accordion	utility	puzzle	played by buskers
peanut	vowels	puzzle	bird's winter feast
barrel	vowels	word stem	BAR
ashtray	vowels	word stem	ash
basket	utility	puzzle	fruit container
clock	utility	word stem	clo
spoon	utility	puzzle	for eating with
envelope	vowels	puzzle	container for letters

Implicit list

word	study	test	test item
candle	vowels	puzzle	burning bright?
monkey	vowels	puzzle	may live in trees
turtle	vowels	puzzle	shelled reptile
bicycle	vowels	word stem	bic
wheel	vowels	word stem	whe
horse	vowels	wordstem	hor
glass	utility	word stem	gla
carrot	utility	word stem	car
glove	utility	word stem	glo
snake	utility	puzzle	boa?
kangaroo	vowels	word stem	Kan
heart	vowels	word stem	hea
lobster	vowels	puzzle	clawed crustacean
mushroom	utility	word stem	mus
lemon	utility	puzzle	citrus fruit
potato	utility	word stem	pot
doorknob	utility	puzzle	turn to open
scissors	utility	puzzle	shears
dress	utility	puzzle	ladies clothing item
mountain	vowels	puzzle	perhaps to climb

Appendix 3.1. Forms of the Implicit and Explicit Memory Tests

FORM 5

Implicit

word	study	test	test item
knife	vowels	puzzle	cutter
hammer	utility	puzzle	to knock in
flower	utility	word stem	flo
pineapple	utility	word stem	pin
football	vowels	word stem	foo
ladder	vowels	puzzle	window cleaners necessity
onion	vowels	word stem	oni
grapes	utility	puzzle	bunched fruit
skunk	utility	puzzle	black and whit animal
guitar	utility	puzzle	to strum
chair	vowels	puzzle	seating?
balloon	vowels	word stem	bal
accordion	utility	word stem	acc
peanut	vowels	word stem	pea
barrel	vowels	puzzle	cask
ashtray	vowels	puzzle	used by smokers
basket	utility	word stem	bas
clock	utility	puzzle	timepiece
spoon	utility	word stem	spo
envelope	vowels	word stem	env

Explicit list

word	study	test	test item
candle	vowels	word stem	can
monkey	vowels	word stem	mon
turtle	vowels	word stem	tur
bicycle	vowels	puzzle	travels beneath
wheel	vowels	puzzle	round invention
horse	vowels	puzzle	hoofed plant eater
glass	utility	puzzle	drink receptacle
carrot	utility	puzzle	loved by rabbits
glove	utility	puzzle	one on each hand
snake	utility	wordstem	sna
kangaroo	vowels	puzzle	Australian animal
heart	vowels	puzzle	vital organ
lobster	vowels	word stem	lob
mushroom	utility	puzzle	fungus
lemon	utility	word stem	lem
potato	utility	puzzle	Raleigh's' gift
doorknob	utility	word stem	doo
scissors	utility	word stem	sci
dress	utility	word stem	dre
mountain	vowels	word stem	mou

Appendix 3.1. Forms of the Implicit and Explicit Memory Tests

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FORM 7

Explicit list

word	study	test	test item
knife	vowels	puzzle	cutter
hammer	utility	puzzle	to knock in
flower	utility	word stem	flo
pineapple	utility	word stem	pin
football	vowels	word stem	foo
ladder	vowels	puzzle	window cleaners necessity
onion	vowels	word stem	oni
grapes	utility	puzzle	bunched fruit
skunk	utility	puzzle	black and white animal
guitar	utility	puzzle	to strum
chair	vowels	puzzle	seating?
balloon	vowels	word stem	bal
accordion	utility	word stem	acc
peanut	vowels	word stem	pea
barrel	vowels	puzzle	cask
ashtray	vowels	puzzle	used by smokers
basket	utility	word stem	bas
clock	utility	puzzle	timepiece
spoon	utility	word stem	spo
envelope	vowels	word stem	env

Implicit list

word	study	test	test item
candle	vowels	word stem	can
monkey	vowels	word stem	mon
turtle	vowels	word stem	tur
bicycle	vowels	puzzle	travels beneath
wheel	vowels	puzzle	round invention
horse	vowels	puzzle	hoofed plant eater
glass	utility	puzzle	drink receptacle
carrot	utility	puzzle	loved by rabbits
glove	utility	puzzle	one on each hand
snake	utility	wordstem	sna
kangaroo	vowels	puzzle	Australian animal
heart	vowels	puzzle	vital organ
lobster	vowels	word stem	lob
mushroom	utility	puzzle	fungus
lemon	utility	word stem	lem
potato	utility	puzzle	Raleigh's' gift
doorknob	utility	word stem	doo
scissors	utility	word stem	sci
dress	utility	word stem	dre
mountain	vowels	word stem	mou

Appendix 3.1. Forms of the Implicit and Explicit Memory Tests

FORM 2

Explicit list

word	study	test	test item
kangaroo	utility	word stem	kan
lobster	utility	puzzle	clawed crustacean
wheel	utility	word stem	whe
scissors	vowel	puzzle	shears
carrot	vowels	word stem	car
candle	utility	puzzle	burning brightly?
glove	vowels	word stem	glo
bicycle	utility	word stem	bic
snake	vowels	puzzle	boa?
doorknob	vowel	puzzle	turn to open
lemon	vowel	puzzle	citrus fruit
monkey	utility	puzzle	may live in trees
dress	vowel	puzzle	ladies clothing item
mushroom	vowel	word stem	mus
potato	vowel	word stem	pot
turtle	utility	puzzle	shelled reptile
horse	utility	word stem	hor
glass	vowel	word stem	gla
mountain	utility	puzzle	perhaps to climb
heart	utility	word stem	hea

Implicit list

word	study	test	test items
football	utility	puzzle	for kicking
spoon	vowels	puzzle	for eating with
chair	utility	word stem	cha
grapes	vowels	word stem	grap
clock	vowel	word stem	clo
ladder	utility	word stem	lad
hammer	vowels	word stem	ham
pineapple	vowels	puzzle	tropical fruit
basket	vowels	puzzle	container for fruit
balloon	utility	puzzle	? at children's parties
barrel	utility	word stem	bar
accordion	vowel	puzzle	played by buskers
peanut	utility	puzzle	birds winter feast
ashtray	utility	word stem	ash
onion	utility	puzzle	brings tears to eyes
knife	utility	word stem	kni
skunk	vowel	word stem	sku
guitar	vowel	word stem	gui
envelope	utility	puzzle	container for letters
flower	vowel	puzzle	found on stem

Appendix 3.1. Forms of the Implicit and Explicit Memory Tests

FORM 4

Implicit list

word	study	test	test item
kangaroo	utility	word stem	kan
lobster	utility	puzzle	clawed crustacean
wheel	utility	word stem	whe
scissors	vowel	puzzle	shears
carrot	vowels	word stem	car
candle	utility	puzzle	burning brightly?
glove	vowels	word stem	glo
bicycle	utility	word stem	bic
snake	vowels	puzzle	boa?
doorknob	vowel	puzzle	turn to open
lemon	vowel	puzzle	citrus fruit
monkey	utility	puzzle	may live in trees
dress	vowel	puzzle	ladies clothing item
mushroom	vowel	word stem	mus
potato	vowel	word stem	pot
turtle	utility	puzzle	shelled reptile
horse	utility	word stem	hor
glass	vowel	word stem	gla
mountain	utility	puzzle	perhaps to climb
heart	utility	word stem	hea

Explicit list

word	study	test	test items
football	utility	puzzle	for kicking
spoon	vowels	puzzle	for eating with
chair	utility	word stem	cha
grapes	vowels	word stem	grap
clock	vowel	word stem	clo
ladder	utility	word stem	lad
hammer	vowels	word stem	ham
pineapple	vowels	puzzle	tropical fruit
basket	vowels	puzzle	container for fruit
balloon	utility	puzzle	? at children's parties
barrel	utility	word stem	bar
accordion	vowel	puzzle	played by buskers
peanut	utility	puzzle	birds winter feast
ashtray	utility	word stem	ash
onion	utility	puzzle	brings tears to eyes
knife	utility	word stem	kni
skunk	vowel	word stem	sku
guitar	vowel	word stem	gui
envelope	utility	puzzle	container for letters
flower	vowel	puzzle	found on stem

Appendix 3.1. Forms of the Implicit and Explicit Memory Tests

FORM 6

Explicit list

word	study	test	test item
kangaroo	utility	puzzle	Australian animal
lobster	utility	word stem	lob
wheel	utility	puzzle	round invention
scissors	vowel	word stem	sci
carrot	vowels	puzzle	loved by rabbits
candle	utility	word stem	can
glove	vowels	puzzle	one on each hand
bicycle	utility	puzzle	travels beneath
snake	vowels	word stem	sna
doorknob	vowel	word stem	doo
lemon	vowel	word stem	lem
monkey	utility	word stem	mon
dress	vowel	word stem	dre
mushroom	vowel	puzzle	fungus
potato	vowel	puzzle	Raleigh's gift
turtle	utility	word stem	tur
horse	utility	puzzle	hoofed plant eater
glass	vowel	puzzle	drinking receptacle
mountain	utility	word stem	moun
heart	utility	puzzle	vital organ

Implicit list

word	study	test	test item
football	utility	word stem	foo
spoon	vowels	word stem	spo
chair	utility	puzzle	seating?
grapes	vowels	puzzle	bunched fruit
clock	vowel	puzzle	timepiece
ladder	utility	puzzle	window cleaners necessity
hammer	vowels	puzzle	to knock in
pineapple	vowels	word stem	pin
basket	vowels	word stem	bas
balloon	utility	word stem	bal
barrel	utility	puzzle	cask
accordion	vowel	word stem	acc
peanut	utility	word stem	pea
ashtray	utility	puzzle	used by smokers
onion	utility	word stem	oni
knife	utility	puzzle	cutter
skunk	vowel	puzzle	black and white animal
guitar	vowel	puzzle	to strum
envelope	utility	word stem	env
flower	vowel	word stem	flo

Appendix 3.1. Forms of the Implicit and Explicit Memory Tests

FORM 8

Implicit list

word	study	test	test item
kangaroo	utility	puzzle	Australian animal
lobster	utility	word stem	lob
wheel	utility	puzzle	round invention
scissors	vowel	word stem	sci
carrot	vowels	puzzle	loved by rabbits
candle	utility	word stem	can
glove	vowels	puzzle	one on each hand
bicycle	utility	puzzle	travels beneath
snake	vowels	word stem	sna
doorknob	vowel	word stem	doo
lemon	vowel	word stem	lem
monkey	utility	word stem	mon
dress	vowel	word stem	dre
mushroom	vowel	puzzle	fungus
potato	vowel	puzzle	Raleigh's gift
turtle	utility	word stem	tur
horse	utility	puzzle	hoofed plant eater
glass	vowel	puzzle	drinking receptacle
mountain	utility	word stem	moun
heart	utility	puzzle	vital organ

Explicit list

word	study	test	test item
football	utility	word stem	foo
spoon	vowels	word stem	spo
chair	utility	puzzle	seating?
grapes	vowels	puzzle	bunched fruit
clock	vowel	puzzle	timepiece
ladder	utility	puzzle	window cleaners necessity
hammer	vowels	puzzle	to knock in
pineapple	vowels	word stem	pin
basket	vowels	word stem	bas
balloon	utility	word stem	bal
barrel	utility	puzzle	cask
accordion	vowel	word stem	acc
peanut	utility	word stem	pea
ashtray	utility	puzzle	used by smokers
onion	utility	word stem	oni
knife	utility	puzzle	cutter
skunk	vowel	puzzle	black and white animal
guitar	vowel	puzzle	to strum
envelope	utility	word stem	env
flower	vowel	word stem	flo

Appendix 3.2. Background Details

Patient Details

identification

1) Information Sheet ☐
Consent sheet ☐

2)Background Information

Date & Time _____ occupation _____
age _____ spouse _____
sex _____ children _____
handedness _____

Highest educational level/qualification/age of School leaving

3) Illness Details

Reason for Clinic attendance _____

current medication _____

IF CFS then

duration _____

time in treatment _____

Other Information

Appendix 3.3. Counterbalance Schedule

id no	self report scales				tests							type
1	FS	BD	PFRS	HAD	S	W1	RT	W2	IM1		EX1	cont
2	FS	HAD	PFRS	BD	S	W1	RT	W2	IM2		EX2	CFS
3	FS	BD	HAD	PFRS	S	W1	RT	W2	IM3		EX3	CFS
4	FS	HAD	BD	PFRS	S	W1	RT	W2	IM4		EX4	CFS
5	PFRS	HAD	BD	FS	S	W1	RT	W2	IM5		EX5	CFS
6	PFRS	BD	HAD	FS	S	W1	RT	W2	IM6		EX6	CFS
7	PFRS	HAD	FS	BD	S	W1	RT	W2	IM7		EX7	CFS
8	PFRS	BD	FS	HAD	S	W1	RT	W2	IM8		EX8	CFS
9	FS	BD	PFRS	HAD	RT	W1	IM1		EX1	W2	S	CFS
10	FS	HAD	PFRS	BD	RT	W1	IM2		EX2	W2	S	CFS
11	FS	BD	HAD	PFRS	RT	W1	IM3		EX3	W2	S	CFS
12	FS	HAD	BD	PFRS	RT	W1	IM4		EX4	W2	S	cont
13	PFRS	HAD	BD	FS	RT	W1	IM5		EX5	W2	S	CFS
14	PFRS	BD	HAD	FS	RT	W1	IM6		EX6	W2	S	CFS
15	PFRS	HAD	FS	BD	RT	W1	IM7		EX7	W2	S	CFS
16	PFRS	BD	FS	HAD	RT	W1	IM8		EX8	W2	S	CFS
17	FS	BD	PFRS	HAD	RT	W2	S	W1	IM1		EX1	CFS
18	FS	HAD	PFRS	BD	RT	W2	S	W1	IM2		EX2	CFS
19	FS	BD	HAD	PFRS	RT	W2	S	W1	IM3		EX3	CFS
20	FS	HAD	BD	PFRS	RT	W2	S	W1	IM4		EX4	CFS
21	PFRS	HAD	BD	FS	RT	W2	S	W1	IM5		EX5	CFS
22	PFRS	BD	HAD	FS	RT	W2	S	W1	IM6		EX6	CFS
23	PFRS	HAD	FS	BD	RT	W2	S	W1	IM7		EX7	CFS
24	PFRS	BD	FS	HAD	RT	W2	S	W1	IM8		EX8	CFS
25	FS	BD	PFRS	HAD	S	W2	IM1		EX1	W1	RT	CFS
26	FS	HAD	PFRS	BD	S	W2	IM2		EX2	W1	RT	CFS
27	FS	BD	HAD	PFRS	S	W2	IM3		EX3	W1	RT	CFS
28	FS	HAD	BD	PFRS	S	W2	IM4		EX4	W1	RT	CFS
29	PFRS	HAD	BD	FS	S	W2	IM5		EX5	W1	RT	CFS
30	PFRS	BD	HAD	FS	S	W2	IM6		EX6	W1	RT	CFS
31	PFRS	HAD	FS	BD	S	W2	IM7		EX7	W1	RT	CFS
32	PFRS	BD	FS	HAD	S	W2	IM8		EX8	W1	RT	CFS
33	FS	BD	PFRS	HAD	IM1		EX1	W1	S	W2	RT	CFS
34	FS	HAD	PFRS	BD	IM2		EX2	W1	S	W2	RT	CFS
35	FS	BD	HAD	PFRS	IM3		EX3	W1	S	W2	RT	CFS
36	FS	HAD	BD	PFRS	IM4		EX4	W1	S	W2	RT	CFS
37	PFRS	HAD	BD	FS	IM5		EX5	W1	S	W2	RT	CFS
38	PFRS	BD	HAD	FS	IM6		EX6	W1	S	W2	RT	CFS
39	PFRS	HAD	FS	BD	IM7		EX7	W1	S	W2	RT	CFS
40	PFRS	BD	FS	HAD	IM8		EX8	W1	S	W2	RT	CFS
41	FS	BD	PFRS	HAD	IM1		EX1	W2	RT	W1	S	CFS
42	FS	HAD	PFRS	BD	IM2		EX2	W2	RT	W1	S	CFS
43	FS	BD	HAD	PFRS	IM3		EX3	W2	RT	W1	S	CFS
44	FS	HAD	BD	PFRS	IM4		EX4	W2	RT	W1	S	CFS
45	PFRS	HAD	BD	FS	IM5		EX5	W2	RT	W1	S	CSF
46	PFRS	BD	HAD	FS	IM6		EX6	W2	RT	W1	S	CFS
47	PFRS	HAD	FS	BD	IM7		EX7	W2	RT	W1	S	CFS
48	PFRS	BD	FS	HAD	IM8		EX8	W2	RT	W1	S	CSF

49	FS	BD	PFRS	HAD	S	W1	RT	W2	IM1		EX1	CFS
50	FS	HAD	PFRS	BD	S	W1	RT	W2	IM2		EX2	cont
51	FS	BD	HAD	PFRS	S	W1	RT	W2	IM3		EX3	cont
52	FS	HAD	BD	PFRS	S	W1	RT	W2	IM4		EX4	cont
53	PFRS	HAD	BD	FS	S	W1	RT	W2	IM5		EX5	cont
54	PFRS	BD	HAD	FS	S	W1	RT	W2	IM6		EX6	CFS
55	PFRS	HAD	FS	BD	S	W1	RT	W2	IM7		EX7	cont
56	PFRS	BD	FS	HAD	S	W1	RT	W2	IM8		EX8	cont
57	FS	BD	PFRS	HAD	RT	W1	IM1		EX1	W2	S	CFS
58	FS	HAD	PFRS	BD	RT	W1	IM2		EX2	W2	S	CFS
59	FS	BD	HAD	PFRS	RT	W1	IM3		EX3	W2	S	CFS
60	FS	HAD	BD	PFRS	RT	W1	IM4		EX4	W2	S	cont
61	PFRS	HAD	BD	FS	RT	W1	IM5		EX5	W2	S	cont
62	PFRS	BD	HAD	FS	RT	W1	IM6		EX6	W2	S	cont
63	PFRS	HAD	FS	BD	RT	W1	IM7		EX7	W2	S	cont
64	PFRS	BD	FS	HAD	RT	W1	IM8		EX8	W2	S	cont
65	FS	BD	PFRS	HAD	RT	W2	S	W1	IM1		EX1	cont
66	FS	HAD	PFRS	BD	RT	W2	S	W1	IM2		EX2	cont
67	FS	BD	HAD	PFRS	RT	W2	S	W1	IM3		EX3	CFS
68	FS	HAD	BD	PFRS	RT	W2	S	W1	IM4		EX4	cont
69	PFRS	HAD	BD	FS	RT	W2	S	W1	IM5		EX5	cont
70	PFRS	BD	HAD	FS	RT	W2	S	W1	IM6		EX6	cont
71	PFRS	HAD	FS	BD	RT	W2	S	W1	IM7		EX7	cont
72	PFRS	BD	FS	HAD	RT	W2	S	W1	IM8		EX8	cont
73	FS	BD	PFRS	HAD	S	W2	IM1		EX1	W1	RT	cont
74	FS	HAD	PFRS	BD	S	W2	IM2		EX2	W1	RT	cont
75	FS	BD	HAD	PFRS	S	W2	IM3		EX3	W1	RT	cont
76	FS	HAD	BD	PFRS	S	W2	IM4		EX4	W1	RT	cont
77	PFRS	HAD	BD	FS	S	W2	IM5		EX5	W1	RT	cont
78	PFRS	BD	HAD	FS	S	W2	IM6		EX6	W1	RT	CFS
79	PFRS	HAD	FS	BD	S	W2	IM7		EX7	W1	RT	cont
80	PFRS	BD	FS	HAD	S	W2	IM8		EX8	W1	RT	cont
81	FS	BD	PFRS	HAD	IM1		EX1	W1	S	W2	RT	cont
82	FS	HAD	PFRS	BD	IM2		EX2	W1	S	W2	RT	cont
83	FS	BD	HAD	PFRS	IM3		EX3	W1	S	W2	RT	cont
84	FS	HAD	BD	PFRS	IM4		EX4	W1	S	W2	RT	cont
85	PFRS	HAD	BD	FS	IM5		EX5	W1	S	W2	RT	cont
86	PFRS	BD	HAD	FS	IM6		EX6	W1	S	W2	RT	cont
87	PFRS	HAD	FS	BD	IM7		EX7	W1	S	W2	RT	cont
88	PFRS	BD	FS	HAD	IM8		EX8	W1	S	W2	RT	cont
89	FS	BD	PFRS	HAD	IM1		EX1	W2	RT	W1	S	cont
90	FS	HAD	PFRS	BD	IM2		EX2	W2	RT	W1	S	cont
91	FS	BD	HAD	PFRS	IM3		EX3	W2	RT	W1	S	cont
92	FS	HAD	BD	PFRS	IM4		EX4	W2	RT	W1	S	cont
93	PFRS	HAD	BD	FS	IM5		EX5	W2	RT	W1	S	cont
94	PFRS	BD	HAD	FS	IM6		EX6	W2	RT	W1	S	cont
95	PFRS	HAD	FS	BD	IM7		EX7	W2	RT	W1	S	cont
96	PFRS	BD	FS	HAD	IM8		EX8	W2	RT	W1	S	cont

97	FS	BD	PFRS	HAD	S	W1	RT	W2	IM1		EX1	CFS
98	FS	HAD	PFRS	BD	S	W1	RT	W2	IM2		EX2	CFS
99	FS	BD	HAD	PFRS	S	W1	RT	W2	IM3		EX3	CFS
100	FS	HAD	BD	PFRS	S	W1	RT	W2	IM4		EX4	CFS
101	PFRS	HAD	BD	FS	S	W1	RT	W2	IM5		EX5	CFS
102	PFRS	BD	HAD	FS	S	W1	RT	W2	IM6		EX6	cont
103	PFRS	HAD	FS	BD	S	W1	RT	W2	IM7		EX7	CFS
104	PFRS	BD	FS	HAD	S	W1	RT	W2	IM8		EX8	CFS
105	FS	BD	PFRS	HAD	RT	W1	IM1		EX1	W2	S	cont
106	FS	HAD	PFRS	BD	RT	W1	IM2		EX2	W2	S	cont
107	FS	BD	HAD	PFRS	RT	W1	IM3		EX3	W2	S	cont
108	FS	HAD	BD	PFRS	RT	W1	IM4		EX4	W2	S	CFS
109	PFRS	HAD	BD	FS	RT	W1	IM5		EX5	W2	S	CFS
110	PFRS	BD	HAD	FS	RT	W1	IM6		EX6	W2	S	CFS
111	PFRS	HAD	FS	BD	RT	W1	IM7		EX7	W2	S	CFS
112	PFRS	BD	FS	HAD	RT	W1	IM8		EX8	W2	S	CFS
113	FS	BD	PFRS	HAD	RT	W2	S	W1	IM1		EX1	CFS
114	FS	HAD	PFRS	BD	RT	W2	S	W1	IM2		EX2	cont
115	FS	BD	HAD	PFRS	RT	W2	S	W1	IM3		EX3	cont
116	FS	HAD	BD	PFRS	RT	W2	S	W1	IM4		EX4	CFS
117	PFRS	HAD	BD	FS	RT	W2	S	W1	IM5		EX5	CFS
126	PFRS	BD	HAD	FS	S	W2	IM6		EX6	W1	RT	cont
145	FS	BD	PFRS	HAD	S	W1	RT	W2	IM1		EX1	cont
146	FS	HAD	PFRS	BD	S	W1	RT	W2	IM2		EX2	cont
147	FS	BD	HAD	PFRS	S	W1	RT	W2	IM3		EX3	cont
148	FS	HAD	BD	PFRS	S	W1	RT	W2	IM4		EX4	cont
149	PFRS	HAD	BD	FS	S	W1	RT	W2	IM5		EX5	cont
150	PFRS	BD	HAD	FS	S	W1	RT	W2	IM6		EX6	cont
151	PFRS	HAD	FS	BD	S	W1	RT	W2	IM7		EX7	cont
152	PFRS	BD	FS	HAD	S	W1	RT	W2	IM8		EX8	cont
153	FS	BD	PFRS	HAD	RT	W1	IM1		EX1	W2	S	cont
154	FS	HAD	PFRS	BD	RT	W1	IM2		EX2	W2	S	cont
155	FS	BD	HAD	PFRS	RT	W1	IM3		EX3	W2	S	cont
156	FS	HAD	BD	PFRS	RT	W1	IM4		EX4	W2	S	cont
157	PFRS	HAD	BD	FS	RT	W1	IM5		EX5	W2	S	cont

KEY

PFRS	Profile For Fatigue Related Symptoms
FS	The fatigue Scale
BD	backgound details
HAD	Hospital Anxiety and Depression Scale
RT	graded reaction time test (chapater 5)
S	lexical decision task followed by semantic pair judejments (chapter 4)
IM1-IM8	Implicit memory task forms 1 to 8, digit span forwasrds and backwards presented between study and recall
EM1-EM8	Explicit task forms 1 to 8, digit span forwasrds and backwards presented between study and recall
W1	logical memory test
W2	Paired associate learning test

0113 233 5748

df/cfs/rec
1 November, 1996

Dear

I am a post graduate researcher at the University of Leeds. I am currently collaborating with Dr. Lynch and Dr. Hill to evaluate how cognitive tasks such as memory, attention and simple reading are affected in Chronic Fatigue Syndrome. We hope also to illustrate differences between those patients who are feeling depressed and those who are not.

The testing session lasts between 40 minutes and an hour. This depends on how severe your symptoms are at the current time. It involves simple tasks, for example counting letters in words, remembering short strings of numbers and words, and deciding whether things (e.g. a wheel) are useful or not.

If you are interested in volunteering to participate in the study, please phone me or write to me at the above address and we can arrange a testing appointment. If you are due to visit the clinic soon, we can arrange for testing to follow your appointment.

Thanking you in anticipation of your reply,

Denise Fairhurst.

Appendix 3.5 Patient reponses by phase and total

Phase One (n=82)

48 made no response (6 responded in phase 2)
3 DNA
4 had clinic appointments cancelled (1 re-appointed in phase 2)
2 declined owing to travel problems
1 incorrect address in patient records
2 awaiting next clinic appointment
1 declined owing to other commitments
2 declined as unwell (1 appointed in phase 2)
2 had altered in diagnosis
1 declined to participate no reason given
1 declined owing to child care problems
15 were tested

Phase two (n=84)

19 did not respond to follow up letter
1 did not arrive
1 had recovered, subsequent to clinic attendance.
1 believed she had done the tests
1 cancelled as unwell
1 child care problems
2 had travel problems
1 was awaiting next clinic appointments
3 had incorrect addresses in patient records
1 cancelled owing to other commitments
53 patients were tested (8 of whom had been contacted in phase 1)

Total of Phases one and two

158 patients were approached
68 patients were tested, of these 15 were recruited in phase one
4 DNA (Did not attend)
1 cancelled and 1 declined owing to illness severity
6 declined on the basis of travel and child care problems
3 were awaiting a clinic appointment which testing would follow
3 had clinic appointments cancelled, resulting in cancellation of testing
4 had incorrect addresses in the patient records
3 changed in diagnosis or illness state
2 declined or cancelled owing to other commitments
2 declined for other reasons (no reason, believed that had participated already)
19 did not respond to follow up letter in phase 2
48 made no response to recruitment letter in phase one (6 responded in phase 2)

INFORMATION SHEET

My name is Denise Fairhurst I am a postgraduate psychology student at the University of Leeds.

The research I am doing is looking at how the way you think is effected in Chronic Fatigue Syndrome. I am also looking at how this varies according to what you think about your illness as well as how you have been feeling recently.

The study involves filling in questionnaires about your illness and how you've been feeling as well some simple mental tests (for example deciding whether a string of letters is or is not a word, deciding how related two words are, remembering a string of numbers).

Most of these tasks will be done whilst you are waiting to see your consultant.

Participation in this research is entirely voluntary. If you decide not to participate this will in no way affect the care that you receive.

You may withdraw from the study at any time (for instance if you become too tired) without giving a reason and again this will not affect the care that you receive.

All information obtained is treated as strictly confidential.

Thank you for your time

INFORMATION SHEET

My name is Denise Fairhurst I am a postgraduate psychology student at the University of Leeds, working with the Psychiatry Liaison Dept. at St James Hospital.

Chronic Fatigue syndrome (CFS) is a debilitating illness that affects between 1 and 5 % of the population. Though it is not a new disease and some suggest it has been around since the 1750's as yet we are unclear of its cause and why some people experience difficulties in thinking. It is important that we explain the difficulties experienced by these people in order to come to a better understanding of CFS.

The research I am doing is looking at how the way people think is effected in Chronic Fatigue Syndrome. I am also looking at how this varies according to what they think about their illness as well as how they have been feeling recently. In order to do this I need to do the same tests on people who do not have chronic fatigue syndrome.

The study involves filling in questionnaires about how you've been feeling recently and some simple mental tests (for example deciding whether a string of letters is or is not a word, deciding how related two words are, remembering a string of numbers). The testing session takes about 40 minutes.

Participation in this research is entirely voluntary. You may withdraw from the study at any time (for instance if you become too tired) without giving a reason.

All information obtained is treated as strictly confidential.

Thank you for your time

COGNITION AND CHRONIC FATIGUE SYNDROME.

CONSENT FORM

Please cross out
as necessary

Have you read the patient information
Sheet?.....YES/NO

Have you had an opportunity to ask questions
and discuss this study? .....YES/NO

Have you received satisfactory answers to your
questions?.....YES/NO

You received enough information about the
study?.....YES/NO

who have you spoken to? .....Dr/Mr/Ms

Do you understand that you are free to withdraw from the study:
at any time,
without having to give a reason for withdrawing,
and without affecting your medical care? ..... YES/NO

Do you agree to take part in this study? .....YES/NO

Signed..... Date.....

NAME (BLOCK CAPITALS).....

Appendix 3.8 Debrief Sheet

What the tests actually looked at

The first set of tests were used to separate the data collected from those of you who are depressed, those of you who have CFS and those of you who have neither. In the case of clinic attendees this categorisation is supported by your consultants judgement.

The purpose of the HAD scale (questions about feeling tense and enjoying activities) was to separate those of you who are depressed from those of you who are not. This is in the hope that we can show there are problems that are the result of CFS and not depression

The next set of tests looked at memory attention and information processing.

The questionnaires asking questions about how tired you feel were done so we could assess how severe your illness is and what are the most important symptoms for you at this time. This is important it is not likely that those of you who experience muscle pain as the worst symptom and have no memory problems will perform in the same way as those of you who have mostly thinking difficulties.

The questions about the story, remembering the string of numbers and the paired word memory tests were used as standard tests of your memory so that these results could be compared with those obtained in other studies and research.

There were actually two further tests of memory, one was measuring implicit memory the other was measuring explicit memory. Implicit memory can be thought of as memory for information that we have not tried to learn or to remember, it just happens. Explicit memory is just the reverse we try to learn the information and then we try to recall it when asked. Within these tests there were 2 ways in which you tried to remember and to learn information. Sometimes learning was perceptual (where you had to count vowels) and sometimes conceptual (where you had to decide whether you thought that the item was useful). On recall some of the cues were perceptual (where you had to complete the word stem) and others were conceptual (where you had a cross word type clue). Some of you had test where the way you learned the information was matched with the way that you remembered it, the rest of you had a mismatch. It is usually thought that it is harder for you to recall words in the mismatched condition. Usually implicit memory is easier for people who have certain types of memory difficulty, however we are not sure whether this is the case in CFS.

The computerised tests were designed to see whether the time that you take to process the information presented to you is affected. Here there were 2 types of test, the time that you took to respond was measured. One test was to see whether items that are closely related were done at a different speed to those that are not so closely related. The other test looked at whether perceptual questions (in other words looking at the features of the word) versus conceptual (thinking about what the words mean) affected your response times.

Aims of The Research.

We are hoping to show whether or not there are deficits in CFS which are independent of those problems that exist with CFS and depression; and to see if we can find out the underlying problems resulting in the diverse cognitive symptoms with which CFS patients present.

If there are any further questions that you would like to ask, we will be happy to answer them. Thank you for your time and co-operation.

Appendix 4.1. Stimuli and instruction screen for the Reaction Time Test

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REACTION TIME INSTRUCTION SCREEN

For the following test a 'statement screen' will be followed by a **'get ready'** screen. After 1.5 seconds a word or a symbol will automatically follow.

This task requires you to decide whether or not the statement about the word that follows is true or false. There are 4 practice trials and 20 'real' ones.

If you think that the description is true, press key **Y**; if you think that the description is false press key **N**. Use the index finger of the hand that you write with.

Try too do this as quickly and accurately as possible.

press key **H** to clear the screen and move onto the get ready and next item

PRACTICE ITEMS

cue: The following item is a word
test: *
Cue: The following item is useful
test: **pillow**
cue: The following item has more than 2 vowels
test: **countryman**
cue: The following item is a symbol
test: *
cue: The following item could be found in the Countryside
test: **lung**

test items follow immediately

TEST ITEMS (20 items presented, 14 words & 6 symbols)

telephone	windmill				
bandage		typewriter			
hedge	weed				
fertiliser		willow			
monkey	cricket				
hare	robin				
ivory	cushion				
luggage	universe				
*	*	*	*	*	*

Appendix 4.2. Further analysis of the graded reactions test

Mean response times (sec.) for the country level of processing

	CFS	Controls
RTC (yes)	2.31230 (1.43)	1.49014 (0.58)
RTC (no)	2.24548 (1.44)	1.86643 (0.87)

Bivariate correlations of CFS duration of illness with each of the 5 conditions

	RTS	RTW	RTC	RTU	RTV
Duration of illness n=63	r=0.0309 p=0.810	r= 0.1694 p=0.184	r=-0.0942 p=0.463	r= 0.1926 p=0.130	r= 0.1230 p=0.337

Stepwise Multiple Regression Analysis for Each of the Processing Levels

	variables entered into equation	B	SE B	Beta	T	Sig T
RTS	PFRS.cd	0.1869	0.0517	0.3171	3.617	0.0004
RTW	PFRS.f	0.1898	0.0752	0.3452	2.522	0.0130
	PFRS.cd	0.2320	0.0944	0.3410	2.457	0.0155
	HAD.anxiety	-0.0719	0.2325	-0.2560	-3.094	0.0025
RTC	PFRS.cd	0.2098	0.0424	0.4160	4.948	<0.00001
RTU	PFRS.cd	0.2993	0.0489	0.4922	6.117	<0.00001

using all symptom variables, PIN 0.050, POUT 1.000

Mean response times (seconds), plus and minus twice the standard error

	CFS		Control	
RTS	1.44	1.96	1.30	1.50
RTW	1.98	2.62	1.33	1.47
RTV	2.32	2.88	2.08	2.32
RTC	1.96	2.44	1.53	1.67
RTU	2.3	2.9	1.72	1.88

Appendix 5.1. Word Pairs used in Study One

Seventy Two word pairs were generated for verification judgements of relationship these were divided into the folowing pairs on the basis of their hyponimic distance into the following categories:

Unrelated Pairs
box Saturn
paper racket
key pen
water watch
stomach Jupiter
card mug
tape glass
window glove

Slightly Related Pairs (5 or more branches apart)
baby diver
cowboy stepchild
asteroid island
cleaver drillbit
penguin nightingale
helicopter car
cat pony

Slightly to Moderately Related Pairs (3 to 4 branches apart)
moor silt
person public
milk medicine
motel hospital
apartment abbey
book-case sideboard
lawnmower spade
drill bolt-cutter
letter-opener scalpel
owl hen
stretcher side-car
hotair-balloon glider
helicopter car
canoe yacht
car truck
moth fly
cement slate
gondola train
cabbage lettuce

Moderately Related Pairs (2 branches apart)
chapel temple
apple lime
chickpea gooseberry
prune coffee-bean
stable barn
garage shed
bus horsebox
gambler adult
clay dust
opera theatre

Appendix 5.1. Word Pairs used in Study One

---

beech -tree oak -tree
brick stone
jet -plane bomber
jeep sports-car
moth fly
cot bunkbed
seat park-bench

Strongly Related Pairs (1 branch separation or synonyms)
child toddler
ballboy altarboy
star sun
moon star
orange satsuma
mud soil
bitter lager
clippers shears
scissors knife
duck swan
conifer pine
pie tart
bat club
tin can
glasses spectacles
mallet club
speedboat cruiser
barge house-boat
mouse rat
eagle bird
carpet rug

My name is Denise Fairhurst I am a PhD student at the University of Leeds looking at the memory and attention in patients with Chronic Fatigue Syndrome. The results of this research will be used to assess problems that patients with CFS experience with their attention concentration and information processing. Participation in this study is entirely confidential and voluntary. Should you decide to participate you may drop out at any point if you wish to do so.

This study requires you to rate how related you think pairs of words are. As there are a number of ways in which words can be related there is no right or wrong answer. For example you might think that oranges and lemons are related, because they are both fruit, or because of the nursery rhyme; or perhaps you think that they are not related all that much as they are different colours and have different uses.

Please mark on the given scale whether you think the word pair is related or unrelated, then if you think they are related, how strong you think this relation is.

Example

chocolate -- --- ice cream. If you think they are related tick this box, then decide how related, if you think the relation is moderate mark the moderately box.

chocolate------ice-cream

□ unrelated
(□) related □slightly
□moderately
□strongly

Appendix 5.2. Semantic Relations Word-Word Pair Questionnaire

---

Your **age**---------- and **Occupation** ----------

cot------ bunkbed ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	can----tin ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	island------asteroid ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
drill -----bolt cutter ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	card------mug ☐unrelated ☐ related ☐slightly ☐moderately ☐strongly	hotair balloon-------glider ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
mouse-----rat ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	cat------horse ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	helicopter-----car ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
tape-----glass ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	car------truck ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	medicine-----milk ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
clay-------dust ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	book case-----sideboard ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	stable-------barn ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
canoe----yacht ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	box------Saturn ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	chapel------temple ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
lawnmower-----spade ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	window-----glove ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	orange------satsuma ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
moon---star ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	key-------pen ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	chick pea----gooseberry ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly

Appendix 5.2. Semantic Relations Word-Word Pair Questionnaire

barge-----houseboat ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	cleaver-----drill bit ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	stretcher------sidecar ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
seat------park bench ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	eagle--------bird ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	speedboat------cruiser ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
pie-----tart ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	glasses-----spectacles ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	garage------shed ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
motel-----hospital ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	shears------clippers ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	bitter------larger ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
churchpew-----armchair ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	jetplane-----bomber ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	bus -------horsebox ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
bat-----club ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	peanut------almond ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	hammer----mallet ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
cabbage------lettuce ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	opera-------theatre ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	duck------swan ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
cowboy-----stepchild ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	water-----watch ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	gambler-----adult ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly

Appendix 5.2. Semantic Relations Word-Word Pair Questionnaire

hen-----owl ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	stomach------Jupiter ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	mud-----soil ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly on
brick-----stone ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	bush-------flower ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	letter opener-----scalpel ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
apple----lemon ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	paper-----racket ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	ostrich-------robin ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
moor-------silt ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	carpet------rug ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	child-----toddler ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
cement-----slate ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	gondola----train ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	sun------star ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
apartment------abbey ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	prune------coffee bean ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	beech tree-----oak tree ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
person--------public ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	baby-----diver ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	jeep-------sports car ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
moth----fly ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	conifer------pine ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	altarboy-----ball boy ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly

Appendix 5.2. Semantic Relations Word-Picture Pair Questionnaire

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My name is Denise Fairhurst I am a PhD student at the university of Leeds looking at the memory and attention in patients with Chronic Fatigue Syndrome. The results of this research will be used to assess problems that patients with CFS experience with their attention concentration and information processing. Participation in this study is entirely confidential and voluntary. Should you decide to participate you may drop out at any point if you wish to do so.

This study requires you to rate how related you think pairs of items are. Soem of the items will be described in words and some will be pictures. As there are a number of ways in which items can be related there is no right or wrong answer. For example you might think that oranges and lemons are related, because they are both fruit, or because of the nursery rhyme, or perhaps you think that they are not related all that much as they are different colours and have different uses.

Please mark on the given scale whether you think the item pair is related or unrelated, then if you think they are related, how strong you think this relation is.

Example

chocolate -- --- ice cream. If you think they are related tick this box, then decide how related, if you think the relation is moderate mark the moderately box.

Chocolate-----

☐ unrelated
☐ related ☐ slightly
☐ moderately
☐ strongly

Appendix 5.2. Semantic Relations Word-Picture Pair Questionnaire

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Your **Age**----------and **Occupation** ----------

car helicopter ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*duck* swan ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*sun* star ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
hotair balloon glider ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*mug* card ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*racket* paper ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
mouse rat ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*horse* cat ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*train* gondola ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
glass tape ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*truck* car ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*box* Saturn ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
orange satsuma ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*book case* sideboard ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*window* glove ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly

Appendix 5.2. Semantic Relations Word-Picture Pair Questionnaire

yacht canoe ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*watering can* lawnmower ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*key* pen ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
Star moon ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*penguin* nightingale ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*bus* horsebox ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
hammer mallet ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*spectacles* glasses ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*fly* moth ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
watch water ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*owl* hen ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*-lettuce* cabbage ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly
bat club ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*apple* lime ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly	*-sports car* jeep ☐ unrelated ☐ related ☐slightly ☐moderately ☐strongly

Appendix 5.3. Picture-word and word-word pair comparisons

Results of independent T test for differences in mean response on relationships of word-word versus word-picture item pairs. Adjusting for mutliple comparisons a p value of 0.003 is needed for significance.

Item pair	mean (word-word)	mean (word picture)	T and P values
paper ***racket***	0.09	0.02	t=-1.70, p=0.34
tape ***glass***	0.10	0.04	t=-1.01,p=0.31
key pen	0.20	0.07	t=-1.80, p=0.07
water ***watch***	0.30	0.14	t=-1.56, p=0.12
penguin nightingale	1.29	1.18	t=-0.047,p=0.64
helicopter ***car***	1.10	1.09	t=-0.07, p=0.95
hotair-balloon glider	1.49	1.63	t=1.25, p=0.22
bookcase sideboard	1.61	1.63	t=0.33, p=0.74
apple lime	1.64	1.74	t=0.59, p=.55
yacht canoe	2.05	1.90	t=0.00, p=1.00
car ***truck***	2.05	2.32	t=1.60, p=0.11
jeep ***sports car***	1.71	1.98	t=2.02, p=0.05
mouse rat	2.64	2.68	t=0.31, p=0.75
orange satsuma	2.80	2.90	t= -0.05, p=0.96
sun ***star***	2.66	2.42	t=-1.71, p=0.09
glasses ***spectacles***	2.98	2.84	t=-1.14, p=0.26

Appendix 5.4. Stimuli and Instruction Screens for Semantic Pairs Tasks

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Stimuli for the Semantic Pairs Task (those in small type, picture forms)

Practice items

cleaver drillbit

stretcher sidecar

house temple

Non Practice Items

cowboy	step child
stomach	Jupiter
island	asteroid
card	mug
churchpew	armchair
lawnmower	spade
gondola	train
cement	slate
garage	shed
moth	fly
speedboat	cruiser
cot	bunkbed
mud	soil
carpet	rug
hazelnut	almond
conifer	pine
paper	racket
tape	glass
key	pen
water	watch250
penguin	nightingale
helicopter	car
bookcase	sideboard
hotairballoon	glider
apple	lime
yacht	canoe
car	truck
jeep	sportscar
mouse	rat
orange	satsuma
sun	star
glasses	spectacles

Instruction Screen

For this task you need to decide whether or not the following pairs of words are related to each other. A **'get ready'** screen will be presented for 1.5 sec, after which the word pair will be presented. If you think that that they are related, press key **Y**; if you think that they are not press key **N**. Use the index finger of the hand that you write with.Try to do this as quickly and accurately as possible.press key **H** to clear the screen and move onto the next item.

Stimuli for the Lexical Decision Task

practice items

refdas shears deyik

Nonpractice items

cowboy	stepchild	stomach	Jupiter	island
asteroid	card	mug	churchpew	armchair
lawnmower	spade	gondola	train	cement
slate	garage	shed	paper	tape
pen	water	nightingale	helicopter	
glider	sideboard	lime	moth	fly
speedboat	cruiser	cot	bunkbed	canoe
car	jeep	mud	soil	carpet
rug	hazelnut	almond	conifer	pine
rat	satsuma	sun	glasses	
rfalwatel	corunni	rafeig	scopteel	marsubney
ramydip	oastte	tokopscu	lepsew	mianod
sutac	rhucc	beraw	inmupp	isthew
roatdo	danswhi	gitp	tibwaw	namowp
tefgo	quetog	cepgis	coljex	weklas

Instruction Screen

This task requires you to decide whether or not the item presented on screen is, or is not a word.

If you think that the item is a word, press key **Y**; if you think that the item is not a word press key **N**.

Use the index finger of the hand that you write with.

Try too do this as quickly and accurately as possible.

press key **H** to clear all screens and move onto the next item

Appendix 6.1. Baseline responses for implicit memory targets.

Aim: In order to demonstrate that there was an implicit memory effect as a result of prior exposure to the word lists, baseline response rates were determined.

Method: 37 healthy volunteers, who did not take part in the main study, mean age 30.9 (6.75), completed test items in the absence of previous exposure to the word lists. In order to compare these scores with controls from the main study the mean total number of 'correct' responses was calculated. This gave a baseline and a priming score per word, which was the probability of correctly identifying the target word.

Results:

Test	mean (sd)	n
Baseline score (control participants)	0.247 (0.08),	37
Priming score (control participants)	0.409 (0.11),	62
Priming score (CFS participants)	0.38 (0.13),	66

As was expected the number of target items identified was greater when participants had been primed by previous exposure to a list of these target items, see the above table. A Mann Whitney test revealed that these scores were significantly different, $z=-6.34$, $p<0.0001$. Mann Whitney comparison of the CFS group with baseline scores of volunteers also showed a significant difference, $z=-5.57$, $p<0.000$.

Conclusion: It was thus concluded that exposure to the target items prior to completion of the test task facilitated performance as measured by the number of target items correctly identified