A longitudinal investigation of information processing biases and self-reported cognitions and behaviours in Chronic Fatigue Syndrome

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King’s College London
Institute of Psychiatry, Psychology and Neuroscience
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A longitudinal investigation of information processing biases and self-reported cognitions and behaviours in Chronic Fatigue Syndrome

By
Alicia Maria Hughes

Thesis incorporating publications submitted for the degree of Doctor of Philosophy of the University of London

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Abstract

Cognitive behavioural models propose the way in which people with chronic fatigue syndrome (CFS) perceive and respond to symptoms and other illness-related information, contributes to the maintenance of fatigue and disability. Self-report studies exploring a number of these factors have proved fruitful. However, data regarding cognitions and behaviours that may occur at earlier, more implicit levels of processing is lacking. This thesis presents a series of experimental studies to investigate the manner in which people with CFS process information. The main work in this thesis is based on a large cross sectional cohort of people with CFS, compared to healthy controls; followed by a nested longitudinal study of the patients who underwent cognitive behavioural treatments for CFS, namely cognitive behavioural therapy (CBT) and graded exercise therapy (GET).

Study 1: A systematic review of attention and interpretation biases found mixed evidence for information processing biases in CFS and highlights methodological issues in experimental design.

Study 2: A published article addresses one of the key methodical issues highlighted in the review, the lack of illness-specific materials, by detailing a step-by-step process of comprehensive/robust stimuli development for experimental research.

Study 3: A published quasi-experimental study indicates that, when using illness-specific materials, people with CFS \( n=52 \) demonstrate attention and interpretation biases, compared to healthy individuals \( n=51 \); which are associated with unhelpful responses to symptoms, but independent of comorbid mood disorder and attentional control deficits.
Study 4: A replication study with a Dutch cohort of CFS participants (n=38) indicates that cognitive biases are a robust finding across cultures and CFS populations, and confirms that these biases are independent of attentional control.

Study 5: A nested longitudinal study (n=26) found that, pre-existing attentional biases, as well as a high capacity to develop an attentional bias (i.e. attention malleability), predicts better functioning, but not fatigue post treatment for CFS. Pre-treatment interpretation biases do not appear to predict treatment outcomes in CFS.

Study 6: A small follow-up study (n=20) found that attentional control capacity significantly improves following treatment for CFS. Whilst attention and interpretation biases did not significantly change across this treated sample, the degree to which they changed was associated with more helpful cognitions and behaviours.

By exploring the more implicit factors within the cognitive behavioural model of CFS, this body of experimental work has added another dimension to the CFS literature and contributes to a more comprehensive and nuanced understanding of information processing in CFS.
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# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>AB</td>
<td>Attentional Bias</td>
</tr>
<tr>
<td>ABM</td>
<td>Attention Bias Modification</td>
</tr>
<tr>
<td>ACT</td>
<td>Acceptance and Commitment Therapy</td>
</tr>
<tr>
<td>ANT</td>
<td>Attention Network Task</td>
</tr>
<tr>
<td>APT</td>
<td>Adaptive Pacing Therapy</td>
</tr>
<tr>
<td>BME</td>
<td>Black and Ethnic Minority</td>
</tr>
<tr>
<td>CB</td>
<td>Cognitive Behavioural</td>
</tr>
<tr>
<td>CBM</td>
<td>Cognitive Bias Modification</td>
</tr>
<tr>
<td>CBM-A</td>
<td>Cognitive Bias Modification for Attention biases</td>
</tr>
<tr>
<td>CBM-I</td>
<td>Cognitive Bias Modification for Interpretation biases</td>
</tr>
<tr>
<td>CBRQ</td>
<td>Cognitive and Behavioural Responses to Symptoms Questionnaire</td>
</tr>
<tr>
<td>CBT</td>
<td>Cognitive Behavioural Therapy</td>
</tr>
<tr>
<td>CCC</td>
<td>Canadian Consensus Criteria</td>
</tr>
<tr>
<td>CDC</td>
<td>Centre for Disease Control</td>
</tr>
<tr>
<td>CFQ</td>
<td>Chalder Fatigue Questionnaire</td>
</tr>
<tr>
<td>CFS</td>
<td>Chronic Fatigue Syndrome</td>
</tr>
<tr>
<td>CIS-R</td>
<td>Clinical Interview Schedule Revised</td>
</tr>
<tr>
<td>DSM-II-R</td>
<td>The Diagnostic and Statistical Manual of Mental Disorders III Revised</td>
</tr>
<tr>
<td>GAD</td>
<td>Generalized Anxiety Disorder</td>
</tr>
<tr>
<td>GET</td>
<td>Graded Exercise Therapy</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>HPA</td>
<td>Hypothalamic-Pituitary-Adrenal</td>
</tr>
<tr>
<td>IB</td>
<td>Interpretation Bias</td>
</tr>
<tr>
<td>ICC</td>
<td>International Consensus Criteria</td>
</tr>
<tr>
<td>IOM</td>
<td>Most recently, the Institute of Medicine</td>
</tr>
<tr>
<td>IPQ-R</td>
<td>Illness Perceptions Questionnaire Revised</td>
</tr>
<tr>
<td>LP</td>
<td>Lightning Process</td>
</tr>
<tr>
<td>ME</td>
<td>Myalgic Encephalomyelitis</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>NIHR</td>
<td>National Institute for Health Research</td>
</tr>
<tr>
<td>PENE</td>
<td>Post-Exertional Neuroimmune Exhaustion</td>
</tr>
<tr>
<td>PFRS</td>
<td>Profile of Fatigue Related Symptoms</td>
</tr>
<tr>
<td>PILL</td>
<td>Pennebaker Inventory of Limbic Languidity</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Control Trial</td>
</tr>
<tr>
<td>RT</td>
<td>Reaction Time</td>
</tr>
<tr>
<td>SAD</td>
<td>Social Anxiety Disorder</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviations</td>
</tr>
<tr>
<td>SEID</td>
<td>Systemic Exertion Intolerance Disease</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short-form Health Survey</td>
</tr>
<tr>
<td>WSAS</td>
<td>Work and Social Adjustment Scale</td>
</tr>
<tr>
<td>SOA</td>
<td>Stimulus-onset asynchrony</td>
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Chapter 1 Introduction

1.1 Chapter overview

This chapter introduces the key features of CFS, including a brief history of CFS, its various case definitions of CFS, prevalence, clinical presentation and aetiology. The controversy surrounding the definition and study of CFS is briefly summarised. This chapter then reviews empirical literature on the pathophysiology and treatment of CFS. Literature regarding the contribution of cognitive and behavioural factors in maintaining fatigue and disability in CFS are summarised.

1.2 Introduction to Chronic Fatigue Syndrome

Fatigue is the experience of extreme tiredness usually resulting from mental or physical exertion or illness. Fatigue is a common symptom; approximately 20% of patients in primary care present with fatigue (Bates, et al., 1993; Buchwald, et al., 1995; Fuhrer, 1994; Kroenke, Wood, Mangelsdorff, Meier, & Powell, 1988; Pawlikowska, et al., 1994) and approximately 13.6% of patients in this setting consider chronic fatigue their primary or secondary complaint (Cathébras, Robbins, Kirmayer, & Hayton, 1992). Most of these occurrences can be accounted for by medical or psychiatric diagnoses (Wessely, Chalder, Hirsch, Wallace, & Wright, 1997). However, there are a proportion of cases who continue to experience debilitating ongoing fatigue that cannot be otherwise medically explained. These cases account for between approximately 0.2% and 0.26% of the population (Johnston, Brenu, Staines, & Marshall-Gradisnik, 2013; Prins, van der Meer, & Bleijenberg, 2006).

Of these cases of persistent fatigue, some may receive a diagnosis of chronic fatigue syndrome (CFS) (Fukuda, et al., 1994), or myalgic encephalomyelitis (ME), as it is often referred to in the UK (Steincamp, 1989). CFS is characterised by severe, debilitating and
enduring, mental and physical exhaustion (Fukuda, et al., 1994). This fatigue lasts for at least 6 months, is not alleviated by rest and is often accompanied by a range of other somatic and neuropsychiatric symptoms, such as muscle pain, sleep disturbance, memory and concentration problems (Fukuda, et al., 1994; Jason, et al., 1999; Sharpe, et al., 1991; Wearden & Appleby, 1997). CFS cannot be explained by any single diagnosis (Fukuda, et al., 1994; Sharpe, et al., 1991). The condition has been likened to an extreme and persistent flu whereby the individual cannot engage in daily activities and struggles to recover their energy levels after a period of activity, in some cases leaving patients bed-bound. People with CFS report substantially higher levels of anxiety and depression than patients with other medical conditions (Cella, Sharpe, & Chalder, 2011b; Cella, White, Sharpe, & Chalder, 2013; Henningsen, Zimmermann, & Sattel, 2003; Skapinakis, Lewis, & Mavreas, 2003). Those with more symptoms report increased anxiety and depression (Skapinakis, et al., 2003).

1.2.1 History of Chronic Fatigue Syndrome

The concept of an illness primarily characterised by fatigue in not new. In fact the cluster of symptoms that describe CFS, as it’s known today, have existed for centuries under an array of illness labels and operational definitions (Shorter, 1993; Straus, 1991). Most memorably, George Beard (Beard, 1869) coined the termed ‘neurasthenia’; a condition of nervous exhaustion, characterised by mental and physical fatigue experienced on the slightest exertion; with headaches, gastrointestinal disturbances and various subjective sensations forming the primary somatic symptoms (Abbey & Garfinkel, 1991; Wessely, 1991). Neurasthenia acquired credibility as a neurological condition and was a popular diagnosis for about 20 years, not only in the US but as far afield as Europe and East Asia (Ware & Kleinman, 1992). More recently, the complex cluster of symptoms implicated in these conditions have been referred to as myalgic encephalomyelitis (ME), chronic
mononucleosis syndrome, postviral fatigue syndrome, or chronic Ebstein-Barr Virus infection (Abbey & Garfinkel, 1991). These all form precursors of the condition now known as Chronic Fatigue Syndrome (CFS).

1.2.2 Diagnostic criteria

In 1987 the Centre for Disease Control (CDC) in the USA introduced the label of Chronic Fatigue Syndrome (CFS), in combination with a case definition, based on consensus opinion of leading researchers and clinicians. It was unanimously agreed that the term CFS was appropriate as it describes the central symptoms of the disorder while avoiding assumptions about aetiology (Demitrack & Abbey, 1996). This was in contrast with previous descriptors such as myalgic encephalomyelitis (ME) (Steincamp, 1989) which implies an organic origin and brain pathology, for instance (Sharpe, et al., 1991).

The associated criteria was put forward to create a more homogenous group of patients for research purposes (Klonoff, 1992). The criteria were based on a distinct symptom profile and the careful exclusion of known medical and psychiatric entities, which have very similar symptom profiles to CFS. Thus, CFS as defined by Holmes, et al., (1988) was characterised by a new onset of fatigue lasting at least 6 months and causing reductions in activity levels by at least 50% compared to premorbid standards. In addition, 8 of 11 minor symptoms, such as sore throat, muscle pain or neuropsychological complaints needed to be present for a diagnosis of CFS to be warranted. At the time this definition was proposed, it was theorized that viral illness was the primary aetiology of CFS; therefore, the criteria focused on physical symptoms.

However, this new case definition was found to be too restrictive for clinical use (Klonoff, 1992). For instance, the requirement of a 50% reduction of activity levels was not only
difficult to assess objectively, but, in turn, excluded patients with less severe presentations of symptoms; thereby failing to acknowledge the patients' illness experiences and not providing a label or diagnosis for presentations which were less severe or less typical (Straus, 1991). Furthermore, the exclusion of psychiatric disorders was problematic, as the presence of psychiatric disorders such as depression or anxiety may well be a result of the disabling illness (Skapinakis, Lewis, & Meltzer, 2000).

In 1994 the CDC put forward a revised set of case criteria for CFS (Fukuda, et al., 1994). The new criteria maintained the main requirement of persistent or relapsing fatigue of more than six months’ duration. However, in addition, it specified a requirement for a smaller number of minor symptoms compared to the original CDC-1988 criteria, reducing the prerequisite number to 4 of 8. It was envisaged that this reduction in symptom criteria would avoid selecting patients with psychiatric disorders, which were considered to be associated with a higher incidence of physical complaints (Hyams, 1998). Additionally, some previously specified minor symptoms were eliminated; such as low grade fever, generalised weakness and the requirement for acute onset of symptoms over a short period of time (Komaroff, et al., 1996b). The criteria provided a comprehensive list of potential comorbidities and specific exclusion of criteria (the full criteria is provided in Appendix A). The latter CDC-1994 case definition has proven influential and remains one of the most frequently used to date, in research, and clinical practice.

Other groups of researchers such as Lloyd, Wakefield, Boughton, and Dwyer (1988) and Sharpe et al. (1991) put forward separate case definitions, termed the Australian and Oxford criteria, respectively. In terms of symptom requirements, the Oxford criteria are broader than either set of the CDC-1994 criteria. The Oxford criteria state that fatigue
should be severe, disabling and affect both mental and physical functioning, be present for at least 6 months’ duration, and more than 50% of the time. There is no requirement for additional minor symptoms, although the potential presence of symptoms such as myalgia, or mood and sleep disturbances is acknowledged (Sharpe, et al., 1991). Similarly, the required symptoms in the Australian definition are post-exertional malaise, substantial functional impairment and cognitive symptoms. No other additional symptoms are required. The Australian and Oxford criteria differ in that the Oxford requires a new onset of fatigue (i.e. not life-long) whereas the Australian definition does not.

More recently, Carruthers, et al. (2003) put forward a Canadian clinical working case definition (or Canadian Consensus Criteria, CCC-2011) of CFS/ME. A revised version was presented as the International Consensus Criteria (ICC-2003) for ME (Carruthers, et al., 2011). The CCC-2003 and ICC-2011 claim to be more selective case definitions for the identification of patients with neuroimmune exhaustion. The main symptom is "post-exertional neuroimmune exhaustion" (PENE) i.e. low stamina, rapid fatigability, symptom exacerbation, and variable onset with prolonged recovery. For a diagnosis of ME, PENE must also be accompanied by symptoms from neurological, immune/gastro-intestinal/genitourinary, and energy metabolism/transport impairment categories, combined with at least a 50% reduction in activity, which is described as "mild". An important revision of the Canadian 2003 criteria was that the ICC-2011 dropped the required six-month waiting period before diagnosis.

Most recently, the Institute of Medicine (IOM) proposed a new name and diagnostic criteria for CFS (Clayton, 2015). A new name was called for as many patient groups felt the term CFS did not accurately represent the severity of the condition and trivialised
their experience of the illness (Jason, Holbert, Torres-Harding, & Taylor, 2004; Sen, Sahoo, Aggarwal, & Singh, 2016; Twisk, 2016). The institute panel recommended that the illness be renamed “systemic exertion intolerance disease” (SEID). The term was developed in an attempt to reflect what patients, clinicians and researchers agree is a core symptom: a sustained depletion of energy following minimal activity, i.e. post-exertional malaise. The diagnostic criteria focus on the central symptoms of ME/CFS in order to make it easier for clinicians to recognize and accurately diagnose these patients in a timelier manner. The committee weighed several factors in reaching consensus on the diagnostic criteria: (1) the frequency and severity with which these symptoms were experienced by patients, (2) the strength of the scientific literature, and (3) the availability of objective measures supporting the association of particular symptoms with the diagnosis. The resulting core criteria were impaired function, post-exertional malaise and unrefreshing sleep; plus, either cognitive impairment and orthostatic intolerance (i.e. symptoms, such as light-headedness, that occur when upright, but are alleviated when reclining). Symptoms should be present for a minimum of 6 months, with moderate or greater frequency and severity, in order to make a diagnosis.

Table 1 outlines the diagnostic criteria to date. A more detailed table comparing the diagnostic criteria is in Appendix A. Broadly, the existing diagnostic criteria focus on similar sets of symptoms, but they differ markedly in the number of symptoms required and how those symptoms are defined. For example, for a diagnosis of ME the CCC-2003 (Carruthers, et al., 2003), and revised ICC-2011 (Carruthers, et al., 2011) criteria require post-exertional neuroimmune exhaustion (PENE); “a pathological inability to produce sufficient energy on demand with prominent symptoms primarily in the neuroimmune regions” (Carruthers, et al., 2003; page 329). This is similar to, but distinct from post-exertional malaise; “worsening of a patient’s symptoms and function after exposure to
physical or cognitive stressors” (Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue, Board on the Health of Select, & Institute of, 2015; page 78); which is a requirement for IOM criteria (Clayton, 2015) but only one of the minor, non-compulsory symptoms in the revised CDC-1994 definition (Fukuda, et al., 1994).

Despite the array of diagnostic criteria for CFS, the definition used extensively to define research populations remains the CDC-1994 (Fukuda, et al., 1994), perhaps because it is the most straightforward to use; requiring 4 of 8 listed symptoms alongside the core symptoms of mental and physical fatigue which are defined in their severity and frequency. It also provides a clear list of exclusionary criteria and potential comorbidities. The CDC-1994 (Fukuda et al., 1994) is also commonly used in clinical practice, alongside the National Institute for Health and Care Excellence (NICE) guidelines (Baker & Shaw, 2007; NICE, 2007). The NICE (2007) guidelines generally follow the CDC-1994 criteria, with the exception of duration of symptoms. NICE (2007) advises clinicians to diagnose patients with CFS after four months of persisting symptoms, rather than six, in order to reduce the delay in access to services and support. Though concerns have been raised as to whether the label of ‘chronic’ at an early stage of an illness is helpful (Chew-Graham, Dowrick, Wearden, Richardson, & Peters, 2010; Huibers & Wessely, 2006), qualitative interviews with people with CFS have found patients want a positive, early diagnosis and information on how to manage their symptoms (Bayliss, et al., 2014). The ICC (Carruthers, et al., 2011) is the only criteria not to define a minimum duration of symptoms before making a diagnosis, despite evidence that many other causes of similar fatigue are likely to become clear within this time frame (Jason, Sunquist, Brown, Evans, Vernon, Frust & Simonis, 2014; Nisenbaum, Reyes, Mawle, & Reeves, 1998). Thus, the
lack of specify in a timeframe over which to rate the symptoms may inadvertently bring individuals without ME or CFS into patient samples.

Some studies have empirically compared case definitions to assess whether they are defining the same or different groups of patients (Brurberg, Fønhus, Larun, Flottorp, & Malterud, 2014; Haney, et al., 2015; Jason, McManimen, Sunnquist, Brown, & Newton, 2015; Jason, et al., 2016; Meeus, et al., 2016). A core argument of the newer case definitions (CCC-2003 and ICC-2011, IOM-2015) is that they capture a more specific set of patients, with a neuroimmunological condition. These patients are assumed to be more fatigued and impaired than those identified by earlier case definitions such as the revised CDC (Fukuda, et al., 1994). However, there are mixed reports as to whether this is the case or not. A systematic review of case comparison studies found no empirical evidence to support this hypothesis for the Canadian definitions (CCC-2003 or ICC-2011) (Brurberg, et al., 2014); whereas, a subsequent review (Haney, et al., 2015) found application of the newer criteria (CCC-2003, ICC-2011 and IOM-2015) produces a more functionally impaired group than the CDC-1994 criteria. However, validation studies are generally methodologically weak and heterogeneous; some basing diagnoses on questionnaire responses only, others following detailed clinical interviews and laboratory testing (Brurberg, et al., 2014). The most cited case definition—the revised 1994 CDC criteria—is also the most extensively validated one. Whereas validation studies are few (CCC-2003; ICC-2011; IOM-2015) or missing (NICE, 2007) for recently presented case definitions.
Table 1 Case definitions for CFS/ME

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<tr>
<td>Fatigue requirement</td>
<td>Persistent or relapsing, debilitating fatigue or easy fatigability, that does not resolve with bedrest</td>
<td>Fatigue present more than 50% of the time</td>
<td>Post exertional fatigue</td>
<td>Fatigue not alleviated by rest</td>
<td>Post-exertional malaise and/or fatigue</td>
<td>Post-exertional malaise and/or fatigue</td>
<td>Post-exertional neuroimmune exhaustion*</td>
<td>Fatigue, not alleviated by rest and post-exertional malaise.</td>
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<tr>
<td>Minimum duration of fatigue</td>
<td>6 months</td>
<td>6 months</td>
<td>6 months</td>
<td>6 months</td>
<td>4 months</td>
<td>Not required</td>
<td>6 months</td>
<td></td>
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<tr>
<td>Functional impairment</td>
<td>50% decrease in activity</td>
<td>disabling</td>
<td>substantial</td>
<td>substantial</td>
<td>50% decrease in activity</td>
<td>substantial</td>
<td>50% decrease in activity</td>
<td>substantial</td>
</tr>
<tr>
<td>New onset</td>
<td>Required</td>
<td>Required</td>
<td>Not required</td>
<td>Required</td>
<td>Not required</td>
<td>Required</td>
<td>Not required</td>
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<tr>
<td>May be present</td>
<td>Impaired mental functioning required</td>
<td>Required</td>
<td>Mental fatigue required</td>
<td>2 or more neurological/cognitive manifestations required</td>
<td>May present</td>
<td>be present from 4 categories: neurocognitive impairment; pain; sleep dysfunction; neurosensory perceptual; motor disturbance</td>
<td>Cognitive impairment or orthostatic intolerance required</td>
<td></td>
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<tr>
<td>Other required symptom(s)</td>
<td>Any 8 of 11 specific symptoms</td>
<td>None</td>
<td>None</td>
<td>Any 4 of 8 specific symptoms</td>
<td>Chronic pain and sleep dysfunction. Plus at least 1 symptom from 3 categories: autonomic, neuroendocrine, immune</td>
<td>Any 1 of 10 specific symptoms</td>
<td>At least 1 symptom from immune gastrointestinal or genitourinary impairment. Plus 1 from energy metabolism or transport impairment</td>
<td>Unrefreshing sleep</td>
</tr>
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*Postexertional immune disorder (PENE) as defined by Carruthers, et al., (2011) is a pathological inability to produce sufficient energy on demand with prominent symptoms primarily in the neuroimmune regions. Characteristics are as follows:
1. Marked, rapid physical and/or cognitive fatigability in response to exertion, which may be minimal such as activities of daily living or simple mental tasks, can be debilitating and cause a relapse.
2. Post-exertional symptom exacerbation: e.g. Acute flu-like symptoms, pain and worsening of other symptoms.
3. Post-exertional exhaustion may occur immediately after activity or be delayed by hours or days.
4. Recovery period is prolonged, usually taking 24 h or longer. A relapse can last days, weeks or longer.
5. Low threshold of physical and mental fatigability (lack of stamina) results in a substantial reduction in pre-illness activity level.

Note: For a more detailed table of diagnostic criteria see Appendix A
1.2.3 Epidemiology

1.2.3.1 Prevalence

The prevalence rate of CFS varies according to the diagnostic criteria used, the method of assessment and the population studied (Brurberg, et al., 2014; Johnston, et al., 2013). The 1994 CDC case definition remains the standard definition for CFS and appears to be the most reliable clinical assessment tool available (Brurberg, et al., 2014; Johnston, et al., 2013). Using the 1994 CDC Fukuda definition of CFS, the commonly assumed population prevalence rate is 0.2% to 0.26% of the population (Baker & Shaw, 2007). Few studies have assessed prevalence rates using the most recent and debated criteria (CCC-2003; ICC-2011; IOM-2015). A recent study compared a range of diagnostic criteria within a relatively small international sample (n=895), that was pre-selected for self-identifying as having CFS, ME/CFS or ME (Jason, et al., 2015). They found, of this pre-selected sample, 92% met the 1994 CDC criteria (Fukuda, et al., 1994), 88% met the IOM criteria for SEID (Clayton, 2015) and 60% met the ICC-2011 (Carruthers, et al., 2011). However, this study provided no information on those who screened negative in the first place. We do not know whether some of those might have had a positive diagnosis if screened with one of the other case definitions.

Whilst community settings find prevalence rates around 0.2% in the UK (Nacul, et al., 2011) and 0.24% in the US (Reyes, et al., 2003), prevalence rates in primary care settings are higher. Using the 1994 CDC criteria, a UK study conducted in primary care found prevalence of CFS of 2.6% or 0.5% when psychological morbidity was excluded (Wessely, et al., 1997). Similarly, high prevalence has been found in primary care across countries; the Netherlands (1%) (van’t Leven, Zielhuis, van der Meer, Verbeek, & Bleijenberg, 2010), US (0.3%) (Bates, et al., 1993), Brazil (1.6%) (Cho, Menezes, Hotopf, Bhugra, & Wessely, 2009), Japan (1.5%) (Kawakami, Iwata, Fujihara, &
Kitamura, 1998), Korea (0.6%) (Kim, Shin, & Won, 2005) and Iceland (1.4%) (Líndal, Stefánsson, & Bergmann, 2002). It may be that those attending primary care clinics are a higher risk group than those in the general community. This is in contrast to the lower prevalence rates of CFS obtained from case reports, (Bazelmans, et al., 1997; Gunn, Connell, & Randall, 1993; Haines, Saidi, & Cooke, 2005; Versluis, de Waal, Opmeer, Petri, & Springer, 1997) suggesting that CFS may be subject to considerable underreporting.

However, given the variation in sample strategies, response rate, strategies for non-response adjustment, as well as the methods and rigor of assessment, prevalence studies cannot be directly compared. Even when using the same case definition and the same study sample, methods of applying the case definition can impact CFS classification (Unger, et al., 2016). For example, a meta-analysis of prevalence studies found that studies which employed self-report assessments yielded higher and more variable prevalence rates of CFS than clinical assessments (Johnston, et al., 2013).

1.2.3.2 Demographic Characteristics

Early studies suggested that individuals with CFS were more likely to be women, white and of higher socioeconomic status (Afari & Buchwald, 2003). However, more recent research suggests that CFS is much higher in Black and minority ethnic (BME) groups and those with lower socioeconomic status than previously thought (Dinos, et al., 2009; Hickie, et al., 2009). The finding of a higher prevalence of CFS in women than in men has been a consistent; with the ratio about 2:1 (Bakken, et al., 2014; Buchwald, Pearlman, Kith, & Schmaling, 1994; Cho, et al., 2009; Nacul, et al., 2011; Prins, et al., 2006; Skapinakis, et al., 2003). It has been suggested that this gender difference is an artefact of recruiting samples from specialist centres and reflects differences in illness behaviour.
and referral patterns (Richman & Jason, 2001). However, many community-based studies confirm this finding (Cella & Chalder, 2010; Jason, et al., 1999; Pawlikowska, et al., 1994), which suggests that there may be a true gender difference. This difference does not seem to be explained by differences in psychological comorbidity (Pawlikowska, et al., 1994; Skapinakis, et al., 2000; Wessely, et al., 1997). Various predisposing vulnerabilities have been proposed to explain this finding; such as, endocrine and stress-related factors. However, to date no singular factor has been identified (Buchwald, et al., 1994).

For adults the most common age of onset for CFS reported in the UK is between early 20s to mid-40s (Jason, et al., 1999; Steele, et al., 1998). Similarly, a population based study in Norway identified the incidence of CFS onset in adults peaked between 30-39 years (Bakken, et al., 2014). In sum, it seems CFS has a similar presentation across cultures, classes and ethnic groups. More women are diagnosed with CFS, however it is still unclear what factors, or indeed combination of factors, underpin this gender difference.

1.2.4 Comorbidities

A high proportion of people with CFS also have comorbid diagnoses of anxiety, depression or both (Cella, et al., 2013; Henningsen, et al., 2003; Janssens, Zijlema, Joustra, & Rosmalen, 2015). About 25% of people with CFS have a current diagnosis of depression and 50%–75% of people with CFS have lifetime history of major depression (Afari & Buchwald, 2003). Levels of anxiety and depression in CFS are substantially higher than that found in the general population, or other similar medical conditions (Cella, et al., 2011b; Cella, et al., 2013; Henningsen, et al., 2003; Skapinakis, et al., 2003). However, there may be an over-estimation of the prevalence of psychiatric disorders in
CFS, as many studies use methodologies to assess psychopathology which confound fatigue and other symptoms with mood disorders. For example, the Diagnostic Interview Schedule (Robbins, Cottler, & Keating, 1989), is most commonly used to assess comorbidity in CFS. It is a highly structured interview administered by lay interviewers, which, rigidly attributes unexplained symptoms, such as fatigue, to psychiatric causes. Indeed, several studies that have used an alternative diagnostic interview- the Structured Clinical Interview for DSM-III-R (Spitzer & Williams, 1988)- have found lower rates of psychiatric disorders in CFS (Hickie, Lloyd, Wakefield, & Parker, 1990; Lloyd, Hickie, Boughton, Spencer, & Wakefield, 1990; Taylor & Jason, 1998). This may be due to the fact that the latter diagnostic interview is administered by a trained clinician and is semi-structured, thus allowing for more nuanced responses.

The high prevalence and premorbid levels of psychopathology in CFS, combined with lack of a consistent physiological marker, has led some researchers to argue that CFS is a manifestation of a psychiatric condition (Greenberg, 1990; Manu, Lane, & Matthews, 1993; Manu, et al., 1989; Stewart, 1990). However, subsequent research has identified that, whilst there is considerable overlap between some psychiatric disorders and CFS (in particular anxiety and depression) they are most likely distinct entities (Griffith & Zarrouf, 2008). The presentation of CFS differs from that of anxiety or depression; primary symptoms of CFS such as post exertional malaise and sore throat, are not typical of psychiatric disorders, and symptoms typical of psychiatric disorder are not always present in CFS (Griffith & Zarrouf, 2008). Furthermore, people with CFS and depression think about and respond to their symptoms differently (Moss-Morris & Petrie, 2001). People with depression tend to have low self-esteem, and generally negative cognitive styles; whereas, people with CFS are more specifically concerned with physical illness and tend to respond to symptoms by limiting stress and activity levels activities (Moss-
Morris & Petrie, 2001). Furthermore, antidepressant medications do not have an effect on CFS as they do with depression (Vercoulen, et al., 1996; Wearden, et al., 1998). Studies of phenomenology also discriminate between psychiatric conditions and CFS; indicating that discrete physiological abnormalities that can distinguish CFS from depression and anxiety (Cho, et al., 2006). It may be that psychiatric comorbidity occurs in response to CFS. Indeed, anxiety and depression are common emotional responses to medical illness generally (Vercoulen, et al., 1996). The particularly high rates of anxiety and depression in CFS compared to other chronic conditions (Cella et al., 2013; Skapinakis, et al., 2003) may be reflective of the lack of illness legitimization experienced by many patients (Lehman, Lehman, Hemphill, Mandel, & Cooper, 2002). Thus, whilst anxiety and depression are risk factors for developing CFS, and have some overlap with the condition, they are likely to be distinct entities.

There is also considerable overlap between CFS and other medically unexplained conditions such as, fibromyalgia, chronic pain, multiple chemical sensitivities and irritable bowel syndrome (Aaron & Buchwald, 2001; Geisser, et al., 2008; Skapinakis, et al., 2000; Whitehead, Palsson, & Jones, 2002). These conditions and other chronic multi-symptom illnesses frequently co-occur and share common associated factors, such as pain, fatigue, sleep disturbance, and memory problems (Aaron & Buchwald, 2001; Geisser, et al., 2008). It has been argued that in many cases these disorders are indistinguishable and debate has centred on whether these disorders should be defined as separate entities or whether in fact there should be an overarching definition which incorporates all of the syndromes (Fink & Schröder, 2010; Moss-Morris & Spence, 2006; Nimnuan, Rabe-Hesketh, Wessely, & Hotopf, 2001; Wessely, Nimnuan, & Sharpe, 1999; Wessely & White, 2004). Similarly to the comorbidity with depression; although similarities between conditions have been documented, there is also evidence that they
differ; specifically in their onset and symptom profile (White, 2010). For example, several prospective studies have identified that CFS and IBS are triggered by different factors; CFS by viral infection and IBS by a gastroenteritis (Hamilton, Gallagher, Thomas, & White, 2009; Moss-Morris & Spence, 2006). Furthermore, CFS is predominantly characterised by post-exertional malaise, which may or may not be accompanied by abdominal discomfort (Maes, Leunis, Geffard, & Berk, 2014; Whitehead, et al., 2002).

Several researchers propose that those with CFS and other comorbid somatic conditions, such as IBS and fibromyalgia, represent a subgroup of CFS patients (Hadzi-Pavlovic, et al., 2000; Williams, Chalder, Sharpe, & White, 2017), who also show increased symptom severity, disability (Creed, et al., 2013; Williams, et al., 2017), anxiety and depression (Janssens, et al., 2015). Indeed, CFS has been described as a heterogeneous condition and researchers have defined subgroups by a diverse range of characteristics; including specific symptoms (Hickie, et al., 1995; Wilson, et al., 2001), biological variables (e.g. body mass index and sleep disturbance (Aslakson, Vollmer-Conna, Reeves, & White, 2009; Aslakson, Vollmer-Conna, & White, 2006; Vollmer-Conna, Aslakson, & White, 2006), mood (Harvey, Wessely, Kuh, & Hotopf, 2009; Hirsch & Wallace, 1996; Williams, et al., 2017) self-efficacy and behavioural patterns (Williams, et al., 2017). This demonstrates the heterogeneity in the presentation of CFS. There is also heterogeneity in the aetiology of CFS.

1.2.5 Aetiology

Self-report studies have found that people with CFS identify a variety of factors as triggers for the initial symptoms; such as episodes of infection (57.9%, of which 74% were reported as viral infections), psychological stress (24.8%), trauma or surgery
(11.3%), and other factors (6.0%) (Nacul, et al., 2011). These and other factors have been explored by empirical research, attempting to identify the aetiology of CFS.

1.2.5.1 Genetic studies

Twin studies have found some evidence for a familial predisposition for chronic fatigue (Buchwald, et al., 2001; Claypoole, et al., 2007; Schur, Afari, Goldberg, Buchwald, & Sullivan, 2007; Sullivan, Pedersen, Jacks, & Evengard, 2005). A study with female twins pairs, found the concordance of twins meeting the 1994 CDC criteria for CFS (Fukuda, et al., 1994) was higher in monozygotic than dizygotic twins (38% versus 11%) (Buchwald, et al., 2001). The discordance was accounted for by additive genetic factors as well as common environmental effects (they each explain around 40% of the discordance). A later study by Schur, et al. (2007), included both male and female twins and found intriguing differences in the patterns of genetic influences for women and men. In women, correlations for prolonged (self-reported fatigue present for ≥1 month) and chronic fatigue (self-reported fatigue present for ≥6 months) were quite similar for monozygotic and dizygotic pairs; suggesting predominantly environmental influences in chronic fatigue in women. This finding was in contrast to the much higher correlations in male monozygotic pairs than in male dizygotic pairs; suggesting a predominantly genetic influence in chronic fatigue in men. However, the findings from this study are inconsistent with other twin studies in Sweden (Sullivan, et al., 2005) and the US (Furberg, et al., 2005). The discrepancy may be due to methodological issues; for example Schur, et al. ’s (2007) sample was predominantly female and smaller than either Sullivan, et al. (2005) or Furberg, et al. (2007). Further studies are needed to establish whether there are gender differences in genetic and environmental contributors for fatigue.
These studies provide some evidence for a partly genetic component of CFS. However, whether this represents a true genetic origin of CFS is unclear. It may be that these studies are detecting a genetic predisposition to distress, which in turn increases the risk of CFS. Indeed, a another much larger twin cohort study by Kato, Sullivan, Evengård, and Pedersen (2006) identified personality traits of emotional instability and distress were also linked to a genetic predisposition to CFS. Whilst there is some basis for a genetic link to CFS, a review by Cho, Skowera, Cleare, and Wessely (2006) argues that environmental effects are still predominant. At this stage the identification of specific genes is still a long way off (Kerr, et al., 2008). In order to reliably detect any genotypic risks, genetic studies need to recruit much larger clinical and control samples and state priori hypothesis, rather than gene scanning.

1.2.5.2 Neuroendocrine studies

Some of the most robust findings concerning the pathophysiology of CFS have been related to the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is under homeostatic control and regulates many of the body’s systems, including the cardiovascular, immune and central nervous systems (Tsigos & Chrousos, 2002). One of the hormones synthesised and secreted as a consequence of HPA axis function is cortisol, a glucocorticoid released in response to stress. A number of studies have shown that, compared to healthy individuals, people with CFS demonstrate a down-regulation of the HPA axis, evidenced by reduced cortisol in response to waking and a blunted HPA response to challenge (Cleare, 2004; Papadopoulos & Cleare, 2012; Powell, Liossi, Moss-Morris, & Schlotz, 2013; Roberts, Wessely, Chalder, Papadopoulos, & Cleare, 2004; Tak, et al., 2011; Tomas, Newton, & Watson, 2013). About one third of patients with CFS exhibit hypocortisolism (i.e. low cortisol levels) (Nater, et al., 2008a; Nater, et al., 2008b; Parker, Wessely, & Cleare, 2001) and treating people with CFS with cortisol
replacement seems to temporarily lessen fatigue (Cleare, et al., 2001). These findings strengthen support for an association between HPA axis dysregulation and CFS.

However, results are not always consistent (Cleare, 2004; Gaab, et al., 2004; Gaab, et al., 2005) and not everyone with CFS shows HPA dysfunction (Parker, et al., 2001). Furthermore, the direction of this relationship is unclear (Tomas, et al., 2013). It may be that for some people neurobiological changes are triggered by a prolonged or early stress response and then in-turn contribute to symptomology. Indeed, studies show a reduced cortisol response in people with CFS who had a history of childhood trauma or early life stress (Heim, et al., 2009; Van Den Eede, Moorkens, Van Houdenhove, Cosyns, & Claes, 2007); and prospective studies have identified that abuse in childhood and major life events are significant risk factors in developing CFS (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Nater, et al., 2008a; Taylor & Jason, 2001).

Conversely, it may be that for some people with CFS neurobiological changes occur in at later stages of the illness, in response to certain symptoms or behavioural changes, i.e. sleep disturbance, physical inactivity, deconditioning (Cleare, 2004). Indeed, studies have found hypocortisolism is more prominent in patients with a longer duration of illness (Cleare, 2004; Gaab, et al., 2004). Furthermore, behavioural treatments seem to increase cortisol levels. Roberts, Papadopoulos, Wessely, Chalder, and Cleare (2009) showed that patients who clinically improved followed CBT, showed a significant rise in cortisol levels post-treatment. Similarly, Hall, et al. (2014) found a stress management program for people with CFS, resulted in reduced post-exertional malaise which was mediated by greater cortisol awakening response. Thus, HPA dysregulation does appear to be implicated in CFS but it may not necessarily have a causal effect.
1.2.5.3 Immune system abnormalities

Despite many studies of the immune system in CFS, few consistent results have emerged (Lyall, Peakman, & Wessely, 2003). The most frequently studied immune changes in CFS are in relation to enhanced inflammatory cytokines and T-cells, and deficient natural killer cell count and function (e.g. Caligiuri, et al., 1987; Kishimoto, Akira, Narazaki, & Taga, 1995; MacDonald, et al., 1996; Tirelli, Marotta, Improta, & Pinto, 1994; Tomoda, et al., 2005). The results of these studies suggest that people with CFS may have chronic low-level immune system activation. Given that the HPA axis is involved in regulating the immune system (amongst others), researchers have investigated immune responses during and after stress. Findings indicate that people with CFS have different immune responses following stress than healthy controls (Gaab, et al., 2004; Gaab, et al., 2005; Wood, Bentall, Gopfert, Dewey, & Edwards, 1994). Although, to what extent these abnormalities relate to symptoms remains unclear. Furthermore, a comprehensive review of immunological studies in CFS indicated that no clear pattern emerges when data are viewed collectively and some findings may be erroneous (Lyall, et al., 2003). While CFS may be related to some immunological dysfunction (in particular changes in T cell number, function and activation), there are a number of inconsistencies in the literature that should be interpreted with caution.

1.2.5.4 Infectious agents

Many patients predate the onset of CFS to an acute infective episode (Nacul, et al., 2011). This led to a number of early studies attempting to pin down the assumed viral pathogen of CFS. Of particular interest was Epstein-Barr virus (EBV), a latent and largely ubiquitous tumourogenic herpes virus that has been implicated in a wide range of illnesses, such as Hodgkin’s disease and B lymphoproliferative disease. It most commonly causes infectious mononucleosis (IM), which is often referred to as glandular
fever (Macsween and Crawford, 2003). Early, retrospective, case control studies implicated increased EBV titres (indicative of a possible EBV infection), as a causal factor in CFS (Hellinger, et al., 1988; Holmes, et al., 1987; Straus, et al., 1985). However, results were inconsistent and subsequent well-designed prospective studies have found little evidence of a relationship between CFS and EBV titres (Buchwald & Komaroff, 1991; Matthews, Lane, & Manu, 1991).

Whilst studies have found little evidence that EBV titres play a role in CFS it seems the clinical manifestation of EBV, i.e. glandular fever, does. Glandular fever is an acute illness characterised by fatigue, sore throat, tender lymph nodes and fever. It usually resolves within two to four weeks (Rea, Russo, Katon, Ashley, & Buchwald, 2001). Prospective studies show that around 12% of adults and adolescents who experience glandular fever, do not fully recover and subsequently develop CFS (Hickie, et al., 2006; Katz, Shiraishi, Mears, Binns, & Taylor, 2009; Petersen, Thomas, Hamilton, & White, 2006; White, et al., 2001). A handful of studies have also reported CFS after cases of other severe infections such as Q fever, parvovirus and Lyme disease (Cleare, et al., 1995; Demitrack, 1997; Hickie, et al., 2006; Torpy, et al., 2001; Wildman, et al., 2002). However, cases do not seem to occur after common infective episodes (e.g. influenza) (Wessely, et al., 1995).

Thus, it seems that not one but several, viral as well as bacterial infections, predict the onset of CFS. Antiviral medications, successful in treating these infections, do not seem to be effective at treating the associated CFS (Bou-Holaigah, Rowe, Kan, & Calkins, 1995; Chambers, Bagnall, Hempel, & Forbes, 2006; Freeman & Komaroff, 1997; Rowe, Bou-Holaigah, Kan, & Calkins, 1995), indicating that though the virus may trigger CFS, it is not necessarily maintaining it. Furthermore, in a study by Cameron, et al. (2006)
people with glandular fever who developed post infective CFS did not differ from those who didn’t when analysing viral load and antiviral immune response. Thus, whilst some immunological factors may trigger the initial fatigue for some individuals (Moss-Morris & Spence, 2006; White, et al., 2001), and some neurobiological differences associated with the syndrome exist (Cleare, 2004; Roberts, et al., 2004), to date no single immunological marker for CFS has been identified. These findings suggest that, whilst the experience of an acute infection may be an important factor in the onset of CFS, other risk factors may interact with the virus to trigger and maintain symptoms.

1.2.5.5 Psychosocial predictors of post infectious fatigue

Patients who experience an acute episode of acute infection, such as glandular fever, provide an ideal group with which to prospectively examine other risk factors in the onset of CFS. Prospective studies have identified that how an individual responds to symptoms and conceptualises the virus at the time of infection, is important for predicting subsequent onset of CFS. For example, spending more days in bed (Jason, Katz, Shiraishi, Mears, Im & Taylor, 2014) and engaging in oscillating all-or-nothing patterns of activity during an infection (Moss-Morris, Spence, & Hou, 2011), increase the risk of post infectious fatigue. Furthermore, expecting that the virus will take a long time to recover from and anticipating that it will have serious consequences, also increases the likelihood of developing CFS (Candy, et al., 2003; Moss-Morris, et al., 2011).

The advantage of exploring these cognitive and behavioural responses to symptoms is that they are amenable to change, and could therefore be useful to target. A study by Candy, Chalder, Cleare, Wessely, and Hotopf (2004) tested this hypothesis. They provided a brief, nurse administered, psychoeducational package to patients shortly after onset of glandular fever. The package provided information about the condition and
advice about management. The findings were promising; the psychoeducational package significantly reduced the number of people who went on to develop CFS six months later, when compared to the treatment as usual control group (Candy, et al., 2004). This study illustrates the potential for cognitive and behavioural factors to play a key role in the onset of chronic fatigue. Research, such as this, exploring amenable factors involved in the development and perpetuation of symptoms, has been the corner stone for the development of effective, evidence based, cognitive and behavioural treatments for CFS (discussed in section 1.5).

1.2.5.1 Predisposing factors

Evidence suggests that people with a history of psychopathology or elevated premorbid distress are predisposed or more at risk for illnesses such as CFS. Two prospective studies of British birth cohorts (1946 and 1958), found that people who had a prior experience of a psychiatric disorder in adulthood, particularly anxiety or depression, had a two-fold increase in the risk of developing CFS (Clark, Goodwin, Stansfeld, Hotopf, & White, 2011; Harvey, Wadsworth, Wessely, & Hotopf, 2008). Furthermore, prospective studies of individuals who had a viral infection indicate that those most likely to go on to develop CFS had higher premorbid levels of distress, depression and anxiety; and these factors were more predictive of CFS onset than the virus itself (Moss-Morris & Spence, 2006; Wessely, et al., 1995; White, et al., 2001). These findings have been linked to a genetic predisposition to distress (as discussed in 1.2.5.1).

Another key predictor of CFS onset is premorbid activity levels. A large UK birth cohort study of data collected in 1970, found childhood experiences of a limiting illness and sedentary lifestyles were predictors of fatigue later in life (Viner & Hotopf, 2004); suggesting that learnt experiences at an early age shape how a person copes with illness.
in adulthood. However, conversely data from the British birth cohort studies in 1946 and 1958, found that those who were more physically active in childhood and adulthood and continued to be active after the initial onset of fatigue, were more likely to develop CFS (Clark, et al., 2011; Harvey, et al., 2008). The latter finding coincides with patients accounts of themselves pre-CFS as being highly active and very driven, and having an ‘over-active’ lifestyle compared to controls (Van Houdenhove, Neerinckx, Onghena, Lysens, & Vertommen, 2001). Some studies have indicated a link between these high levels of activity and the personality characteristic of perfectionism (Van Houdenhove, et al., 2001). Findings from cross-sectional and post-infectious prospective studies suggest that those with negative perfectionism (characterised by particularly high standards and expectations of themselves) are more likely to develop CFS (Deary & Chalder, 2010; Luyten, Van Houdenhove, Cosyns, & Van den Broeck, 2006; Moss-Morris, et al., 2011; White & Schweitzer, 2000).

Other studies of personality in CFS, have indicated people with CFS score highly on neuroticism (Blakely, et al., 1991; Buckley, et al., 1999; Fiedler, et al., 2000; Johnson, DeLuca, & Natelson, 1996; Masuda, Munemoto, Yamanaka, Takei, & Tei, 2002; Taillefer, Kirmayer, Robbins, & Lasry, 2003); however, it is difficult to draw general conclusions from this data as study methods, patient populations, control groups and CFS case definitions vary. A review of the personality studies in CFS suggests that, whilst personality is an important factor to investigate in CFS, studies should move away from a narrow focus on trait personality factors or disorders, and begin to consider how personality may evolve and change in response an individual’s environment (van Geelen, Sinnema, Hermans, & Kuis, 2007). Indeed multiple studies have now provided evidence that personality traits change across the life-span (Helson, Jones, & Kwan, 2002; Roberts, Walton, & Viechtbauer, 2006) and a recent systematic review has indicated that
psychological treatments can change personality traits, in particular emotional stability and extraversion were identified as most amendable to change (Roberts, et al., 2017). Research still needs to establish whether these multidimensional aspects of personality play a role in CFS and explore whether there are critical phases, when changing personality structures may interact with or precipitate the onset of CFS. For instance, during an acute illness whereby a person’s sense of identity may be challenged.

These studies indicate that a diverse range of physiological and psychological factors may predispose or precipitate CFS. It is likely that many of these factors interact; for example predisposing genetics, personality factors, infection and distress may all, to varying degrees, affect neurobiological mechanisms. The relative weight of each of these components in predicting CFS onset may vary according to individual and environmental factors. In sum, it seems unlikely that CFS is caused by a single agent.

1.2.6 Controversy

The exploration of psychological factors in CFS has sparked fierce debate about the aetiology of CFS, namely whether it is physical or psychological in its nature. This is reflected in the contention about the case definitions and terminology of CFS (as discussed under ‘diagnostic criteria’ section 1.2.2). For example, the Oxford-1991 (Sharpe, et al., 1991), CDC-1994 (Fukuda, et al., 1994) and NICE-2007 have been criticised, especially by patient organisations, for undue overlap with psychopathology. Proponents of the recent Canadian case definitions, (CCC-2003; Carruthers, et al., 2003 and ICC-2011; Carruthers, et al., 2011), claim to achieve a narrow selection of patients with ME conforming to a hypothesised specific pathophysiology. However, Brurberg, et al. (2014) demonstrated that these case definitions do not necessarily exclude patients with psychopathology. As outlined earlier in this chapter (section 1.2.2).
The proposed terminology of CFS is also hotly debated. The newest label- systematic exertion intolerance disorder (SEID)-proposed by the IOM (Clayton, 2015), was an attempt to appease patient groups who championed a more ‘biological’ term, whilst refraining from making unfounded assumptions about the aetiology of the condition. However, the proposed new terminology is still not acceptable to many of those diagnosed with this syndrome or advocates of a purely biological aetiology (Sen, Sahoo, Aggarwal, & Singh, 2016; Twisk, 2016a, 2016b). Many patient groups still prefer the term myalgic encephalomyelitis (ME), a term which eludes to inflammation of the central nervous system (myelitis) (Evengård, Schacterle, & Komaroff, 1999; Ramsay, 1988).

If current definitions are referring to a similar group of patients with the same core symptoms does it matter which terminology of ME/ CFS/ SEID is used? A study comparing the prognosis of different diagnostic labels of fatigue found that patients with ME had the worst prognosis while patients with ‘postviral fatigue syndrome’ had the best (Hamilton, et al., 2009). This could mean that the patients destined to the worst prognosis were labelled with the ME diagnosis, or it might be explained as an adverse effect of being labelled with ME. Research points to the latter conclusion. Studies show that those who attribute the cause of symptoms fixedly to an exclusive organic origin or label themselves as having ‘ME’, engage in reduced physical activity and report worse fatigue than those who attribute symptoms to other factors (Vercoulen et al., 1998; Wilson et al., 1994; Chalder, Power, & Wessely, 1996). Thus, it seems that the terminology of CFS/ME/SEID does matter; as terminology is inextricably linked with how an individual conceptualises their illness and responds to symptoms (i.e. monitoring symptoms and avoiding activity), which in turn influences the experience of fatigue and disability.
It is important to bear in mind that these illness attributions are formed in the context of the high profile controversy around the aetiology of CFS. A UK survey published in 2013 identified that 89% of patient organisations thought the illness is physical, compared with 58% of newspaper articles and 24% of medical authorities (Hossenbaccus & White, 2013). Patients may form illness attributions based on these sources of information, perhaps in the absence of, or indeed in spite of the medical profession. Numerous authors have highlighted how a poor or absent relationship with a general practitioner can reinforce unhelpful illness behaviour and symptom interpretations (Dowrick, Ring, Humphris, & Salmon, 2004; Nimnuan, Hotopf, & Wessely, 2000; Salmon, Dowrick, Ring, & Humphris, 2004; Simon, VonKorff, Piccinelli, Fullerton, & Ormel, 1999). Many patients with CFS report dissatisfaction with their care (Deale & Wessely, 2001) and GPs report feeling ill equipped to make a diagnosis of CFS/ME (Chew-Graham, Dowrick, Wearden, Richardson, & Peters, 2010). These factors are likely to cause delays in treatment and reinforce the patient’s belief that there is single, toxic, organic and undiscovered cause for their symptoms.

Clearly trying to categorize illnesses into either biological or psychological models has created division among healthcare professionals and patients. This illustrates the importance of the biopsychosocial model, first expressed by George Engel (Engel, 1980). The advantage of this model is that it moves away from the traditional biomedical models of illness, which focus on discovering the pathology. Rather it focuses on understanding the illness and emphasises that disease is only one factor contributing to illness and illness behaviour. Indeed, most medical disorders have a complex aetiology, and, as with most illnesses, psychological and social factors can be important in understanding illness and helping patients recover.
1.3 Cognitive behavioural model of CFS

The biopsychosocial model of CFS proposes that CFS is caused by a complex interaction between biological, affective, behavioural and cognitive factors (Vercoulen, et al., 1998). The bio-psychosocial framework has been elaborated in Cognitive Behavioural (CB) models, which suggest that certain individuals are predisposed to CFS by a range of factors, such as genetic vulnerabilities, premorbid psychopathology and some immune abnormalities (discussed in section 1.2.5). For these predisposed individuals fatigue may be triggered by an organic insult (such as a virus), stress or social factors, and is subsequently maintained by a cycle of cognitive, behavioural and emotional responses. This formulation was later expanded into predisposing, precipitating and perpetuating factors (Surawy, Hackmann, Hawton, & Sharpe, 1995).

1.3.1 Predisposing factors

According to the CB model of CFS, the aetiological factors identified by genetic, immunological and prospective studies (outlined in section 1.2.5) may make an individual more vulnerable to developing CFS but are unlikely to be the main factors that drive or maintain the illness. These predisposing factors are thought to include; an experience of a severe illness (such as glandular fever) (Hickie, et al., 2006), a genetic predisposition to distress (Buchwald, et al., 2001), premorbid psychopathology (Clark, et al., 2011), high levels of negative perfectionism (Deary & Chalder, 2010; White & Schweitzer, 2000), neuroticism and chronic stress (Kato, et al., 2006) as well as childhood experiences, such as abuse (Heim, et al., 2009) and having a limiting illness (Viner & Hotopf, 2004).
1.3.2 Precipitating factors

Precipitating factors are factors proposed to trigger the initial symptoms. Prospective studies (discussed earlier in this chapter, section 1.2.5.4), have identified that the experience of a serious infection can trigger CFS for some people. Numerous studies have also identified major life events, such as divorce, job loss, death of close relative or friend, as clear precipitating factors in CFS (Deary, Chalder, & Sharpe, 2007; Hatcher & House, 2003). Chronic life difficulties, such as work problems and ill health in the immediate family, also increase the risk of CFS and be a trigger for some people (Hatcher & House, 2003). The CB model proposes that a toxic combination of predisposing and precipitating factors leads to the development of the initial symptoms of extreme fatigue. For example, dealing with chronic stress combined with a lack of social support leaves someone vulnerable to developing CFS and may precipitate its onset. Indeed, a study of patients who consulted primary care for fatigue, found a fast recovery in male patients, who were not providing care to others (e.g. older people or primary carer of children) and reported better perceived health, and fewer (serious) prolonged difficulties (Nijrolder, van der Windt, & van der Horst, 2009). Conversely, a more chronic course of fatigue was predicted by baseline pain intensity and less social support (Nijrolder, et al., 2009). The CB model proposes that these diverse factors can predispose some people to developing CFS and may play a role in triggering the initial symptoms.

1.3.3 Perpetuating factors

According to the CB model, in most individuals, symptoms cease when the trigger (e.g. a virus or stressful event) disappears or lessens. However, in some cases, especially for those who are vulnerable to develop CFS, perpetuating factors can cause the persistence of symptoms long after the initial trigger has abated. Precipitating factors include an individual’s interpretation of symptoms as well as their cognitive, behavioural and
emotional responses to symptoms (Deary, et al., 2007; Vercoulen, et al., 1998). For example, when faced with an acute infection or excessive stress, a predisposed individual may respond by continuing to press on in order to achieve their high standards (e.g. negative perfectionism). This behaviour may lead to on-going symptoms, which are more closely related to pushing too hard than to the initial insult or injury. The individual may interpret symptoms as a sign of ongoing physical illness and, concerned they have not recovered within the timeframe they would expect, begin to monitor their symptoms and engage in illness behaviours, resting for longer periods in an attempt to recover. However, reduced activity conflicts with individuals’ high standards and, in an attempt to meet expectations, they may engage in periodic bursts of activity, which ultimately exasperates symptoms and disability. In this way the CB model proposes that cognitive and behavioural factors play an important role in maintaining fatigue and disability in CFS (Figure 1).
These cognitive and behavioural responses to symptoms can result in further fear and avoidance of activity (fear avoidance) and physical deconditioning (i.e. loss of muscle and fitness). The person may become sensitized to lower levels of external stress and and, attributing symptoms to an unknown but organic origin, become hypervigilant for signs of illness. When the individual attempts to resume activates they experience normal signs of increased physiological arousal (e.g. aching muscles and fatigue after exertion), however, having reduced their activity levels they may misinterpret these signals as further evidence of illness. Over-time CFS patients may perceive the condition in an increasingly negative way, attributing a wide range of symptoms to the illness and

Figure 1 Boom and bust cycle of activity in CFS
believing symptoms to be harmful, uncontrollable and incurable. Thus, begin the vicious
cycle of chronic fatigue and disability (Figure 2).
Figure 2 The Vicious circle of perpetuating chronic fatigue and disability, adapted from (Sharpe, 1997).
1.4 Empirical support for the cognitive behavioural model of CFS

1.4.1 Illness beliefs

Several decades of research testing this model has proved fruitful. Studies have identified how people perceive and respond to symptoms play a key role in perpetuating fatigue and disability in CFS. Cross-sectional studies have identified that negative illness perceptions (i.e. believing symptoms to be harmful, uncontrollable and incurable) account for almost 40% of the variance in self-reported disability and around 30% of the variance of psychological well-being (Edwards, Suresh, Lynch, Clarkson, & Stanley, 2001; Heijmans, 1998; Moss-Morris, Petrie, & Weinman, 1996). It could be argued that these illness perceptions may simply develop in response to the chronicity of the condition. However, this is unlikely as prospective studies have identified illness perceptions are a risk factor in developing CFS (as discussed in section 1.2.5.5); furthermore, people with CFS attribute more symptoms to their condition and report more severe consequences when compared to patients with other chronic conditions (e.g. arthritis, diabetes and chronic back pain) (Dickson, Toft, & O'Carroll, 2009; Komaroff, et al., 1996a; Moss-Morris & Chalder, 2003; Moss-Morris, et al., 1996).

The CB model suggests that these illness perceptions guide the way in which patients cope with their illness (Leventhal, Meyer, & Nerenz, 1980). Indeed, negative beliefs about the identity (i.e. how many symptoms are linked to the illness label), time-line (i.e. expected duration of illness) and consequences of their illness has been shown to correlate with unhelpful coping strategies such as fear of injury or further damage and subsequent disengagement or avoidance of activity (fear-avoidance); which in turn are associated with greater psychological distress, illness worry and illness-related disability (Edwards, et al., 2001; Heijmans, 1998; Moss-Morris, 2005; Moss-Morris & Chalder, 2003; Moss-

1.4.2 Behavioural responses to symptoms

Research has identified two different types of coping responses; (i) avoidance and limiting behaviours; with associated beliefs that rest and reduced activity are helpful in controlling symptoms and (ii) all-or-nothing behaviours, whereby the individual pushes themselves to keep going until they ‘crash’ (Ray, Jefferies, & Weir, 1995; Skerrett & Moss-Morris, 2006; van der Werf, Prins, Vercoulen, van der Meer, & Bleijenberg, 2000). Research has identified that all-or-nothing behaviours during an acute infection is associated with the onset of CFS, whereas limiting behaviours are not (Spence, Moss-Morris, & Chalder, 2005). It is likely that coping and behavioural responses to symptoms change over the course of the illness. Once an individual has CFS, limiting behaviours are associated with increased disability, whereas all-or-nothing behaviours are more strongly associated with fatigue (Skerrett & Moss-Morris, 2006). Changing these cognitive and behavioural responses to illness have been identified as key mechanisms of efficacious treatments for CFS, thus demonstrating the importance of these factors in CFS (e.g. Nijs, et al., 2013; Wiborg, Knoop, Prins, & Bleijenberg, 2011).

1.4.3 Symptom focusing

The belief that symptoms are indicative of a long-term, harmful and biological condition would plausibly lead the individual with CFS to focus on and closely monitor symptoms. We know that within healthy individuals focusing attention on the body increases symptom reporting (Pennebaker, 2000). Therefore, it is unsurprising that a reportedly heightened focus on symptoms in CFS is associated with increased levels of fatigue and illness-related impairment (Knoop, Prins, Moss-Morris, & Bleijenberg, 2010; Moss-
Morris, 2005; Ray, et al., 1995; Ray, Jefferies, & Weir, 1997; Vercoulen, et al., 1998). Furthermore, reducing attention to symptoms has been shown to be partly responsible for reducing fatigue and disability within treatment for CFS (Heins, Knoop, Burk, & Bleijenberg, 2013; Moss-Morris, Sharon, Tobin, & Baldi, 2005b; Wiborg, et al., 2011).

1.4.4 Psychosocial influences

These cognitive and behavioural responses to symptoms are shaped by a range of factors, including social and cultural experiences. For example, how other people in the patient’s life, such as family and partners, understand and respond to the illness can be influential. A solicitous spouse or family member may limit the opportunity for the person with CFS to engage in activity and reinforce unhelpful illness beliefs and behaviours, thus further exasperating fatigue and disability (Band, Wearden, & Barrowclough, 2015). Conversely, discord between patients and significant others about the cause and validity of the patients symptoms is associated with increased patient distress, depression and poorer relationship quality (Band, et al., 2015). The response of significant others is particularly important in CFS given the high levels of stigma (Looper & Kirmayer, 2004) and social isolation (Assefi, Coy, Uslan, Smith, & Buchwald, 2003) associated with the condition.

In sum, the CB model proposes that symptoms in CFS are generated and/or maintained, not by one specific disease process, but by the interaction of multiple factors in distinct domains. Deary, et al. (2007) described this as ‘autopoietic cycle’; referring to a system consisting of several interacting processes which reproduce and maintain one another. The model is supported by the current data and the efficacy of treatments based on a CB model formulation.
1.5 Treatments

Current recommended treatments for CFS are cognitive behavioural therapy (CBT) and graded exercise therapy (GET) (NICE, 2007). Both are based on the CB model of CFS and tend to focus initially on perpetuating factors in an attempt to break the vicious cycle of symptom maintenance and dismantle the self-maintaining interlock of cognitive, behavioural and physiological responses, hypothesised to perpetuate CFS.

1.5.1 Cognitive Behavioural Therapy (CBT)

CBT for CFS aims to help the participant to change how they interpret symptoms and reduce the associated fear, symptom focusing and avoidance, which are assumed to be partially responsible for perpetuating the participant’s symptoms and disability (White, Sharpe, Chalder, DeCesare, & Walwyn, 2007). Participants are encouraged to see symptoms as temporary and reversible and not as signs of harm or evidence of fixed disease pathology. As the predisposing, precipitating and perpetuating factors are multifaceted and specific to the individual, CBT relies on the CB model to formulate a coherent, individualised case conceptualisation that forms the rational for treatment (Deary & Chalder, 2010). This model also acknowledges that the participant’s beliefs and behaviours are influenced by contextual factors, such as available information, attitudes of families and friends, and that these may also need to be addressed.

CBT treatment for CFS is usually structured as course of 10-14, one to one sessions between the person with CFS and a trained health professional (NICE, 2007). CBT treatments involve the following components: initial stabilisation of activity and rest, establishing a regular sleep pattern and then graded increases or changes in activity to work towards planned goals. CBT also actively addresses the participant’s understanding of their illness which may involve challenging unhelpful beliefs, e.g., about symptoms or
activity that may be preventing recovery (White, Sharpe, Chalder, DeCesare, & Walwyn, 2007). Techniques such as ‘thought records or diaries’ are used to encourage the patient to recognise unhelpful thought processes and generate alternative, more balanced appraisals.

1.5.2 Graded Exercise Therapy (GET)

GET for CFS aims to reverse the physical inactivity (deconditioning) that is thought to play a role in maintaining CFS; and to re-engage the participant in aerobic exercise (e.g. brisk walking) and physical activity (e.g. housework) (Edmonds, McGuire, & Price, 2004). Participants are encouraged to see symptoms as temporary and reversible, as a result of their current physical weakness, and not as signs of progressive pathology (White, et al., 2007). The rational is that reversing deconditioning and improving fitness and physical functioning will alter the person’s perception of effort and enable the body to gain fitness and strength; leading to a reduction in symptoms and an increase in activity capacity (Fulcher & White, 1997).

GET is delivered on a one to one basis by a trained exercise therapist, usually a physiotherapist (NICE, 2007). The number of sessions vary according to the treatment protocols used. The most widely used GET protocol within specialist CFS clinics provides a course of 10-14 sessions (White, et al., 2007). GET involves establishing an agreed baseline of physical activity, at a manageable and low level of intensity. The duration and intensity of the physical exercise is then increased slowly and carefully, at the right time for each participant. GET focuses on avoiding overexertion by advising participants not to exceed the agreed levels of physical exercise/activity but at the same time maintaining, rather than stopping, physical exercise/activity in the presence of symptoms. Recent approaches to GET advocate flexibility in the graded exercise
programs according to the individuals tolerance level (Nijs, Paul, & Wallman, 2008; Wallman, Morton, Goodman, Grove, & Guilfoyle, 2004). Thus, the level of activity is mutually reviewed on a regular basis and plans adjusted depending on the participant’s current health and symptoms. Techniques include heart rate monitoring and a keeping a record of daily activity.

1.5.3 Pragmatic Rehabilitation

Pragmatic rehabilitation is another treatment for CFS which follows the CB model. Pragmatic rehabilitation has elements in common with both CBT and GET but differs in that it starts with the explicit delivery of an explanatory model for patients’ symptoms (Powell, Bentall, Nye, & Edwards, 2004; Wearden, et al., 2006). The explanatory model focuses on factors that may be maintaining fatigue and activity limitations, including cardiovascular and muscular deconditioning, disturbed sleep–wake cycles, and the somatic manifestations of arousal. The patient and therapist then collaborate to design a rehabilitation programme based on addressing these factors. Recent trials have also assessed a multidisciplinary treatment approach which combines GET, CBT and some pharmacological treatment for specific complaints, such as sleep disorders (Houlton, Christie, Smith, & Gardiner, 2015; Vos-Vromans, et al., 2016). The results of these trials will be discussed in section 1.5.5.

1.5.4 Other treatments

Other treatments which do not follow the CB model of CFS include adaptive pacing therapy (APT), the Phil Parker Lightning Process® (LP) and pharmacological treatments. APT is espoused by patient support groups. It regards CFS as an organic disease process that is not reversible by changes in behaviour and which results in a reduced and finite amount (envelope) of available energy (Jason, 2008; Jason, et al., 2013). The aim of APT
is to achieve optimum adaptation to the illness, by helping the participant to plan and pace activity in order to reduce or avoid fatigue and achieve prioritised activities (Jason, et al., 2013). Therapeutic strategies consist of identifying links between activity and fatigue by use of a daily diary. Patients are encouraged to plan activity to avoid exacerbations, i.e. limiting stress, planning regular rest and avoiding activities that exceed 70% of their perceived energy envelopes. APT encourages vigilance for early warnings of exacerbation and when such signs are observed patients are advised to stop the activity in order not to exceed the finite envelope of energy. Increased activities are encouraged, if the participant feels able, and as long as they do not exacerbate symptoms.

The Phil Parker Lightning Process® (LP) is a trademarked intervention that claims to train individuals to recognize when they are stimulating or triggering unhelpful physiological responses (i.e. the stress response); and to help participants develop more appropriate responses to situations. Little is known about the theoretical underpinning or therapeutic techniques involved in the LP and no study to date has assessed the efficacy of the LP for CFS. A trial in the UK (the SMILE trial) is currently underway to compare specialist medical care with specialist medical care plus the LP for CFS (Crawley, Mills, Hollingworth, Deans, Sterne, Donovan, Beasant & Montgomery 2013). If LP is a viable treatment for CFS it shall be theoretically and therapeutically valuable to establish the specific components of the treatment which are beneficial.

1.5.5 Treatment efficacy

In support of the CB model for CFS, studies have found that treatments based on a CB formulation are the most effective treatments for CFS (Castell, Kazantzis, & Moss-Morris, 2011; Malouff, Thorsteinsson, Rooke, Bhullar, & Schutte, 2008; Marques, De Gucht, Gouveia, Leal, & Maes, 2015; Wearden, et al., 2010; White, Goldsmith, Johnson,
Chalder, & Sharpe, 2013). Whereas, little evidence has emerged for the efficacy of any pharmacological treatments, complimentary therapies or APT (Chambers, et al., 2006; NICE, 2007). Three Cochran reviews (Edmonds, et al., 2004; Larun, Brurberg, Odgaard-Jensen, & Price, 2016; Price, Mitchell, Tidy, & Hunot, 2008), three systematic reviews (Chambers, et al., 2006; Raine, et al., 2002; Whiting, et al., 2001) one non-systematic review (Clark & White, 2005) (Clarke & White, 2005), and three meta-analyses (Castell, et al., 2011; Malouff, et al., 2008; Marques, et al., 2015) have demonstrated CBT and GET have positive effects on fatigue and functioning in patients with CFS.

A meta-analysis by Castell, et al. (2011) compared the effects of CBT (n=16) and GET (n=5) trials and found both types of intervention presented similar overall post-treatment effects (g=0.33 and g=0.28 respectively) for CFS patients. These findings are further supported by recent randomized control trials (Burgess, Andiappan, & Chalder, 2012; Núñez, et al., 2011; Van Damme, Bulcke, Durnez, & Crombez, 2016; Vos-Vromans, et al., 2016; White, et al., 2011b; Wiborg, van Bussel, van Dijk, Bleijenberg, & Knoop, 2015), the most high profile and largest of these being the PACE trial (White et al., 2011). The PACE trial (n= 641) demonstrated superiority of CBT and GET in reducing fatigue and improving functioning over that of APT or specialised medical care alone (involving an explanation of CFS and generic advice, such as to avoid extremes of activity and rest). There was no clear superiority of either CBT or GET in their treatment effects; both equally improved outcomes of fatigue, functional impairment, anxiety, and depression (White, et al., 2011b). Similarly, positive but smaller effects have been found following CBT and GET delivered in routine clinical practice (Crawley, Collin, White, Rimes, Sterne & May, 2013; Fernie, Murphy, Wells, Nikčević, & Spada, 2016; Quarmby, Rimes, Deale, Wessely, & Chalder, 2007). These differences may be due to differences in the delivery or content of treatments given in routine clinical practice. For example, many
patients in NHS services appear to be offered five or six sessions whereas PACE trial participants attended 12–14 sessions (Crawley, Collin, White, Rimes, Sterne & May, 2013).

Fewer trials have assessed the efficacy of other CB based treatments. Two randomized controlled trails show positive effects of pragmatic rehabilitation (Taylor, 2004; Wearden, et al., 2010); one being a nurse lead home based treatment (Wearden, et al., 2010) and the other a patient led illness management group, plus one to one peer support (Taylor, 2004). These findings are collaborated by non-randomized, observational studies (Masuda, Nakayama, Yamanaka, Koga, & Tei, 2002; Schreurs, Veehof, Passade, & Vollenbroek-Hutten, 2011; Thomas, Sadlier, & Smith, 2008; Torenbeek, et al., 2006). However, reported treatment effects are smaller than that following CBT or GET, and the effects do not appear to be maintained at one year follow up (Wearden, et al., 2010). Similarly, trials of multidisciplinary treatment approach have shown only short-term improvements (Cox, 1999; Houlton, et al., 2015; Thomas, et al., 2008; Vos-Vromans, et al., 2016). These findings may reflect that fact that most CBT/GET trials have been delivered within secondary care and specialist treatment centres; which are associated with better treatment outcomes than primary care (Castell, et al., 2011; Marques, et al., 2015). Other accounts for these differences in treatment outcomes may be related to the level of training and experience of the providers, as well as the therapeutic alliance (Castell, et al., 2011; Huibers & Wessely, 2006; Wearden, et al., 2010). A meta-analysis of behavioural interventions for CFS found interventions delivered by psychologists or psychotherapists were more effective in reducing fatigue severity (Marques, et al., 2015).
1.5.6 Long term treatment efficacy

A systematic review of longitudinal studies, found that the benefits of CB treatments for CFS, including CBT, GET and pragmatic rehabilitation, were maintained at follow-up in about 40% cases (Cairns & Hotopf, 2005). Several subsequent longitudinal studies support the finding of maintained treatment effects of CBT and GET for CFS (Knoop, Stulemeijer, de Jong, Fiselier, & Bleijenberg, 2008; Nijhof, Bleijenberg, Uiterwaal, Kimpen, & van de Putte, 2012; Núñez, et al., 2011). Most recently a follow-up of the PACE trial found CBT and GET treatment effects were maintained after a median of 2.5 years after randomization, with no evidence of deterioration in overall health from end of treatment to follow-up (Sharpe, et al., 2015). However, maintained improvements in fatigue and functioning do not necessarily equate to recovery.

Recovery can be measured in a number of ways. The most meaningful depiction of recovery may be the individuals’ perception of improvement; both in terms reduced symptoms and the associated impact of symptoms everyday life. Several non-randomized studies (Flo & Chalder, 2014; Quarmby, et al., 2007) have found that 6 months after receiving CBT in routine clinical practice, over half of patients report feeling “better” or “much better” (57% to 60.8% respectively). Similar subjective improvements have been reported in randomized control trials of CB treatments for CFS, ranging from 70% (Deale, Husain, Chalder, & Wessely, 2001) to 40% (White, et al., 2013) reporting feeling “better” or “much better”.

Recovery can also reflect a return to premorbid levels of health and wellbeing. Some researchers have defined this as 1-2 standard deviations (SD) from the population mean of fatigue and functioning. The SD allows for fluctuation around baseline levels of fatigue and functioning (Deale, et al., 2001; Knoop, Bleijenberg, Gielissen, van der Meer, &
White, 2007; White, et al., 2013). Using this definition of recovery, a meta-analysis of RCT’s of CBT for CFS, reported that 50% of the patients improved to the point of no longer being clinically fatigued (Malouff, et al., 2008). The most recent and largest RCT to assess CFS recovery rates- the PACE trial- found that, 40% of patients were within 1SD of the normal range of fatigue following CBT and 33% following GET, one year after starting treatment. In terms of physical functioning, 52% of participants who received CBT were within 1 SD of the population mean and 53% of those who received GET (White, et al., 2013). Similar proportions of patients meet this definition of recovery in routine clinical practice. Knoop, et al., (2008) found 48% of patients were within 2 SD of the population mean of fatigue immediately after treatment; whereas, Flo and Chalder (2014) found 49% of their sample were within 1SD of normal level 6 months after receiving CBT in clinical practice.

The most objective measure of recovery entails no longer meeting the diagnostic criteria for CFS (Oxford and CDC criteria). Employing this criteria, early RCTs indicate that 23%-24% of patients fully recover following CBT (Deale, et al., 2001; Knoop, et al., 2008) and between 0% and 31% of the CFS patients show full recovery in routine clinical practice (Cairns & Hotopf, 2005). This large variability is likely to be due, at least in part, to the range of treatment protocols and delivery methods. Since then treatments have become more standardized. The recent PACE trial being the largest RCT to date in this area, provided treatment protocols for each of the arms of the multi-centred trial (CBT; GET; APT) (White, et al., 2013). They employed a stricter criterion for recovery; defined as no longer meeting the Oxford criteria for CFS (Sharpe, et al., 1991), combined with a self-rated improvement in overall health as ‘much better’ or ‘very much better’. Using these criteria they found that 22% of patients recovered after CBT, 22% after GET, 8% after APT and 7% after specialist medical care (White, et al., 2013). The odds for
recovery after CBT or GET were 3.36 and 3.38 respectively when compared to APT. Similar proportions recovered when the additional condition of not meeting the CDC-1994 criteria for CFS (Fukuda et al., 1994) was applied. These findings confirm that recovery from CFS is possible and cognitive behavioural treatments currently offer the mostly likely route to achieving this.

However, whilst it seems CB treatments for CFS provide some lasting benefits, some people with CFS have difficulty making further improvements and maintaining changes in the long term. In their 5-year longitudinal study, Deale et al. (2001) reported 63% of patients were within 1 SD of the normal population mean of fatigue, 6 months post CBT for CFS, however this dropped to 28% when assessed 5 years post treatment. Similarly, though 63% were within normal range of functioning 6 months’ post CBT, this dropped to 48% over 5 years (Deale et al., 2001). This attenuation of treatment effect may be because patients fall into old habits of thinking or responding to symptoms. However, it is important to bear in mind that there was a high attrition rate in this study (at 5 years n=25), thus these results should be interpreted with caution.

The prognosis for people with CFS who do not receive treatment is poor. Naturalistic follow-up studies have found that, if untreated, full recovery rates are 5% and the median proportion of patients who improve over-time, without intervention is less than 40% (Cairns & Hotopf, 2005). In light of this, the evidence for the effectiveness of CBT and GET is surely auspicious. However, despite favourable outcomes for some patients with CFS, CB treatments for CFS have been met with extreme cynicism from those espousing a purely biological aetiology of the condition (Twisk & Maes, 2008). Despite evidence to the contrary, patient groups resolutely espouse unwavering support for APT as an efficacious treatment for CFS (Kindlon, 2011). Advice dispensed by some CFS groups
may have a negative effect on recovery, for example by advocating the avoidance of activity (Surawy, et al., 1995). Indeed, one study found that being a member of a support group predicted less favourable response to CB based treatments (Bentall, Powell, Nye, & Edwards, 2002). Some patient organisations and researchers have claimed that behavioural and psychological treatments for CFS pose harm to patients and do not tally with results from patient surveys (Twisk & Maes, 2008). This has been accompanied by calls for NICE to revoke their recommendation that all patients with CFS should be offered CBT or GET (Coyne & Laws, 2016; Shepherd, 2013, 2016; Wilshire, Kindlon, Matthees, & McGrath, 2016).

However, the claim that behavioural treatments cause harm is empirically unfounded; analysis of adverse events after the PACE trial found no difference in the number or severity of adverse events reported in GET or CBT compared to APT or standard medical care (Dougall, et al., 2014). Indeed, deterioration in physical function was more likely after APT (Dougall, et al., 2014). The safety of cognitive behavioural treatments for CFS has been further supported by a number of RCTs conducted by a variety of research groups (Heins, et al., 2010; Price, et al., 2008).

Thus, to date CBT and GET offer the most effective and safe treatments to improve levels of fatigue and functioning in CFS. Nevertheless, it is clear that for some people with CFS, CB treatments do not result in clinically significant improvements. Even with effective treatment, a relatively small proportion of patients fully recover (Knoop, et al., 2007; White, et al., 2013) and even for those that do recover, the risk of relapse increases over time (Deale, et al., 2001). Work is needed to optimise treatment efficacy for CFS and bolster long-term treatment effects. One way of doing this could be to add more treatment sessions. A meta-analysis found higher number of treatment sessions improved efficacy
(Castell, et al., 2011). Increasing the number of sessions or offering alternative, more flexible methods of treatment delivery (e.g. over the internet, Nijhof, et al., 2012; or telephone, Burgess, Andiappan, & Chalder, 2012) may prove therapeutically beneficial. Another avenue to optimize treatment effects would be to explore factors that predict and mediate treatment outcomes. By identifying factors that predict treatment response, we can establish who will benefit most from certain treatments and tailor service/treatment delivery and allocation accordingly. By identifying factors that mediate the effect of existing treatments, we can capitalize on effective treatment components and further strengthen our theoretical understanding of CFS.

1.5.7 Predictors of treatment outcome

Despite claims that some diagnostic classifications identify patients characterised by a more severe neuroimmune disorder (e.g. CCC and ICC), it seems CB treatments are equally effective across diagnostic classifications (Brurberg, et al., 2014). Patient characteristics which do predict how an individual will respond to CB treatments include, older age, increased disability, weight fluctuation and pain (Cairns & Hotopf, 2005; Cella, Chalder, & White, 2011a; Chalder, Godfrey, Ridsdale, King, & Wessely, 2003; Crawley, Collin, White, Rimes, Sterne & May, 2013; Flo & Chalder, 2014; Quarmby, et al., 2007). Some studies suggest the severity of fatigue pre-treatment is also predictive of worse treatment outcomes (Heins, et al., 2010; Kempke, et al., 2010); however, others find do not find this effect (Bentall, et al., 2002; Chalder, et al., 2003; Flo & Chalder, 2014; Kempke, et al., 2010). This discrepancy may be due to the different treatment protocols. For example, Kempke, et al. (2010) found that the initial level of fatigue predicted response to a multi-component treatment for CFS, which varied in content, duration and intensity for each patient (i.e. some received additional psychoeducational content; some attended group sessions weekly, others monthly). This type of flexible, group based
treatment for CFS may be most effective for those with less fatigue pre-treatment; whereas, other treatments such as individual face-to-face CBT may be equally effective for those mildly to more severely fatigued (e.g., Flo & Chalder, 2014). Similarly, the duration of illness seems to predict response to some treatments for CFS but not others. The duration of illness does not appear to predict how people will respond to CBT and GET for CFS (Bentall, et al., 2002; Chalder, et al., 2003; Kempke, et al., 2010), suggesting that these treatments for CFS can be effective at any stage of the illness trajectory. However, Wearden, Dunn, Dowrick, and Morriss (2012) found longer illness durations predicted poorer treatment outcomes for nurse lead, home based pragmatic rehabilitation and treatment as usual (combined treatment arms), at 70 weeks follow-up. It might be that for those with longer illness durations more intensive, specialist delivered treatments are required.

Certain beliefs about the illness and coping in general, are also associated with treatment response. For example, believing that expression of emotions is unacceptable is related to worse outcomes for CFS (Flo & Chalder, 2014) and a poorer prognosis (Cairns & Hotopf, 2005; Sharpe, Hawton, Seagroatt, & Pasvol, 1992); whereas, conversely, processing, expressing and accepting distressing emotions has been found to predict more favourable responses to CB treatments for CFS (Godfrey, Chalder, Ridsdale, Seed, & Ogden, 2007). Illness attributions pre-treatment also influence treatment outcome. Patients with CFS who believe that their illness is primarily physical are more likely to respond poorly to CBT (Butler, Chalder, & Wessely, 2001) and experience symptom deterioration, either with or without treatment (Heins, et al., 2010). This may be related to associated unhelpful responses to symptoms. For example, attributing symptoms to a physical cause predicts less activity (Chalder, Power, & Wessely, 1996) which in turn may result in deconditioning and further exasperation of symptoms (Marques, De Gucht,
Gouveia, Leal, & Maes, 2015). Other specific cognitive and behavioural responses to symptoms have also been identified as predicting treatment outcomes in CFS. Symptom focusing, catastrophic beliefs about the consequences of engaging in activity, and a passive activity pattern have been found to predict less improvement following CB treatments for CFS (Cella, et al., 2011a; Flo & Chalder, 2014; Prins, et al., 2001). These relationships further support the CB model of CFS and highlights the need for patients to receive a coherent bi-psychosocial explanation of the condition, highlighting the multiple contributory factors of CFS.

One of the most important factors in predicting how an individual will respond to CFS treatments is psychiatric comorbidities. In particular, having co-morbid depression has been consistently found to predict poorer response to CBT for CFS (Bentall, et al., 2002; Bonner, Ron, Chalder, Butler, & Wessely, 1994; Cairns & Hotopf, 2005; Flo & Chalder, 2014; Kempke, et al., 2010; Prins, Bleijenberg, & Rouweler, 2005; Sharpe, et al., 1992). A latent class analysis found that those with CFS who responded poorly to CBT had higher levels of anxiety pre-treatment than those who responded well (Cella, et al., 2011a). Similarly, Wearden, et al. (2012) found depressive symptoms at baseline significantly moderated the effect of pragmatic rehabilitation on fatigue at 1-year follow-up. It may be that those with more severe mood disorders are more resistant to treatment and may benefit from additional treatment sessions (Wearden, et al., 2012) or increased number of treatment hours (Malouff, et al., 2008). These findings are of particular pertinence given depression and anxiety represent the most common co-morbid disorders among CFS patients (Cella, et al., 2013).

These studies highlight the range of different factors that predict how an individual may respond to CB treatments for CFS. Auspiciously many of these factors are amendable.
However, whether changes in these predictive factors equate to improved treatment outcomes is a separate question. In order to assess the mechanisms of change underlying the efficacy of CB treatments for CFS, mediation analyses are needed.

1.5.8 Mediators of treatment outcome

Pre-post treatment designs have assessed factors that mediate improvements in fatigue and functioning over the course of treatment for CFS. These studies have found that key mediators of CB treatments for CFS (CBT, GET and pragmatic rehabilitation) are changes in cognitive and behavioural factors such as, fear and avoidance of activity, symptom focusing and self-efficacy (Chalder, Goldsmith, White, Sharpe, & Pickles, 2015; Moss-Morris, Sharon, Tobin, & Baldi, 2005a; Stahl, Rimes, & Chalder, 2014b; Wearden & Emsley, 2013; Wiborg, et al., 2011). These findings correspond with longitudinal mediation studies (Chalder, et al., 2015; Stahl, Rimes, & Chalder, 2014a; Wearden & Emsley, 2013). The FINE trial of a nurse delivered pragmatic rehabilitation programme for CFS found changes in catastrophizing and activity limitation were associated with a reduction in fatigue following treatment (Wearden & Emsley, 2013). Similarly, a mediation analysis of the PACE trial found that changes in avoidance behaviours and increased walking distance, alongside changes in fear avoidance beliefs and self-efficacy were associated with better fatigue and functioning outcomes post CBT and GET (Chalder, et al., 2015).

Interestingly, an increased fitness capacity and physical activity do not appear to mediate treatment effects. One study objectively measured levels of physical activity via a motion sensor watch, worn for 12 days before and after treatment (Wiborg, Knoop, Stulemeijer, Prins, & Bleijenberg, 2010). They found that, although CBT effectively reduced fatigue and improved functioning, it did not change levels of physical activity. Furthermore,
changes in physical activity were not related to changes in fatigue. Similarly, though some improvements in objectively measured fitness (e.g. step test) have been reported, changes in fitness have not been shown to mediate the effects of treatments (Chalder, et al., 2015; Marques, et al., 2015; Moss-Morris, et al., 2005a; Wearden & Emsley, 2013). It may be that these studies have not adequately assessed what constitutes a meaningful increase in activity levels for the patient. For example the motion sensor used by Wiborg, et al. (2010) measures movement but not necessarily physical activity per se. Perhaps alternative objective measures are needed to assess physical activity more accurately. Alternatively, these findings may suggest that increases in physical fitness and activity do not necessarily lead to improved fatigue or functioning. It seems that treatment effects may arise primarily from changes in cognitive and behavioural responses to symptoms rather than necessarily getting fitter.

Though broadly consistent, mediation studies highlight different cognitive and behavioural mechanisms of treatment. In particular, there are inconsistent findings regarding the role of symptom focusing. Some studies have found reducing symptom focusing is a key mechanism of CBT for CFS (Moss-Morris, et al., 2005a; Wiborg, et al., 2011) whereas others found a weak association in mediating CBT or GET (Chalder, et al., 2015) or not at all in the case of pragmatic rehabilitation within the FINE trial (Wearden & Emsley, 2013). Methodological differences may account for this variability; for example Wiborg, et al. (2011) adapted a version of the Pain Coping Inventory, including 8 items to assess symptom focusing (Jensen, Turner, Romano, & Strom, 1995), and Moss-Morris, et al., (2005a) used the 9 item ‘focusing on symptoms’ subscale of the Illness Management Questionnaire (Ray, Weir, Stewart, Miller, & Hyde, 1993). Whereas both PACE (Chalder, et al., 2015) and FINE trials (Wearden & Emsley, 2013) used the 6 item symptom focusing subscale on the Cognitive Behavioural Response to Symptoms.
Questionnaire (CBSQ; Skerrett & Moss-Morris, 2006). Perhaps the CBRQ is less sensitive at detecting change in symptom focusing than the others. Another explanation for this disparity may be the large heterogeneity within CFS; a mechanism of change for one individual may be vastly different to that of another. It may also reflect heterogeneity in treatment content and delivery. Even when the same process changes it may be achieved through different means; for example, reducing symptom focusing and fear-avoidance of activity may be a mechanism of both CBT and GET but achieved through different techniques.

1.6 Gap in the literature
Mediation studies of CBT and GET have provided good support for the CB model of CFS. Findings suggest that targeting specific cognitive and behavioural factors could enhance treatment effects. However, the specific cognitions and behaviours measured in these studies explain only a relatively small amount of variance in treatment effect (Deary, et al., 2007; Knoop, et al., 2010). Thus, other processes of change may be occurring during treatment that, as yet, have eluded investigation; either through measurement error or omission. Two themes in particular have been espoused for further investigation; symptom appraisal (Petrie & Weinman, 2003) and attention (Deary, et al., 2007). Though self-report measures have gone some way in assessing the explicit facets of these concepts, such as self-reports of symptom focusing and catastrophic interpretation of symptoms, few studies have experimentally assessed how people with CFS appraise and attend to illness-related information at more implicit, habitual levels of information processing. A hypervigilance for somatic cues, and/or bias to interpret benign information as health threatening may reinforce unhelpful cognitive and behavioural responses to symptoms and thus perpetuate chronic fatigue and disability. Experimental methods can help us explore some of these more habitual cognitive processes in CFS.
This will be the focus of the work presented in this thesis. The next chapter will introduce the concept of cognitive biases and explain how they may play a role in CFS.
Chapter 2 Information processing

2.1 Chapter overview

The previous chapter outlined a number of cognitive and behavioural factors, amongst others, which are important in maintaining fatigue and disability in CFS. Self-report studies exploring a number of these factors have proved fruitful. However, data regarding cognitions and behaviours that may occur at earlier, more implicit levels of processing is lacking. The next chapter will introduce the concept of cognitive processing biases and explain how they may play a role in CFS.

The chapter begins by introducing the concept of information processing and describing how, theoretically, information processing can become biased to detect and preferentially process illness-specific information. Two key biases in information processing are defined, attentional bias and interpretation bias, followed by contextual information about how these biases are measured. The chapter draws on the plethora of experimental work within anxiety and depression, to demonstrate the methodological and conceptual underpinning of cognitive bias research; and highlights experimental work in the pain literature, drawing parallels between chronic pain and CFS. This chapter also outlines the hypothesised mechanisms underpinning these cognitive biases, namely attentional control and attentional malleability.

2.2 What is information processing?

At the heart of cognitive psychology is the idea of information processing. A common analogy of information processing is to consider how a computer processes information; the computer takes in information, codes (i.e. changes) information, stores information in a limited capacity central processor, uses information, and produces an output (retrieves info). Similarly, humans process information in the environment
through a number of processing systems (e.g. attention, perception, and short-term memory); these processing systems transform or alter the information in systematic ways, which results in behavioural responses.

However, human information processing is clearly more complex than this computer analogy suggests. How humans process incoming information is influenced by a number of conflicting emotional and motivational factors and unlike computers, people have the capacity for extensive parallel processing (i.e. a number of complex processing tasks occur at the same time). In order to appropriately respond to information and avoid overloading our limited working-memory capacity (Miyake & Shah, 1999), humans need to select the most important information for further processing (Broadbent, 2013). This process is known as ‘selective attention’.

Treisman (1969) proposed that information is selected based on a recognition threshold, i.e. people have lower thresholds for certain information, the lower the threshold, the more easily and likely an input is to be perceived. Recognition thresholds are lowered by several factors including: (i) context and expectation- certain information that is context relevant or expected, can become momentarily more pertinent and accessible; and (ii) subjective importance- words that possess subjective importance, such as ‘help’ or ‘fire’, or information with salient personal meaning, will have a lower threshold and will be able to come into awareness more easily. This filtering system of incoming information is built for maximum economy: while facilitating the potential for important, unexpected, or relevant stimuli to be perceived, it ensures that those messages sufficiently attenuated do not get through much more than the earliest stages of analysis, preventing an overburden on sensory processing capacity (Shiffrin & Schneider, 1977).
The processes described thus far all assume that the environmental stimuli are driving how information is processed. These processes are referred to as ‘bottom-up’, ‘stimulus driven’ or ‘automatic’ and are thought to occur very quickly, outside of our control and awareness (Isen & Diamond, 1989; Schneider & Shiffrin, 1977; Shiffrin & Schneider, 1977). However, although it is agreed that stimulus driven information in cognition is important, an individual’s expectations and past experiences are also important in determining how information is processed. These influences are known as ‘top-down’, ‘goal-directed’ or ‘strategic’ and refer to more controllable, intentional and conscious processes (Isen & Diamond, 1989; Schneider & Shiffrin, 1977; Shiffrin & Schneider, 1977).

These ‘top-down’ processes are thought to occur at later stages of the information processing system, after the stimuli has been selected; and serve to assimilate and organize the selected information (Buschman & Miller, 2007). For example, pain is known to capture ‘bottom up’ attention when it is new or novel, intense, or is threatening (Legrain, et al., 2009). This means that vague and commonplace pains like epigastric pain, can often be ignored. However, ‘top down’ attention can also direct attention towards painful events – for example, if an individual is expecting pain or they are particularly fearful and catastrophic about the experience of pain (Keogh, Ellery, Hunt, & Hannent, 2001; Keogh, Thompson, & Hannent, 2003).

However, the dichotomy of these ‘top-down’ and ‘bottom-up’ processes has been subject to debate (Awh, Belopolsky, & Theeuwes, 2012; Moors & De Houwer, 2007). It is thought that ‘bottom up’ attention, while unintentional, is influenced by ‘top-down’ processes; and vice versa. For example, ‘bottom-up’ attentional capture of novel, pain related information can act as a distraction from ‘top-down’ task-relevant goals;
conversely, a ‘top-down’ strategy to monitor or expect pain can sensitize the ‘bottom-up’ recognition and attentional selection of pain related information.

2.3 Biases in information processing

Cognitive models propose that how information is processed can become biased for certain types of information. For example, Beck’s Schema Theory of Emotion and Cognition (Beck & Clark, 1988) proposes that cognitive schema (i.e. core knowledge and related beliefs about people, situations, and events) guide the encoding, comprehension, and retrieval of new information (i.e. information processing) (Beck & Clark, 1988). Beck and Clark (1988) propose that people with mood disorders have maladaptive schemata; i.e. predominantly negative (depression) or fearful (anxiety) ways of viewing the world, which bias the processing of incoming information for schema congruence. Depressed individuals will selectively process negative information related to loss and failure, whereas anxious individuals will selectively process information related to danger and threat (Beck & Perkins, 2001). Cognitive models proposed more recently maintain that some groups of people (e.g. anxious and depressed) preferentially process certain types of information e.g. negative and threatening information in anxiety and depression. However, rather than a ‘schema’ driving these processes these models refer to distorted cognitive processes, that may be determined by a genetic vulnerability or poor attentional control (De Raedt & Koster, 2010; Derakshan & Eysenck, 2009; Disner, Beevers, Haigh, & Beck, 2011; Eysenck & Derakshan, 2011; Eysenck, Derakshan, Santos, & Calvo, 2007; Hertel & Mathews, 2011; Joormann & D'Avanzato, 2010). These issues are discussed further in section 2.5.

Two biases in information processing have dominated the research in this area; attentional bias and interpretation bias. Attentional bias refers to the preferential allocation of
attention towards certain types of information. Interpretation bias refers to the tendency or habit to interpret ambiguous information in particularly negative, threatening or schema-congruent ways. The next section will briefly describe the types of experimental paradigms used to assess these processing biases, followed by an overview of some of the key research findings using these experimental methods.

2.3.1 Experimental research into cognitive biases

Experimental paradigms have been developed that tap into these cognitive biases at both early, automatic or ‘bottom-up’ stages of processing as well as biases at later more elaborative, ‘top-down’ stages of processing. Tasks attempting to tap into ‘automatic’ cognitive biases measure how an individual responds to stimuli (usually measured by reaction times) presented very briefly and subliminally (i.e. below the threshold of conscious awareness). Tasks measuring cognitive biases at later stages of ‘top-down’ processing, measure responses to stimuli after the person has had time to recognize the stimuli and reflect upon it.

For instance, a commonly used measure of attentional bias is the visual probe task (VPT; MacLeod, Mathews, & Tata, 1986). In this task, participants are presented with two stimuli, which have contrasting valence, i.e., a threatening versus a neutral word or image (an illustration of a trial in the VPT is presented in Appendix C, Figure 5). According to the principles of information processing, these two stimuli will be competing for attentional selection and processing within our limited working-memory capacity (Miyake & Shah, 1999; Treisman, 1969). The person will direct their attention to the stimuli that is of most personal and contextual salience. In this task, the direction or allocation of their attention is measured by reaction times to probes that replace the stimuli. Faster reaction times to probes replacing the threatening stimuli, indicates an
attentional bias to this type of information. In order to tap into different stages of processing (i.e. automatic versus strategic), the conditions under which stimuli are presented is adapted. To assess ‘bottom-up’ or automatic attentional capture, stimuli are presented very briefly (under 500ms) and under masked conditions (i.e. a string of letters appears immediately before and after the stimuli). To assess ‘top-down’ ‘strategic’ attentional processes, stimuli are presented for longer durations (over 500ms), which allows time for the individual to exert effortful attentional control to direct their attention to task-relevant or goal-driven information (Bradley, Mogg, Falla, & Hamilton, 1998).

Similarly, tasks that measure interpretation biases have been adapted to tap into different stages of processing. Rapid, ‘automatic’ or spontaneous interpretations of stimuli are assessed by reaction times indicating the immediate interpretation of ambiguous information (on-line tasks). Tasks that assess interpretation biases that occur at later stages of processing (off-line tasks), allow participants time to reflect on the ambiguous materials without being forced to report the first inference that comes to mind; for example, writing five words that come to mind after hearing homophones (e.g. ‘pain’ pane’). More detail on these and other measures of attention and interpretation bias is provided later in the thesis (Chapter 2, section 2.5)

Using these and other, similar, experimental paradigms studies have identified that healthy people tend to show positive biases in processing information (Pool, Brosch, Delplanque, & Sander, 2016); preferentially attending to positive over neutral stimuli and interpreting ambiguous information in a particularly positive way. Conversely, clinical populations, for example people with anxiety and depression disorders, have a distinct lack of positive biases and show attention and interpretation biases for negative, disorder-congruent information. For example, in generalized anxiety disorder (GAD) attention is
‘captured’ by salient, threatening information in the environment (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van Ijzendoorn, 2007), and people with GAD tend to interpret ambiguous information as less benign and more threatening in general, compared to healthy people (Anderson, et al., 2012; Eysenck, Mogg, May, Richards, & Mathews, 1991; Mathews, Richards, & Eysenck, 1989; Mogg, Baldwin, Brodrick, & Bradley, 2004). However, a consistent limitation of the interpretation bias studies in GAD is that they are unable to distinguish whether the bias occurs when ambiguity is first encountered (on-line), or only later on reflection (off-line). Studies in social anxiety disorder (SAD) have used both on-line and off-line interpretation paradigms and have identified that, compared with non-anxious controls, people with SAD interpret ambiguous material more negatively and less positively, both when reflecting on situations (i.e. offline) and in the moment (i.e. online) (Amir, Beard, & Bower, 2005; Amir, Prouvost, & Kuckertz, 2012; Hirsch, Clark, & Mathews, 2006; Hirsch & Mathews, 2000; Voncken, Bögels, & Peeters, 2007; Voncken, Bögels, & de Vries, 2003).

Experimental research in depression has identified similar cognitive processing biases, but occurring at different stages of information processing and for content specific to depression (Mogg & Bradley, 2005; Mogg, Bradley, & Williams, 1995). For example, people with clinical depression show attentional biases for stimuli relating to themes of loss and sadness, but only when presented for longer, not shorter durations (Peckham, McHugh, & Otto, 2010). This indicates that while attention may not be ‘captured’ by depression relevant information, attention may be held longer by this type of information. Recently, studies have also shown that, not only do people with depression preferentially attend to negative information, but that they also avoid positive information (Winer & Salem, 2016).
In terms of interpretations, similar patterns of processing biases have been identified. A meta-analysis of interpretation biases, showed that people with clinical depression interpreted information in a more negative and less positive way than healthy participants when interpretation biases were measured using ‘off-line’ tasks (i.e. tapping into later elaborative or ‘top down’ interpretations); but not ‘on-line’ tasks (i.e. tapping into spontaneous interpretation when material is first encountered). These findings for biases occurring at later more elaborate stages of processing may relate to the ruminative nature of depression (Donaldson, Lam, & Mathews, 2007; Koster, De Lissnyder, Derakshan, & De Raedt, 2011).

2.3.2 Do cognitive biases matter?

It seems that cognitive biases in anxiety and depression are hallmarks of these conditions; but do these cognitive biases matter? To what extend are these biases a bi-product of the condition; and to what extent do they have an active role in maintaining symptoms?

Consider the computer processing analogy referred to at the start of this chapter. If the inputted information is consistently negative, and ambiguous information is encoded as negative, the resulting output is likely to reflect the negative information that has been processed. Similarly, an individual who constantly attends to threatening information in their environment (attentional bias) and tends to interpret ambiguity in a particularly threatening way (interpretation bias) is likely to have a heightened sense of threat. Cognitive models propose that these mechanisms reinforce already salient concerns (e.g. schemas) and play a key role in maintaining symptoms of anxiety, depression and distress.
Cross-sectional and longitudinal studies have gone some way supporting this hypothesis. Studies have demonstrated that not only do people with anxiety and depression have cognitive biases for condition-congruent information but also, importantly, these biases can be associated with increased symptom reporting and other clinically relevant outcomes (Bar-Haim, et al., 2007; Dickson, 2015; Hirsch, Meeten, Krahé, & Reeder, 2016b). It is still unclear, however, whether this is indicative of a causal role of cognitive biases on symptoms (i.e. biases result in symptoms), or indeed vice-versa (i.e. symptoms result in biases) (Van Bockstaele, et al., 2014).

In support of the causal hypothesis of cognitive biases, several prospective studies have shown that an increased attentional bias is predictive of later stress vulnerability (Pérez-Edgar, et al., 2010) and increased fear responses; including biological markers of distress, such as elevated cortisol levels and cardiovascular activity (Egloff, Wilhelm, Neubauer, Mauss, & Gross, 2002; Fox, Cahill, & Zougkou, 2010). For instance, Fox, Cahill, and Zougkou, (2010) found that in a sample of healthy university students, an attentional bias towards threat at baseline, predicted their cortisol response to a real-life stressor (i.e. an exam period) 8 months later. This suggests that attentional biases are a precursor of increased anxiety in response to stess. However, the absence of large-scale longitudinal, predictive studies constitutes a major gap in the literature. Furthermore, some studies have found evidence for the inverse relationship, i.e. symptoms precede the onset of an attentional bias (Koster, Crombez, Van Damme, Verschuere, & De Houwer, 2004; Van Damme, Crombez, Hermans, Koster, & Eccleston, 2006). A review of the relationship between attentional biases and anxiety suggests that current evidence points to bidirectional, maintaining, or mutually reinforcing relation; rather than a strictly causal one (Van Bockstaele, et al., 2014).
2.3.3 Cognitive bias modification studies (CMB)

Another line of research to test the causal/ maintaining role of cognitive biases, has been the development of cognitive bias modification techniques (CBM). CBM aims to modify the attention or interpretation bias, by repeatedly training attention towards more positive or benign information, or reinforcing positive or benign resolutions of ambiguity (respectively). CBM can test the causal relationship between cognitive biases and symptoms by experimentally manipulating the bias and measuring any associated change in symptoms. CBM is discussed in more detail in subsequent chapters (Chapter 8 and Chapter 9 in particular). The following paragraphs, highlight some key findings from CBM studies in the anxiety and depression literature, where most of this research has been conducted, which illustrate the potentially maintaining role of cognitive biases in these conditions.

2.3.3.1 CBM in Anxiety

A recent meta-analysis pooled data from children and adults with anxiety, who had received CBM for attentional biases (Price, et al., 2016b). The study found that, when CBM was effective at shifting the attentional bias, there were associated reductions in symptoms. Furthermore, the degree of change on attentional bias mediated improvements in levels of anxiety. This provides support for the hypothesis that attentional biases maintain some core aspects of anxiety. However, it should be noted that across the heterogeneous sample, (including GAD, SAD and other anxiety disorders), levels of anxiety did not differ between those who had completed CBM or the placebo training; and reduced attentional bias only mediated the treatment effects in younger groups and those who completed the CBM training in the lab. This suggests that, CBM thus far is only effective at modifying attentional biases in some groups and under certain conditions. These findings correspond with other meta-analyses of attentional bias CBM.
There have been a number of meta-analyses of CBM studies which have aimed to modify interpretation biases in anxiety disorders. A recent meta-analysis by Menne-Lothmann, et al., (2014) found that CBM can be effective at facilitating more benign interpretations of ambiguity, and importantly the attenuation in interpretation biases is associated with a range of clinically important outcomes, such as reduced anxiety, worry, rumination and intrusive memories. These findings are supportive of the causal role of interpretation biases in the maintenance of anxiety disorders. However, similarly to the attentional bias CBM research, findings are not always consistent. Modifying IB in sub-clinical populations who have high anxiety sensitivity (i.e. fear of bodily sensations related to anxiety, such as dizziness or a racing heart), do not result in changes in fear/anxiety post CBM training (Clerkin, Beard, Fisher, & Schofield, 2015; MacDonald, Koerner, & Antony, 2013; Steinman & Teachman, 2010). Perhaps to assess and modify interpretations of bodily sensations, other sensory methods are required.

2.3.3.2 CBM in Depression

CBM studies in depression have similarly found mixed results. A meta-analysis of clinically depressed populations, found CBM had a medium effect on reducing both attention and interpretation biases when these studies were grouped together (Hallion & Ruscio, 2011). When CBM for attention and interpretation were analysed separately, the effect was stronger for interpretation than for attention biases (Hallion & Ruscio, 2011). However, neither CBM for attention or interpretation biases significantly modify levels of depression post intervention. The lack of change across the CBM studies is likely to be due, in part, to the different CBM protocols. Hallion and Ruscio (2011) included CBM
that administered just one training session, which arguably is not sufficient for any meaningful change to occur. Studies which assess participants before and after completing multiple CBM training sessions have found more promising results. For instance, Williams, Blackwell, Mackenzie, Holmes, and Andrews (2013) found that interpretation bias training reduced depressive symptoms in a group of clinically depressed participants. Importantly, this change was at least partially mediated by the change in interpretation bias; thus supporting the hypothesis that interpretation biases are maintaining some core aspects of depression. In terms of attentional bias CBM, recent papers have provided some indications, that under certain conditions, training aimed at modifying attention biases can be effective in depression (Baert, Koster, & De Raedt, 2011; Blackwell, et al., 2015; Wells & Beevers, 2010). However, whether changes in attentional bias lead to symptom reduction in depression is still unclear.

It is fair to say that CBM research has provided mixed results. There is no single protocol for CBM and effect sizes for changing cognitive biases are modest at best (Mogoase, David, & Koster, 2014). Some studies fail to demonstrate a significant change in a bias, and even when change in a bias is observed it is not always associated with changes in symptoms (Beard, 2011; Hakamata, et al., 2010; Hallion & Ruscio, 2011; Mogoase, et al., 2014). A particularly critical meta-analysis of CBM in anxiety and depression concluded that while ‘CBM may have small effects on mental health problems….it is also very well possible that there are no significant clinically relevant effects.’ (Cristea, Kok, & Cuijpers, 2015).

However, crucially, this meta-analysis combined data from a range of disorders and did not differentiate among them in the analysis, nor did they assess whether the benefits of CBM are moderated by type of disorder. Furthermore, they pooled the results of CBM
studies which were targeting different biases (attention and interpretation) and using a range of different techniques (CBM, concreteness training and avoidance training). This analytic strategy makes it difficult to tease apart specific causal processes, and to assess the effectiveness of different techniques in modifying biases for different disorders. Importantly, Cristea, et al. (2015) determined the effects of CBM on symptoms without examining whether CBM had actually been effective at modifying the bias in the first place. If CBM does not change the bias (which is after all the treatment target and assumed mechanism of CBM), then associated changes in other clinical outcomes cannot be expected.

Clearly, much more work is needed in CBM before any definitive conclusions can be drawn about the malleability of cognitive biases and the associated benefits of modifying cognitive biases. What experimental research has established, thus far, is that cognitive biases operate at various stages of information processing in both anxiety and depression. There is also growing evidence from CBM and longitudinal studies in anxiety and depression, that these biases are not merely mood-dependent correlates of the disorder, but rather may be key causal, maintaining factors.

2.4 How might cognitive biases be relevant in CFS?

Experimental research has established that cognitive biases occur in mood disorders and may have a role in maintaining these problems. As established in Chapter 1 there are high rates of comorbid mood disorders in CFS. Perhaps cognitive biases have a role to play in maintaining the comorbid depression or anxiety for some people with CFS. However, as was also established in Chapter 1, not everyone with CFS has psychiatric comorbidity. In fact, research has shown that CFS is distinct from psychiatric conditions in its presentation and cognitive characteristics (Moss-Morris & Petrie, 2001). Given that
cognitive biases occur for condition specific information, it is unlikely that people with CFS will show biases for generally negative or threatening content, as in depression and anxiety. It may be that, in line with the content specificity hypothesis in Beck’s Schema theory (Beck & Clark, 1988), people with CFS have cognitive biases specific to their illness concerns, such as fear of activity which may exasperate symptoms and subsequent avoidance of activity (fear-avoidance).

The hypothesis that cognitive biases may also occur in CFS is supported by CB models of CFS. For instance, Vercoulen, et al. (1998) proposes that a hypervigilance to symptoms and misinterpreting stimuli as signs of damage and disease, are central in driving disability and symptom severity in CFS. These processes could be conceptualised as cognitive biases. For example, experiencing ongoing, debilitating and unexplained fatigue would understandably create a high personal relevance of fatigue and illness-related information; thus lowering the threshold at which such personally salient information is perceived. The increased perception of illness-related information may reinforce the individual’s concerns that they are suffering from a dangerous organic disease (core beliefs that are referred to by Beck and as an ‘illness schema’). The individual may become hypersensitive and vigilant to illness-related information in their environment (attentional bias); or interpret ambiguous information in a way that is consistent with their illness-schema (interpretation bias). These cognitive biases in turn may keep illness-related information salient, which further reinforces beliefs that symptoms are pervasive, uncontrollable and diverse. Prior research (detailed in Chapter 1) has identified that these types of illness beliefs can perpetuate an unhelpful cycle of responses to symptoms, such as fear and avoidance of activity, catastrophic thinking styles and symptom monitoring (Knoop, et al., 2010; Moss-Morris, 2005; Nijs, et al.,
In this way, cognitive biases may play a role in the cognitive behavioural model of CFS.

Whilst cognitive biases in CFS are theoretically plausible, few studies have experimentally tested these hypotheses. The available experimental research in CFS is reviewed in Chapter 3. In order to provide some context as to how cognitive biases may operate in chronic, physical conditions, I will outline some of the experimental research conducted in the pain literature, with particular reference to chronic pain studies. Chronic pain can be thought of as closely related to CFS in that they both share some comorbidity with anxiety and depression (Scott, et al., 2007), they are both primarily characterised by a physical but difficult to define symptom (Clauw & Chrousos, 1998), and both are proposed to have key cognitive and behavioural components in maintaining some aspects of the conditions; specifically fear avoidance beliefs and catastrophizing (Nijs, Van de Putte, Louckx, Truijen, & De Meirleir, 2008).

2.4.1 Experimental research in chronic pain

As summarised above for CFS, the theoretical underpinning for cognitive biases in chronic pain is that people experiencing chronic pain, will have a heightened expectation and sensitivity for detecting pain relevant information, which is congruent with their current concerns or ‘schemas’. This may lead them to be hypervigilant for pain relevant information (attentional bias) and interpret otherwise ambiguous information as pain related (interpretation bias).

A recent meta-analysis of attentional biases in pain, indicated that individuals who experience chronic pain display an attentional bias towards supraliminal (i.e. above the threshold of conscious awareness) presented, sensory pain-related information (Crombez,
Van Ryckeghem, Eccleston, & Van Damme, 2013). This indicates that in chronic pain, attentional biases occur for information related to the experience of pain and, similar to depression, these biases occur at later stages of processing. The authors hypothesized that repetitive negative thinking about chronic pain and related problems (i.e., worrying) maintains attention on pain-related information. However, the effect sizes in these studies were generally small and although plausible, this view awaits empirical corroboration. A meta-analysis of interpretation bias studies, suggested individuals with chronic pain demonstrate biased interpretation of ambiguous information favouring pain-related/illness-related interpretations (Schoth & Liossi, 2016). However, at this stage it is not possible to determine, from the paradigms that have been used, whether interpretation bias occurs at early or later stages of processing in chronic pain.

An important limitation of this experimental work is that many studies fail to specify what it is about pain that the materials are trying to tap into; is it the physical threat of pain, or the sensory pain experience itself? For example, most of the studies assessing both attention and interpretation biases in chronic pain, have grouped together a range of different types of stimuli; those related to the experience of pain (e.g. sensory pain words such as ‘agonizing’) as well as affective-pain/illness-related stimuli (e.g. words such as ‘miserable’). This is important, as biases are hypothesised to occur for information specific to individuals concerns (Beck & Perkins, 2001; Pergamin-Hight, et al., 2015); a person who is concerned about their experience of pain may have an attentional bias for somatic information (e.g. ‘aches’) but not necessarily for generic illness-related information (e.g. ‘hospital’). For instance, a study with people with chronic headache found people showed an attentional bias for images pertaining to headache but not general pain-images, health-threaten imaging or general threat pictures (Schoth & Liossi,
Without this level of specificity in the materials developed and selected for experimental tasks, it is difficult to draw definitive conclusions from the data.

Taken together, the evidence suggests that people with chronic pain demonstrate illness-specific attention and interpretation biases, and these biases seem to occur at later stages of processing. Biases in chronic pain do not appear to be dependent on levels of anxiety and depression (Crombez, Viane, Eccleston, Devulder, & Goubert, 2013). Whether or not these biases are associated with clinically relevant outcomes is yet to be established. Theoretical models of pain (e.g. the fear-avoidance model of pain and threat-interpretation model) propose a role for cognitive biases in maintaining key aspects of pain; specifically, fear avoidance beliefs and catastrophizing (Crombez, Eccleston, Van Damme, Vlaeyen, & Karoly, 2012; Leeuw, et al., 2007; Todd, et al., 2015). However, empirical evidence for this association is tentative. Several cross-sectional studies have found that those who catastrophize and who are highly fearful about pain also demonstrate increased attentional bias towards pain stimuli and an interpretation bias favouring more negative pain/illness related resolutions of ambiguity (Asmundson, Kuperos, & Ron Norton, 1997; Heathcote & Jacobs, 2015; Heathcote, Jacobs, Eccleston, Fox, & Lau, 2017; Heathcote, et al., 2015; Keogh, et al., 2001; Keogh, et al., 2003; Vancleef, Hanssen, & Peters, 2015; Vancleef & Peters, 2006). Several CBM studies also suggest that training people with chronic pain to direct attention away from pain-related information (i.e. reducing an attentional bias) is associated with reduced anxiety sensitivity and pain related fear (Carleton, Richter, & Asmundson, 2011; Schoth, Georgallis, & Liossi, 2013; Sharpe, et al., 2012). However, CBM research in this area is just beginning, and, as yet, mediation has not been established in these studies.
In sum, experimental research in chronic pain indicates that cognitive biases do indeed occur for chronic physical conditions, with some indications of relationships between these biases and maintaining factors. It is plausible that similar illness-specific biases may occur in CFS.

### 2.5 Hypothesised mechanisms of cognitive biases

The experimental literature has identified heterogeneity in the existence and expression of cognitive biases. Some groups and individuals show illness-specific biases at early, almost ‘automatic’ stages of processing; others demonstrate biases at later, more elaborative stages; and some indicate no biases at all. So why might some people have cognitive biases at some stages of processing, and others not? Research has explored several potential mechanisms that mediate the expression of cognitive biases. Below I will outline two of the prominent mechanistic candidates, attentional control and attentional malleability.

#### 2.5.1 General attentional control

Attentional control is a plastic cognitive resource (Petersen & Posner, 2012; Posner & Petersen, 1990). Its function is to direct attention to task orientated information and inhibit attentional capture by irrelevant information. As such, attentional control is conceptualised as a ‘top-down’ regulatory ability (Posner & Rothbart, 2000); it inhibits the ‘bottom-up’ influence of irrelevant distracters (Eysenck et al., 2007). The degree of attentional control varies between people and is influenced by emotional states. For example, older people have poorer attentional control than younger people (Verhaeghen & Cerella, 2002) and attentional control is reduced when under increased mental load or worry (Stefanopoulou, Hirsch, Hayes, Adlam, & Coker, 2014).
Attentional control theory (Eysenck, et al., 2007) suggest that cognitive biases are a result of poor attentional control capacity. It posits that difficulties in the regulation and allocation of attention (i.e. poor attentional control) result in salient, but task-irrelevant information ‘grabbing’ attention more readily and, once attention has been captured, makes it more difficult to disengage from this information. There is some empirical research to support this hypothesis. For instance, Taylor, Cross, and Amir (2016) found that people with high levels of social anxiety combined with poor attentional control (objectively measured), demonstrated an increased attentional bias to threatening stimuli compared to those with good attentional control. Attentional control has also been implicated in interpretation biases. Salemink and Wiers (2012) found that people with high levels of social anxiety combined with poor attentional control (objectively measured) had stronger threat-related interpretations of ambiguity than those with good attentional control; suggesting that, in line with attentional control theory, people with poor attentional control and who were anxious were more fixed on negative interpretations.

Attentional control has also been proposed as a mechanism through which cognitive biases are modified. For instance, several studies have indicated the degree of attentional control influences the degree of attentional bias change following a CBM (Clarke, Browning, Hammond, Notebaert, & MacLeod, 2014). However, interestingly, researchers have also demonstrated the inverse relationship i.e. changing cognitive biases influences attentional control. Chen, Clarke, Watson, MacLeod, and Guastella (2015) observed that individuals who completed CBM to modify attentional biases, subsequently demonstrated increased attentional control. These findings indicate that there may be a reciprocal relationship between attentional control and change in attentional biases. It
may be that there are processes within the CBM procedure that target both content-specific cognitive biases, as well as generic attentional control abilities.

Outside of the anxiety and depression literature, there has been little research testing attentional control theory. Though studies in chronic pain have identified deficits in information processing speed and attentional control (Oosterman, Derksen, van Wijck, Kessels, & Veldhuijzen, 2012), to my knowledge, no study has assessed whether these deficits help or hinder cognitive biases for pain. One study assessed self-reported attentional control and attentional bias to pain in healthy adolescents (Heathcote, et al., 2015). The study found that participants who scored highly on pain catastrophizing and reported poor attentional control ability demonstrated an increased attentional bias towards pain-related information. Furthermore, when pain stimuli were presented for longer durations (1,250ms) poorer attention control was associated with increased attention bias to pain (regardless of pain catastrophizing level). These findings suggest that poor self-reported attentional control may be important for top-down processing of pain related information; i.e. when people reported having good attentional control they were more capable of exerting control over their ‘top-down’ goal-directed processing of pain related information. Whilst this study goes some way in supporting attentional control theory in attentional bias towards pain, we do not know how objectively measured attentional control affects pain-related processing. Furthermore, these findings cannot necessarily be extrapolated to chronic pain patients, who are likely to have more pervasive and salient pain schema and thus stronger attentional biases than healthy individuals.
However, contrary to the attentional control hypotheses, poor attentional control is not always accompanied by cognitive biases, and vice versa (Berggren & Derakshan, 2013). The lack of consistency in the relationship between attentional control and cognitive biases may be explained by attentional control only acting upon cognitive biases that are occurring at later, accessible stages of ‘top-down’ processing. For example, if attentional biases are occurring quickly, almost automatically, without the individuals’ conscious awareness, the individual will not be able to deploy effortful attentional control to correct them. Relatedly, attentional control theory does not adequately take into account an individuals’ current goals; which drive ‘top-down’ processing (Van Damme, Legrain, Vogt, & Crombez, 2010; Verhoeven, et al., 2010). Rather, attentional control theory assumes that attention is being ‘grabbed’ by salient threatening information. It may be that cognitive biases reflect a strategic, goal-driven behaviour, a prioritization of certain information; for instance, a considered response that a person has engaged in to recognise and avoid further injury or relapse. Indeed, there is some evidence from the anxiety literature that conflicting attentional processes (attentional avoidance of threat and an attentional dwelling on threat) are driven by strategic ‘top-down’ processes. For example, an individual may engage in attentional avoidance of threat in an attempt to reduce subjective discomfort elicited by aversive stimuli (Cisler & Koster, 2010; Mogg & Bradley, 1998); whereas, another may engage in prolonged dwelling on negative stimuli in order to facilitate its more extensive elaborative processing (e.g. to assess ‘is this threat illness-related? Is it damaging?’ Is it controllable?’) (Armstrong & Olatunji, 2012; Fox, Russo, & Dutton, 2002).

In sum, while attentional control seems important in relation to cognitive processing biases, it is still unclear as to what extent attentional control moderates cognitive biases. A primary feature of CFS is difficulty with attention and concentration (Fukuda, et al.,
1994; Sharpe, et al., 1991). Indeed, cognitive difficulty is a core feature across the diagnostic criteria for CFS (as discussed in Chapter 1, section 1.2.3). Neuropsychological testing has shown that people with CFS have generally slowed information processing speed (Cockshell & Mathias, 2010) and deficits in attentional control compared to healthy individuals (Togo, Lange, Natelson, & Quigley, 2015). However, the degree to which these neuropsychological deficits correlate with the subjective impairment reported by patients is unclear (Cockshell & Mathias, 2013, 2014; Moss-Morris, Petrie, Large, & Kydd, 1996; Schmaling & Betterton, 2016). Given the findings described above we might expect that poor attentional control in CFS would moderate cognitive biases.

2.5.2 Attentional malleability

Another potential mechanism underlying these cognitive biases is ‘attentional malleability’. Attentional malleability is an individual’s readiness to acquire an attentional bias. It is measured as the ability to adopt an attentional bias after a very brief training (i.e. on an adapted VPT, MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002); whereby attention towards or away from threat is repeatedly reinforced (more detail on this task is provided in Chapter 7).

Notably, people vary widely in the extent of their attentional malleability (Chen, et al., 2015; Clarke, MacLeod, & Shirazee, 2008; Clarke, Chen, & Guastella, 2012; Taylor, Bomyea, & Amir, 2011). The degree of attentional malleability can be mapped on to a genetic marker or ‘plasticity gene’; alternate forms of the serotonin transporter gene (5-HTTLPR) (Fox, Zougkou, Ridgewell, & Garner, 2011). Fox, et al. (2011) found those with a low-expression form of the gene (i.e. indicating high malleability) demonstrated greater change in attentional bias following CBM, relative to those with the high-expression form of the gene. Furthermore, this effect was consistent regardless of whether
attentional malleability was measured as the readiness to adopt an attentional bias towards threatening stimuli or away from threatening stimuli.

Other studies of attentional malleability have explored this concept only in relation to developing an attentional bias towards threat. Clarke, et al. (2008) found those with an increased malleability towards threatening information, were more likely to naturally develop an attentional preference for threat when exposed to extended mild stress (i.e. the first semester at university), which in turn predicted an elevation of trait anxiety. Thus, increased attentional malleability was a risk factor in developing attentional biases and anxiety, in response to the environment. Conversely, Clarke, et al. (2012) found that the same attentional malleability was adaptive for people with SAD when undergoing treatment. This study found people who had increased attentional malleability had larger reductions in anxiety following a course of group CBT, than those who had low malleability (Clarke, et al., 2012). Thus, people with high attentional malleability may be more at risk of developing attentional biases and anxiety in response to stressful environments. However, these same people may also be more likely to benefit when exposed to environments (i.e. treatment) which promote the adoption of a reverse processing bias. While Clarke et al. (2008, 2012) only measured attentional malleability towards threatening information, they hypothesised these effects would remain constant regardless of whether attentional malleability was measured towards threatening or neutral information. They termed this the ‘bias plasticity’ account (Clarke, et al., 2008; Clarke, et al., 2012).

The concept of attentional malleability is relatively new; however, initial results are promising. Attentional malleability may provide a cognitive/ genetic marker to predict how people respond to different environments and treatment. Further investigation is
obviously required to determine whether such applications of this concept are useful. It may be fruitful to investigate whether attentional malleability predicts response to treatment in CFS, similarly to findings in SAD. This information could help us understand the cognitive characteristics predicting those most likely to benefit from current treatment protocols for CFS. This is particularly pertinent given the heterogeneity in treatment response and recovery in CFS (e.g. White, et al., 2013) (discussed in Chapter 1, section 1.5.7).

2.6 Thesis rational and overview

The experimental research outlined in this chapter has identified that certain groups of people (e.g. anxious, depression, in pain) demonstrate cognitive biases in how they process incoming information, in favour of information that is salient and congruent with their current concerns. There is some evidence that these distortions in how information is processed reinforces unhelpful schemas/beliefs and may play a role in maintaining distress and other symptoms. Whilst CB models provide a theoretical rational for similar cognitive biases in CFS, there is little experimental research in this area to date. This thesis addresses this gap in the literature, employing experimental methods to explore information processing in CFS.

The empirical studies contained in this thesis are conducted with a view to understanding the nature of cognitive biases in CFS; and elucidating relationships with self-reported symptoms, cognitions and behaviours. The key aims are to determine whether (1) people with CFS have cognitive biases and attentional control deficits compared to healthy individuals, (2) these factors predict how people will respond to behavioural treatments for CFS and (3) current evidenced-based behavioural treatments for CFS are associated with changes in these cognitive processes.
Figure 3 outlines the recruitment flow for the empirical studies within thesis and the chapters where this data is reported. Table 2 outlines the research aims and objectives of each chapter presented in the thesis, alongside the design of the study, participant populations included and the measures that were administered at each stage.

As can be seen in table 2, chapter 3 is a systematic review, which synthesises the evidence for attention an interpretation biases in CFS to date, and determines the nature of these biases (published article, British Journal of Health Psychology). Chapter 4 aims to establish a robust and systematic method to developing illness-specific materials that tap into these cognitive biases (published article, British Journal of Health Psychology). Chapter 5 is a large cross-sectional, experimental study, which aims to assess whether people with CFS have illness-specific attention and interpretation biases and the role of attentional control (published article, Psychological Medicine). Chapter 6 is a replication study conducted with a Dutch cohort of CFS participants, which aims to establish whether these biases are replicable and cross-cultural (under review, International Journal of Behavioural Medicine). Chapter 7 is a longitudinal analysis of cognitive predictors of treatment outcomes in CFS, which aims to establish whether attentional bias, interpretation bias and attentional malleability are important for treatment outcomes in CFS (submitted, Behaviour Research and Therapy). Chapter 8, the final empirical chapter, is a longitudinal analysis assessing whether cognitive biases and attentional control change over the course of treatment for CFS; and secondly whether change in

\[1\] All citations within published articles have been converted to APA 6th style and are included in the final reference section of the thesis.
these experimentally measured variables is associated with changes in self-reported outcomes. Chapter 9 includes a discussion of findings and limitations across the studies included in the thesis, providing directions for future research.
Figure 3. Flow chart of participants included in the empirical studies within the thesis.
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Aims/ Objectives</th>
<th>Design</th>
<th>Sample</th>
<th>Reported measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.</td>
<td>A systematic review of attention and interpretation biases in CFS</td>
<td>Do people with CFS have an attention and/or interpretation bias? What are the nature of these biases (i.e., at what stage do these biases occur and for what type of stimuli)?</td>
<td>Systematic review</td>
<td>n/a</td>
</tr>
<tr>
<td>4.</td>
<td>Developing illns-specific materials for experimental research</td>
<td>What are the types of stimuli that are relevant for people with CFS? What is the optimum way to develop illness-specific materials for experimental research?</td>
<td>Position piece</td>
<td>CFS Breast Cancer</td>
</tr>
</tbody>
</table>
| 5.      | A cross-sectional study of cognitive biases and deficits in CFS | Using illness-specific materials, do people with CFS have attention and interpretation biases, or general attentional control deficits compared to healthy individuals? | Cross-sectional study | 52 UK CFS 51 UK healthy controls | Time 1 questionnaires:  
  - Demographics  
  - Fatigue  
  - Disability  
  - Mood  
  - Cognitions and behaviours  
  Time 1 experimental data:  
  - Attentional bias  
  - Interpretation bias  
  - Attentional control |
| 6.      | A cross-cultural replication study of cognitive biases and deficits in CFS | Can cognitive biases and attentional control deficits in CFS be replicated in another CFS population from another culture? | Cross-sectional study | 52 UK CFS 51 UK healthy controls 38 Dutch CFS | Time 1 questionnaires:  
  - Demographics  
  - Fatigue  
  - Disability  
  - Mood  
  - Cognitions and behaviours  
  Time 1 experimental data:  
  - Attentional bias  
  - Interpretation bias  
  - Attentional control |
<table>
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<tr>
<th>Chapter</th>
<th>Aims/ Objectives</th>
<th>Design</th>
<th>Sample</th>
<th>Reported measures</th>
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</table>
| 7.      | Cognitive predictors of treatment outcomes in CFS | Do cognitive biases and attentional malleability predict how people with CFS will respond to current treatments for CFS? | Nested longitudinal study | 26 UK CFS | Time 1 and Time 2 questionnaires:  
  - Fatigue  
  - Disability  
  - Mood |
|         |                  |        |        | Time 1 experimental data:  
  - Attentional bias  
  - Attentional malleability  
  - Interpretation bias |
| 8.      | Do cognitive processes change over the course of treatment? | Do cognitive biases and attentional control deficits in CFS change pre- to post treatment? | Nested longitudinal study | 20 UK CFS | Time 1 and Time 2 questionnaires:  
  - Fatigue  
  - Disability  
  - Mood  
  - Cognitions and behaviours |
|         |                  |        |        | Time 1 and Time 2 experimental data:  
  - Attentional bias  
  - Interpretation bias  
  - Attentional control |

2 Cognitions and behaviours were not analysed in this study as it was not within the scope of the submitted article.

3 Attentional malleability was measured at Time 1 (pre-treatment); it was analysed in Chapter 7 as a predictor of treatment outcome in line with previous studies of malleability (Clarke et al. 2008; Clarke et al. 2014).
Chapter 3 A systematic review of attention and interpretation biases in CFS

3.1 Chapter overview

This chapter is published in the following article:

3.2 Published article

**Title:** Attentional and interpretive bias towards illness-related information in chronic fatigue syndrome: A systematic review

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**Conflict of Interest Statement:** TC receives royalties for self-help books on chronic fatigue.

**Key words:** attentional bias; chronic fatigue syndrome; cognitive behavioural model; illness representations; information processing; interpretive bias; symptom interpretation
Abstract

**Purpose:** Chronic fatigue syndrome (CFS) is characterised by severe and debilitating fatigue. Studies based on self-report measures suggest negative illness representations, related symptom interpretations and heightened symptom focusing are maintaining factors of fatigue. This paper reviews studies which have investigated these cognitive biases using experimental methods, in order to (a) review the evidence for information processing biases in CFS, (b) determine the nature of these biases; i.e. the stages cognitive biases occurs and for what type of stimuli (c) provide directions for future methodologies in this area.

**Methods:** Studies were included that measured attention and interpretation bias towards negative and illness related information in people with CFS and in a comparison group of healthy controls. PubMed, Ovid, Cinhal, PsychInfo, Web of Science and EThoS were searched to December 2014.

**Results:** The evidence for cognitive biases was dependent on the methodology employed as well as the type and duration of the stimuli presented. Modified Stroop studies found weak evidence of an attentional bias in CFS populations, whereas Visual Probe studies consistently found an attentional bias in CFS groups for health threatening information presented for 500ms or longer. Interpretative bias studies which required elaborative processing, as opposed to a spontaneous response, found an illness related interpretive bias in the CFS group compared to controls.

**Conclusions:** Some people with CFS have biases in the way they attend to and interpret somatic information. Such cognitive processing biases may maintain illness beliefs and symptoms in people with CFS. This review highlights methodological issues in experimental design and makes recommendations to aid future research to forge a consistent approach in cognitive processing research.
Introduction

Chronic fatigue syndrome (CFS) is characterised by disabling mental and physical fatigue, which lasts at least six months and cannot be attributed to any other medical condition (Fukuda, et al., 1994; Sharpe et al., 1991). As well as fatigue, people may experience muscle pain, malaise, sleep disturbance (Fukuda, et al., 1994; Sharpe, et al., 1991) and concentration and memory problems (Jason, et al., 1999; Wearden & Appleby, 1997). People with CFS report increased rates of anxiety or depression compared to healthy people and other illness groups (Cella, White, Sharpe & Chalder, 2013) and poor quality of life (Johnson, DeLuca, & Natelson, 1996).

The aetiology of CFS has been hotly debated. However, the findings to date suggest a biopsychosocial model best explains the condition in terms of a complex interaction between biological, affective, behavioural and cognitive factors (Moss-Morris, Deary, & Castell, 2013). The biopsychosocial framework has been elaborated in Cognitive Behavioural (CB) models which suggest that people can be predisposed to developing CFS by factors such as genetics, distress and/or personality traits. For predisposed individuals, stressful life events and/or an acute infection can trigger the initial symptoms. These symptoms and associated disability are in part perpetuated by cognitive and behavioural factors such as negative illness representations, symptom focusing and all-or-nothing behaviour (Deary, Chalder, & Sharpe, 2007; Knoop, Prins, Moss-Morris, & Bleijenberg, 2010).

Illness representations are patients’ common-sense beliefs about their illness (Beck & Clark, 1988), which give personal meaning to the existing symptoms and influence the development of coping strategies and their appraisal (Leventhal, et al., 1997). Most patients with CFS attribute their illness to physical factors (e.g. immune system
dysfunction) and/or stress, and believe associated symptoms to be serious, damaging, uncontrollable and incurable (Moss-Morris & Petrie, 2003). These negative illness beliefs are associated with the onset of CFS post glandular fever, as well increased severity of symptoms and disability in those who already have the illness (Moss-Morris, Spence, & Hou, 2011). Self-reported symptom focusing also appears to play an important role. Two randomised controlled trials (RCTs) of behavioural treatments for CFS found reduced symptom focusing mediated reductions in fatigue (Moss-Morris, Sharon, Tobin, & Baldi, 2005; Wiborg, Knoop, Prins, & Bleijenberg, 2011). Thus, how people interpret and attend to somatic information appears to be important in the development and perpetuation of CFS.

To date research has largely used self-report methods to tap into these illness representations and related constructs, such as, negative interpretation of symptoms and symptom focusing. Self-reports tap into peoples’ explicit and conscious beliefs and are open to response bias. People may also hold less conscious beliefs which may drive behaviour. Experimental methods can help tap into more implicit beliefs.

Experimental methods can also help us understand how explicit illness beliefs may influence the way in which people process information. Leventhal’s Common Sense Model of Illness (Leventhal, et al., 1997) suggests that illness representations or schema drive coping strategies. Appraisals of the success of these strategies serve to maintain or change illness representations. We know from the literature on anxiety and depression, that dominant schemas also influence the way in which information is processed which in turn helps to maintain these schemas (Beck & Clark, 1988). In the case of CFS, a negative illness representation (schema) may lead to heightened attention to somatic information and a corresponding tendency to interpret symptoms in an overly negative
fashion. These information processing biases may in turn help to maintain the original beliefs.

Research into these cognitive processes may enhance our understanding of the mechanisms underlying CFS and may also point to possible interventions to alter or change illness representations. This review aims to explore whether people with CFS show biases in cognitive processes and whether these biases are symptom or illness specific, (i.e. related to negative illness representations) rather than reflective of those seen in anxiety and depression, as comorbid mood disorders are evident in approximately half of people with CFS (Deal & Wessely, 2000).

The mental health literature has identified cognitive processing biases which can differentiate between anxiety (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007) and depression (Mogg & Bradley, 2005). Anxiety is characterized by attentional bias for threatening stimuli presented subliminally for short periods of time (100ms or less) (Koster, et al., 2006); reflecting a bias in the initial orientation of attention. In depression attentional bias occurs for stimuli that reflect a negative view of the self which are presented under conditions that encourage elaborative processing, (i.e. relatively long stimulus duration; when the negative self-concept has been primed) (Dohr, Rush, & Bernstein, 1989; Donaldson, Lam, & Mathews, 2007; Mogg & Bradley, 2005). This reflects biases in top down processes which are involved in the effortful assimilation and organization of incoming information (Mogg & Bradley, 2005). It is currently unclear as to whether negative illness schema characteristic of CFS are related to either an elaborative processing bias as in depression or a more habitual initial orienting bias as seen in anxiety.
This review is the first synthesis and analysis of studies in cognitive processing biases in CFS. Such a review is needed to expand the girth of self-report literature in CFS and provide a more complete profile of both explicit and implicit cognitions in CFS. This will not only help us elaborate the CB model of CFS but may also provide guidance as to how the common-sense model could be expanded to understand how illness schema drive information processing. The review will separately examine studies assessing attentional bias and interpretation bias. Studies will be grouped according to the methods they employ (explained in the methods section) and summarized collectively.

The primary objective is to investigate whether people with CFS show biases in cognitive processing. Specifically, we wanted to ascertain (a) whether people with CFS have an attentional bias for health threatening stimuli; and a bias towards interpreting ambiguous information in an illness related manner, when compared to healthy controls or other illness groups (b) the nature of any biases (i.e. are these early orientation biases or elaborative processing biases?) The secondary objective is to determine if individual differences in anxiety and depression in CFS are related to cognitive processing biases. Finally, clear recommendations for future research in this area will be made.

Methods

Inclusion and exclusion criteria

Studies were included if their primary aim was to assess cognitive biases in attention and/or interpretation; in a CFS group (defined using a standardized research and/or clinical definition; Fukuda, et al., 1994; Sharpe, et al., 1991); compared to a healthy control group or other chronic illness group. Studies needed to be published in English. Studies were excluded if they were non-experimental, case methodologies, discussion and/or review papers; and where the studies primary aim was to assess neuropsychological markers of cognitive deficits i.e. motor functioning, visuospatial
ability, verbal abilities and language, working memory, global functioning and cognitive reasoning.

The methodologies used to investigate attentional biases are based on reaction times. The Modified Stroop task (see Williams, Mathews & MacLeod, 1996 for review) presents participants with emotionally toned words, displayed in different colours. The participant is required to rapidly name the colour of each word. Attentional bias is measured as the latency to name colours of ‘threatening’ words compared to neutral or positive words. A common criticism of the modified Stroop task is that it is more accurately a measure of ‘interference effect’ as opposed to a biased attention (De Ruiter & Brosschot, 1994).

The Visual probe paradigm (MacLeod, et al., 1986) measures attentional bias by presenting two cues, one threatening and one non-threatening, followed by a probe in the prior location of one of them (for reviews see Bar-Haim, et al., 2007). Quicker responding to probes replacing threatening cues as opposed to non-threatening reflects an attentional bias towards threatening information. Posner and colleagues (Posner, 1980; Posner, Walker, Friedrich, & Rafal, 1984) developed an exogenous cueing task; similar to the visual probe task, but with only one stimulus presented at a time. Attentional bias is measured as assessing two aspects of attention; reflecting either engagement (when the target is in the same location as the cue), or difficulty in disengagement of the emotive stimuli (when the response is quicker when the target is in the opposite location to the cue).

Methodological variations of these tasks include masked exposure conditions to investigate the role of awareness, and manipulations of stimuli duration to investigate different stages of processing. Exposure durations of a second or more are viewed as
assessing processes involved in the maintenance of attention, whereas shorter exposure durations (e.g. 100ms) intend to capture biases which operate in early, relatively automatic attentional capture (e.g. Bradley, Mogg, Falla, & Hamilton, 1998).

Interpretative bias is a tendency to interpret ambiguous information in a negative, illness or symptom related way. Interpretive bias tasks rely on presenting participants with ambiguity which can be resolved with either positive or negative interpretations. Tests then assess whether people consistently generate positive or negative interpretations of ambiguous material, indicating a bias towards a given type of interpretation (Hirsch, Meeten, Krahé & Reeder, 2016). These tasks can be dichotomized into on-line tasks referring to immediate interpretation of stimuli; and off-line tasks, referring to later, more reflective interpretations. For example, Hirsch and Mathews (2000) conducted an online task measuring interpretation at the moment the ambiguity is first encountered; whereas Stopa and Clarke (2000) used an off-line task whereby participants were asked open questions after being presenting with ambiguous scenarios. Table 1 details the paradigms described above and the proposed cognitive mechanisms and stage of processing they tap into.

**Search Strategy**

The MEDLINE, PsychINFO, Web of Science (WOS) and Cinahl databases were searched for ‘chronic fatigue syndrome’ and alternate terms combined with attention bias and interpretation bias (and related terms). The references of all the obtained articles and relevant review articles were searched for additional relevant studies. The Electronic Theses Online Service (EThOS) providing access to UK theses (www.ethos.bl.uk) was searched to identify any relevant unpublished theses and authors were contacted for publications in press. A 17 item adapted version of the Downs and Black “Checklist for
Measuring Quality” (Downs & Black, 1998) was used to assess the quality of the studies (See Appendix A).

**Results**

Twelve eligible studies were identified from eight articles (Figure 1). Three of these were PhD theses (Papitsch, 2005; Gillings, 2007; Arroll, 2009). The published studies reviewed were of high quality (scores 12-15 out of 17); unpublished studies were of poorer quality (10-12), suffering from inadequate sample matching and underpowered sample sizes. There was marked heterogeneity of the methodologies (i.e. different paradigms, stimuli, exposure conditions) each tapping into different aspects of cognitive processing, thus a meta-analysis would not be informative.
Articles identified through database searching =1,038
- Medline (n= 353)
- WOS (n= 398)
- Psychinfo (n= 283)
- CINAL (n= 6)

Unpublished Articles = 8
- ETHoS (n= 4)
- Conference Proceedings (n= 3)
- Identified in relevant literature (n= 1)

Records after duplicates removed = 458
- Published (n= 453)
- Unpublished (n=5)

Records screened = 458

Records excluded on title & Abstract = 436

Full-text articles assessed for eligibility = 22

Full-text articles excluded = 14
- Stimulus used not illness related (n= 4)
- Diary study measuring recall of previously reported fatigue (n= 2)
- Neuropsychological study of cognitive deficits (n= 8)

Articles included in qualitative synthesis = 8

Total studies within articles=12
- Attentional Bias (n=8)
- Interpretative Bias (n=4)

Figure 1. PRISMA Flow Diagram of Study Selection
<table>
<thead>
<tr>
<th>Paradigm</th>
<th>Cognitive mechanism</th>
<th>Proposed type of processing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Emotional Stroop task</td>
<td>Interference effect (lack of inhibitory control) of emotive words on attention</td>
<td>Masked task measures AB prior to conscious recognition, tapping into automatic processing; unmasked task measures AB when stimuli are visible allowing for more strategic processing.</td>
</tr>
<tr>
<td>Visual Probe task</td>
<td>Attentional bias towards threatening over neutral stimuli</td>
<td>Stimuli presented for &lt;500ms taps into early automatic orientation of attention.</td>
</tr>
<tr>
<td>Exogenous Cueing task</td>
<td>Orientation of attention</td>
<td>Stimuli presented for &gt;500ms taps into later strategic processing. 500ms is viewed as having potential for automatic and strategic processing.</td>
</tr>
<tr>
<td>On-line interpretative bias task</td>
<td>Interpretation of ambiguous stimuli when first encountered</td>
<td>More automatic, spontaneous processing</td>
</tr>
<tr>
<td>Off-line interpretative bias task</td>
<td>Interpretation of ambiguous stimuli when there is opportunity for reflection</td>
<td>Allows for more elaborative processing</td>
</tr>
</tbody>
</table>
Participant Characteristics

Table 2 summarises the study demographics. Six articles used the US Centres for Disease Control and Prevention (CDC) criteria (Fukuda, et al., 1994) to define CFS; 2 articles (Creswell & Chalder, 2001; Gillings, 2007, unpublished) used the Oxford criteria (Sharpe, 1995), which requires the presence of mental as well as physical fatigue. Healthy controls were required to have no history of CFS, and no current acute or chronic illnesses. Two studies included an additional control group of participants with a chronic condition; diabetes (Creswell & Chalder, 2002) and arthritis (Gillings, 2007, unpublished).

There were fewer males than females in the included studies which is in line with population based studies of CFS demographics (Wessely, et al., 1997). All studies included self-reported levels of anxiety and depression (Hospital Anxiety and Depression Scale, HADS; Zigmond, & Snaith, 1983) which ranged from normal to moderate levels representative of typical psychiatric comorbidity in CFS (Cella, White, Sharpe & Chalder, 2013). Martin and Alexeeva (2010) reported particularly high anxiety in their healthy control group which was controlled for in subsequent analysis. Illness duration ranged from 4- 16 years, with an average of 8.3 years.

Papitsch (2005, unpublished) dichotomised their CFS group into those with and without co-morbid depression (defined as a cut off score of 9 or above on the HADS); and Arroll (2009, unpublished) dichotomised their CFS group into those with high and low symptomatology using the Profile of Fatigue Related Symptoms (PRFS; Ray, Weir, Phillips, & Cullen, 1992) and Pennebaker’s Inventory of Limbic Languidness (PILL; Pennebaker, 1982).
Four of the eight articles reported a measure of symptomology. Moss-Morris and Petrie (2003) and Hou et al. (2008) reported the PFRS (Ray, et al., 1992), a 54 item measure designed specifically to measure the intensity of a range of CFS related symptoms experienced over the last week. Data confirmed that CFS patients had significantly higher symptom scores than healthy controls. Papitsch (2005) reported the Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash & Steinberg, 1989), a measure of fatigue severity and functional impairment, with a minimum score of 1 indicting no fatigue/impairment and a maximum score of 7 indicating greater fatigue severity. Hou et al. (2014) reported symptom severity scores on the 14 item Chalder Fatigue Questionnaire (Chalder et al., 1993), which measures both mental and physical fatigue (0-42). All studies report high levels of fatigue severity on their respective scales.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Diagnostic criteria</th>
<th>Participants, n (male)</th>
<th>HADS Depression Mean (SD)</th>
<th>HADS Anxiety, Mean (SD)</th>
<th>Illness Duration, Years (SD)</th>
<th>Symptom measure</th>
<th>Symptomology, Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creswell, 2002</td>
<td>Oxford Diagnostic Criteria</td>
<td>CFS, 24 (4) Diabetes, 20 (10) HC, 24 (4)</td>
<td>6.29 (3.37) 3.65 (3.18) 1.96 (1.92)</td>
<td>9.42 (3.94) 6.35 (3.18) 5.71 (2.49)</td>
<td>3.62 (2.2) 10.96 (6.88) p&lt;0.001†</td>
<td>NR</td>
<td>9.42 (3.94) 6.35 (3.18) 5.71 (2.49) p&lt;0.001†</td>
</tr>
<tr>
<td>Moss-Morris, 2003</td>
<td>Diagnosis with the CDC criteria in the past year</td>
<td>CFS, 25 (3) HC, 24(3)</td>
<td>7.21 (2.38) 2.38 (2.59)</td>
<td>7.63 (3.89) 5.21 (3.16)</td>
<td>11.25 (8.75) PFRS 118.09 (30.09) p&lt;0.001</td>
<td></td>
<td>19.29 (15.26)</td>
</tr>
<tr>
<td>Papitsch, 2005 (unpublished)</td>
<td>CDC criteria</td>
<td>CFS, 27 (7) CFS/D, 21 (5) HC, 21 (5)</td>
<td>4.96 (1.93) 11.0(1.67) 1.33(1.8)</td>
<td>9.19(4.39) 12.0(3.26) 3.910(2.84)</td>
<td>4.11 (4.00) FSS 6.22 (0.53) p&lt;0.001</td>
<td></td>
<td>4.11 (4.00) 6.46 (0.43) 2.73 (0.81) p&lt;0.001</td>
</tr>
<tr>
<td>Gillings, 2007 (unpublished)</td>
<td>Oxford criteria</td>
<td>CFS, 26 (8) Arthritis, 36 (4) HC, 27 (5)</td>
<td>6.57 (4.14) 5.29 (3.60) 1.73 (2.32)</td>
<td>7.35 (4.06) 7.65 (4.12) 5.33 (3.32)</td>
<td>NR NR NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hou, 2008</td>
<td>CDC criteria</td>
<td>CFS, 11 (3) HC, 17 (6)</td>
<td>7.00 (5.33) 2.71 (2.73)</td>
<td>7.70 (4.72) 5.76 (3.85)</td>
<td>NR PFRS 121.9 (58.68) 38.83 (32.52)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued
### Table 2. (Continued)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Diagnostic criteria</th>
<th>Participants, n (male)</th>
<th>HADS Depression Mean (SD)</th>
<th>HADS Anxiety, Mean (SD)</th>
<th>Illness Duration, Years (SD)</th>
<th>Symptom measure</th>
<th>Symptomology, Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arroll, 2009</td>
<td>CDC criteria</td>
<td>CFS, 21 (5)</td>
<td>6.00 (2.08)</td>
<td>7.14 (3.46)</td>
<td>15.82 (10.63)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low Symptoms, 14</td>
<td>8.29 (4.75)</td>
<td>9.71 (5.28)</td>
<td>15.79 (14.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High Symptoms, 7</td>
<td>8.29 (4.75)</td>
<td>9.71 (5.28)</td>
<td>15.79 (14.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HC, 10 (2)</td>
<td>5.97 (3.71)</td>
<td>8.25 (3.48)</td>
<td>7.6 (6.7)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Martin, 2010</td>
<td>CDC criteria</td>
<td>CFS, 33 (16)</td>
<td>5.97 (3.71)</td>
<td>8.25 (3.48)</td>
<td>7.6 (6.7)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HC, 33 (11)</td>
<td>3.72 (2.30)</td>
<td>8.44 (3.41)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hou, 2014</td>
<td>CDC diagnosis</td>
<td>CFS, 27(8)</td>
<td>9.6 (3.7)</td>
<td>10.0 (4.0)</td>
<td>5.6 (5.2)</td>
<td>CFQ</td>
<td>28.9 (3.3)</td>
</tr>
<tr>
<td></td>
<td>within 6 months</td>
<td>HC, 35 (15)</td>
<td>1.9 (2.8)</td>
<td>4.5 (2.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: CFS/D=Chronic Fatigue Syndrome with co-morbid depression (defined as a cut off score of 9 or above on HADS scale); HC=Healthy Control group; NR= Not Reported; CFQ= Chalder Fatigue Questionnaire (Chalder, et al., 1993); † Controlled for in subsequent analysis; HADs Anxiety and Depression Scale score 0-7 normal range, 8-10 mild case, 11-15 moderate case, 26 or above represents severe case.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Task</th>
<th>Stimuli Type</th>
<th>Stimuli Duration</th>
<th>Masked</th>
<th>Main between group findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creswell, 2002</td>
<td>Modified Stroop (card)</td>
<td>Positive and negative personally descriptive words v. neutral words</td>
<td>Until response</td>
<td>No</td>
<td>CFS group had an attentional bias towards negative words compared to HC** which continued to approach significance when co-varied out HADS and self-esteem (p=.06)</td>
</tr>
<tr>
<td>Moss-Morris, 2003</td>
<td>Modified Stroop (card)</td>
<td>CFS related words v. depression words v. neutral words</td>
<td>Until response</td>
<td>No</td>
<td>No attentional bias (p=.42)</td>
</tr>
<tr>
<td>Gillings, 2007 (unpublished)</td>
<td>Modified Stroop (computer)</td>
<td>CFS/ME related words v. negative emotional words v. neutral words</td>
<td>Until response</td>
<td>No</td>
<td>No attentional bias (p&gt;.05)</td>
</tr>
<tr>
<td>Papitsch, 2005 (unpublished)</td>
<td>Dot-probe (computer)</td>
<td>Fatigue, illness and depression relevant words v. neutral words v. positive words</td>
<td>500ms</td>
<td>No</td>
<td>An attentional bias in the CFS/D group for illness words compared to HC (p=.05). No other group differences.</td>
</tr>
<tr>
<td>Hou, 2008</td>
<td>Dot- Probe (computer)</td>
<td>Health threat words and pictures v. neutral words and pictures</td>
<td>500ms</td>
<td>Yes</td>
<td>CFS group had an attentional bias towards threat words compared to HC (p&lt;.01).</td>
</tr>
</tbody>
</table>

Continued
Table 3. (Continued)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Task</th>
<th>Stimuli Type</th>
<th>Stimuli Duration</th>
<th>Masked</th>
<th>Main between group findings</th>
<th>Quality Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arroll, 2009 (unpublished)</td>
<td>Modified Stroop (computer)</td>
<td>Symptom words v. neutral words</td>
<td>Until response</td>
<td>No</td>
<td>CFS group did not differ from HC in Stroop interference effect ($p &gt; .05$).</td>
<td>11</td>
</tr>
<tr>
<td>Martin, 2010</td>
<td>Exogenous cueing task (computer)</td>
<td>Illness words v. social threat words v. neutral words</td>
<td>100ms</td>
<td>Yes</td>
<td>No attentional bias ($p = .41$)</td>
<td>15</td>
</tr>
<tr>
<td>Hou, 2014</td>
<td>Dot-Probe (computer)</td>
<td>Health threat words and pictures v. neutral words and pictures</td>
<td>500ms and 1250ms</td>
<td>Yes</td>
<td>CFS group had an attentional bias towards threat words ($p = .05$) but not pictures compared to HC. This effect was more pronounced for CFS participants with poor executive attentional control ($p &lt; .001$).</td>
<td>15</td>
</tr>
</tbody>
</table>

Notes: CFS=Chronic Fatigue Syndrome; CFS/D=Chronic Fatigue Syndrome with co-morbid depression (defined as a cut off score of 9 or above on HADS scale); HC=Healthy Control group; NR= Not Reported; Quality Score rated out of 16 using a revised Downs and Black (Downs & Black, 1998) quality checklist.
Table 4. Summary of Interpretative Bias Results

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Task</th>
<th>Stimuli</th>
<th>Main findings</th>
<th>Quality Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moss-Morris, 2003</td>
<td>Homophone task and ambiguous cues</td>
<td>30 homophones; 15 ambiguous illness related interpretations and 15 unambiguous words.</td>
<td>Participant had to write down first word that came to mind CFS participants made significantly more somatic interpretations than HC ($p&lt;.001$)</td>
<td>14</td>
</tr>
<tr>
<td>Papitsch, 2005</td>
<td>Word completion task</td>
<td>Not primed. 17 two letter word fragments presented. Fragments consisted of beginnings of fatigue, illness and depression words.</td>
<td>No interpretative bias in CFS group compared to controls ($p&gt;.05$)</td>
<td>9</td>
</tr>
<tr>
<td>Study 1 (unpublished)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papitsch, 2005</td>
<td>Second word stem completion task</td>
<td>No explicit priming but authors suggested that concepts were primed by previous word completion task (above) and a dot-probe task using the same stimuli.</td>
<td>As above plus 5 fragments pertaining to positive and neutral stimuli. Responses rated by 4 independent researchers as positive, negative, fatigue, illness or depression related. Analysed for generating the same words as in the first word stem task.</td>
<td>9</td>
</tr>
<tr>
<td>Study 2, Analysis 1 (unpublished)</td>
<td></td>
<td></td>
<td>No group differences in word type generated or recalled from the first completion task (all $p&gt;.05$)</td>
<td></td>
</tr>
</tbody>
</table>

*Continued*
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Task</th>
<th>Stimuli</th>
<th>Main findings</th>
<th>Quality Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papitsch, 2005</td>
<td>Study 2, Analysis 2 (unpublished)</td>
<td></td>
<td>Analysed for proportion and type of words generated which were not presented in the previous dot-probe task.</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Priming Stimuli</td>
<td>Target Stimuli</td>
<td>No overall difference between groups in word type completions. However, post hoc analysis found both CFS groups generated a higher number of illness completions compared to controls.</td>
</tr>
<tr>
<td>Martin, 2010</td>
<td>Lexical decision task</td>
<td>60 homophones with illness, social threat or neutral interpretations.</td>
<td>4 types of target stimuli; non-word, unrelated word, related non-threat word and related threat word.</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No interpretative bias in CFS group compared to controls ($p=.68$)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: CFS=Chronic Fatigue Syndrome; CFS/D=Chronic Fatigue Syndrome with co-morbid depression (defined as a cut off score of 9 or above on HADS scale); HC=Healthy Control group; NR= Not Reported; Quality Score rated out of 16 using a revised Downs and Black (Downs & Black, 1998) quality checklist.
Do people with CFS show an attentional bias?

Findings from the attentional bias studies are summarised in table 3.

Studies using modified stroop paradigms. Four CFS studies used the Emotional Stroop paradigm which measures interference of emotionally relevant stimuli (or inability to inhibit interference of emotional stimuli) (Arroll, 2009; Creswell & Chalder, 2002; Gillings, 2007; Moss-Morris & Petrie, 2003). Two published studies used card versions of the modified Stroop task and found contradictory results (Moss-Morris & Petrie, 2003; Creswell & Chalder, 2002). Moss-Morris and Petrie (2003) presented three sets of words; CFS related, depression related and neutral words matched for length and frequency of use. CFS related stimuli were developed in conjunction with clinical experts and based on interviews with CFS participants. Moss-Morris and Petrie (2003) found the CFS group were slower in colour naming in general than healthy controls \((p<.01)\) however the groups showed no significant differences in reaction times to the word categories \((p=.42)\).

Creswell and Chalder (2002) also used a card version of the modified Stroop task, however rather than somatic illness related stimuli they used positive and negative personal description words (e.g. calm, lazy) and matched neutral words. They found a statistically significant interference effect in the CFS population compared to healthy controls \((p=.004)\); which continued to approach significance when controlling for anxiety and depression \((p=.06)\). Further analysis revealed that negative personal descriptors (e.g. lazy, weak, foolish) significantly interfered with attention in the CFS group when compared to a healthy control group \((p<.05)\) but not when compared to a diabetes group. Both chronic illness groups showed a bias for personally descriptive negative information.
The two unpublished studies used computerized versions of the Stroop paradigm (Gillings, 2007; Arroll, 2009). Gillings (2007) used three sets of word stimuli; fatigue (e.g. exhausted), negative (e.g. lonely) and neutral. Gillings (2007) found no significant differences between CFS participants, arthritis patients and healthy controls in terms of how they responded to stimuli, however, all groups responded faster to negative information than fatigue or neutral stimuli. Gillings (2007) provided no information on how stimuli were developed or selected and no measure of symptomology or illness duration.

Arroll, (2009) used CFS related and neutral stimuli, selected solely on matched word length. They found the CFS group had slower reaction times to all stimuli compared to healthy controls \( (p=.07) \). There was a significant group difference in response times to the neutral and symptom related words \( (p<.05) \); the control group were slower to respond to symptom related stimuli than neutral stimuli \( (p<.05) \) but people with CFS were not. However, when these mean scores were used to calculate interference effects, they found no significant group differences \( (p>.05) \).

**Studies using visual probe and exogenous cueing paradigms.** Three studies used the Visual Probe paradigm in CFS (Hou, Moss-Morris, Bradley, Peveler, & Mogg, 2008; Hou, et al., 2014; Papitsch, 2005).

Hou et al. (2008) used words and images relating to general health threats and contrasted these with matched neutral stimuli, presented for 500ms. This study found that people with CFS were quicker to respond to cues in the location of health threatening words and images compared to neutral stimuli; an attentional bias that was not found in the healthy
control group. These findings were independent of anxiety and depression when HADS scores were entered as co-variants.

A larger study by the same authors was able to detect more detailed sub-group results (Hou, et al., 2014). Using the same stimuli they found people with CFS had an attentional bias towards health threatening words, but not for threatening pictures presented for both 500ms and 1250ms (Hou, et al., 2014), indicating attentional biases continue to occur at later stages of processing. There were no significant correlations between attentional bias scores and anxiety or depression. Hou et al. (2014) also measured attention processes using the Attention Network Task (Fan, McCandliss, Sommer, Raz, & Posner, 2002); an objective measure of the alerting network, orientation of attention, and executive attention control. There were no groups differences in alerting or orientating of attention however people with CFS had impaired executive attentional control ($p=.01$) compared to healthy participants which was associated with increased attentional bias for threat words ($p<.001$) but not pictures ($F<1.$)

One unpublished study employed a visual probe task (Papitsch, 2005). The CFS group was dichotomised into those with and without co-morbid depression and compared to a healthy control group. Papitsch (2005) used five sets of 12 words relating to fatigue, illness, depression, positive control and neutral words; presented for 500ms. Papitsch (2005) found no significant differences between groups in response to fatigue or depression words but a significant effect in relation to illness stimuli ($p<.05$), with depressed CFS patients responding slower to illness stimuli, whereas healthy controls responded quicker ($p<.01$). Planned contrasts also found CFS participants with concurrent depression had an attentional bias for depression related information when compared to non-depressed CFS participants ($p<.05$). These effects were not controlled
for anxiety despite the depressed CFS group reporting significantly higher anxiety than the non-depressed CFS group \((p<.005)\) and healthy controls \((p<.001)\). These findings should be treated with caution as this unpublished study was underpowered and had poor quality rating compared to the published studies in this review.

Martin & Alexeeva (2010) employed an exogenous cueing task. Stimuli were presented for 100ms and consisted of neutral, social threat, and illness words; based on stimuli from Moss-Morris and Petrie (2003) and the pain literature (Keogh, Ellery, Hunt, & Hannent, 2001). Before the exogenous cueing task all participants were randomly allocated to either a rumination induction (instructed to read/ think about present physical sensations, emotions and thoughts) or distraction induction (instructed to read/ think about neutral external matters, such as objects). Martin and Alexeeva (2010) found no support for an early attentional bias towards either illness related or social anxiety words in a CFS sample compared to healthy controls, even when participants were induced into a ruminative state.

**Do people with CFS show an Interpretation bias?**

Table 4 summarises the interpretative bias studies. Moss-Morris and Petrie’s (2003) asked participants to write down the first word that came to mind after hearing an ambiguous illness-related (e.g. weak/ week) or neutral (e.g. fish) word. Responses were rated by two independent researchers as either neutral or illness-related. Moss-Morris and Petrie (2003) found CFS participants were significantly more likely to interpret ambiguous words in a threatening manner than healthy controls \((p < .001)\); an effect which remained when depression was controlled for. Illness related interpretations were significantly positively correlated with the somatic checklist and PFRS \((p<.001)\); this relationship was independent of both level of depression and negative affect.
Martin and Alexeeva (2010) used an online lexical decision task to measure interpretive bias after inducing a neutral or ruminative state. The lexical decision task required participants to quickly identify whether a string of letters (target) that appeared on screen was a word or non-word, whilst they listened to homophones with illness, depression or neutral interpretations. The study found there was a trend for CFS participants to be slower than controls to identify if the text was a word or non-word \((p=.05)\) and neutral homophones produced significantly faster reaction times than illness and social threat homophones \((p<.001)\). However, there was no significant interaction between group (CFS and healthy controls), homophones and the target \((p=.68)\) regardless of induction.

An unpublished study by Papitsch (2005) used an offline word stem completion task whereby participants were presented with the first three letters of a word and asked to complete it. The word stems had at least two possible completions, one of which was illness related (e.g. weak/ week). Papitsch (2005) conducted this task at two time points, before and after a visual-probe task. Two separate analyses were conducted. The first word stem completion task was assessed for the proportion of illness related completions compared to neutral or positive word completions. There were no significant differences between CFS participants with and without depression and healthy controls in the proportion of positive, negative, health-related or neutral word completions.

The second word stem completion task was analysed for the types of responses generated and for the proportion of illness word completions which had not appeared in the previous visual-probe task. There were no significant differences between groups, however, there was a trend for depressed CFS participants to recall a higher proportion of depressed words than the control group \((p=.06)\). There was also a trend for groups to differ with
regard to illness related completions which had not appeared in the previous visual probe task \((p=.05)\); with CFS participants generating a significantly higher number of health-related word completions than healthy controls \((p<.05)\). However, it should be noted that these unpublished interpretative biases studies score particularly low in the quality assessment \((9/16)\) and as such results should be viewed with caution.

**Are cognitive biases associated with anxiety and depression?**

Group effects of attention and interpretation biases remained significant when controlling for HADS anxiety and depression scores (Cresswel & Chalder, 2002; Hou, et al., 2008; Hou et al., 2014; Moss-Morris & Petrie, 2003), suggesting cognitive biases in CFS are independent of self-reported mood and affect. One study compared CFS participants with and without co-morbid depression and found only depressed CFS participants showed cognitive biases for depression related stimuli (Papitsch, 2005), suggesting content specific processing in depression. However, these findings are based on a small number of studies, thus these findings are indicative only.

**Discussion**

This review shows preliminary evidence that CFS is associated with biases in attention and interpretation of negative or illness related information. These effects do not appear to be explained by the presence of comorbid anxiety and depression. It is also important to note that there was generally large heterogeneity in the CFS findings suggesting that cognitive processing biases may be more evident in some people with CFS than others.

**The nature of the attentional bias.** The Stroop studies found little support for an interference effect of illness related stimuli in CFS populations. In contrast, findings from the Visual Probe studies indicated that, for people with CFS, health threatening and illness
related information engages (500ms) and maintains (1250ms) their attention more than neutral information; an attentional bias effect was not found for 100ms (Martin & Alexeeva, 2010), indicating that in a CFS population, attentional bias may occur at the elaboration phase of the information processing system, rather than the initial orientation phase. Thus, cognitive biases in CFS may represent a specific cognitive strategy developed to avoid further injury and disability. Such a strategy requires an initial appraisal of the information which may explain the lack of attentional bias at earlier, pre-attentive levels of processing (i.e. 100ms).

Whilst illness specific biases were not related to anxiety and depression, there was some evidence that the existence of co-morbid depression in CFS may result in attentional bias to negative personal descriptors. This finding may represent a non-specific bias in a subset of patients who have developed depressive symptoms in response their illness. Arguably many of the stimuli used in the attentional studies thus far may not be integral to CFS; health threatening stimuli related to general health anxiety rather than CFS per se, and the effects here may relate to anxiety about health and symptoms in general as opposed to chronic fatigue specifically. Given that research shows attentional biases for personally salient concepts (Riemann & McNally, 1995), research is needed to optimize stimuli valence in CFS. Due to the heterogeneity of CFS (Cella & Chalder, 2010) these stimuli are likely to extend beyond fatigue related information.

Additionally, there was some evidence for attentional bias to illness threat words as opposed to images, suggesting a verbal thought process, which may reflect a ruminative/worry thought pattern. The anxiety and depression literature has demonstrated that verbal worry takes up more attentional capacity and is associated with attentional bias (Stefanopoulou, Hirsch, Hayes, Adlam, & Coker, 2014; Williams, Mathews, &
Hirsch, 2014). It may be that people with CFS think about their condition and symptoms verbally which reduces their attentional control and contributes to the development and/or maintenance of an attentional bias towards illness related information. This hypothesis is supported by Hou, et al.’s (2014) finding that poor attentional control was associated with attentional bias in CFS.

The nature of the interpretation bias. An interpretative bias was found when participants had time to elaborate on the stimuli and generate their own responses (off-line tasks; Moss-Morris & Petrie, 2003); but not when participants were required to make spontaneous automatic responses (on-line tasks; Martin & Alexeeva, 2010). This suggests that people with CFS may generate illness related interpretations when there is an opportunity to draw upon their existing illness schemas. This theory is further supported by Moss-Morris and Petrie’s (2003) finding that CFS patient’s interpretative bias scores were associated with their self-reports of how much they focused on symptoms. Symptom focusing and meta-cognitive beliefs about the helpfulness of symptom monitoring has been found to play a role in the persistence of CFS (Moss-Morris, Sharon, Tobin, & Baldi, 2005; Wiborg, Knoop, Prins, & Bleijenberg, 2011), suggesting that this is a maladaptive coping strategy. It may be that interpretation biases form a part of this coping strategy by habitually processing information in an illness related way, activating symptom monitoring and perpetuating fatigue.

Together the findings from these attention and interpretation studies suggest that people with CFS have illness related top down processing biases (i.e. biases in effortful assimilation and organization of incoming information) which affects how information is interpreted and attended to. The bias for illness stimuli, but not negative or depression related information would indicate that people with CFS (without self-reported comorbid
depression) have developed illness specific schemas or representations based on previous experiences. It may be that illness specific rumination activates this illness schema which then filters incoming information for congruence, resulting in cognitive processing biases.

Studies found these illness biases to be independent of anxiety and depression, indicating that attention and interpretative biases in CFS are not just a function of negative affect or con-current depression. However, it is important to note these studies used self-reported levels of distress as measures of anxiety and depression (Norton, et al., 2013). Further research is needed to explore the role of common comorbidities in CFS using clinical diagnostic assessments.

These findings mirror those in chronic pain, whereby an attentional bias occurs for sensory pain information at later elaborative phases of processing (top-down processing) (Crombez, Van Ryckegehem, Eccleston & Van Damme, 2013); and a pain related interpretative bias is related to fear of pain, catastrophizing (Khatibi, Sharpe, Jafari, Gholami & Dehghani, 2015) and symptom reporting (Pincus and Morley, 2001). This suggests that illness specific representations affect how information is processed and that these processes may help maintain the severity of these symptom experiences.

**Methodological issues**

The stimuli selection processes varied substantially across the studies. Some researchers drew upon stimuli previously developed for pain and depression, which may not be relevant for this specific patient group. Largely the studies used health anxiety and a fatigue stimulus to tap into symptom related processing. However, other processing biases may also be relevant to CFS, for example biases for effort and repercussions of
over-activity. Mediation analysis of behavioural interventions has shown that fear avoidance beliefs about activity as well as catastrophic thinking habits are relevant for CFS patients and the perpetuation of symptoms (Chalder et al., 2015). Research is needed to optimize stimuli valence in CFS and tap into the implicit processes maintaining a range of negative illness beliefs.

Additionally, many papers failed to report how control stimuli were decided upon. Without such information, it is hard to determine whether the control and target stimuli are appropriately matched. One study failed to match words on frequency of use in the English language (Arroll 2009), an important consideration as unusual words take longer to process (Moss-Morris, et al., 1996). Furthermore, a variety of recruitment procedures were used from specialist clinics to support groups and the community, which may have introduced a recruitment bias or a self-selection bias.

Given that no one measure of symptomology was used, this review cannot compare severity of symptom reporting. Some studies reported mean illness durations over 11 years; thus, cognitive biases may reflect the chronicity of their illness generally rather than a unique CFS effect. In order to account for this, two studies included other chronic illness groups (Gillings, 2007; Creswell & Chalder, 2002) but failed to use illness specific stimuli and illness duration or symptomology were not reported. Future research should compare CFS with another illness groups with similar levels of disability.

Given that many of the studies just missed statistical significance, it is likely that small samples sizes limited their power to detect an effect. Additionally, the large standard deviations among the CFS groups in both self-report and laboratory cognitive measures indicates heterogeneity. Despite the small sample sizes, sub-group analysis provided
some significant and intriguing findings. Sub-grouping in future studies may lead to a more detailed picture. It may be that only some people show an attentional bias, for example those with certain cognitive tendencies or poor attentional control.

The methods used in these studies emphasize the interplay between effortful top down process and more habitual bottom up processes. The studies which used methods that required more elaborative processing or maintained attention, reflecting top down processes, found cognitive biases; whereas, those which used methods tapping into earlier stages of processing (e.g. the exogenous cueing task and lexical decision task), reflecting more habitual processing, did not. Collectively these findings suggest that in CFS cognitive biases occur at later stages of processing, which may reflect a cognitive strategy to avoid further injury and disability. However, the division between different stages of processing is not clear cut. For example, an attention bias at 500ms may represent initial orientating of attention or a maintained attention. Alternative methods, such as eye tracking, would be beneficial in exploring the time course of attentional biases. The methods presented here present only a ‘snap shot’ of biases at predefined durations.

The findings of this review are limited by a small number of studies. Nevertheless, the studies reviewed represent a novel approach to studying cognitive factors in CFS. By providing a synthesis of the findings to date, this review has highlighted several issues for future research to consider in order to forge a consistent approach to cognitive biases research. Replication studies are needed using the paradigms, with stimuli specifically developed to tap into patient group symptoms and illness related concerns.

Conclusions
Taken together, the results from the cognitive processing studies provide a preliminary profile of the underlying cognitive processes in people with CFS. Some people with CFS have attention and interpretation biases at elaborative stages of processing. These findings fit with Beck’s schema theory (1976) whereby underlying schema filter incoming stimuli and direct attention to congruent information; a robust finding in anxiety (Bradley et al., 1998; Hayes & Hirsch, 2007; Mogg & Bradley, 2005) depression (Dohr, et al., 1989) and chronic pain (Pincus & Morley, 2001). People with CFS appear to have a dominant schema of their illness as having serious consequences, being uncontrollable and long lasting (Moss-Morris, 2005). These coupled with the belief that fatigue is a sign of physical damage and that activity will likely make it worse, may result in information processing biases for symptom related information. These biases in CFS were found to be relatively independent of anxiety, depression and negative affect.

These findings reinforce and elaborate the current CB model of CFS (Chalder, et al., 1996; Surawy, et al., 1995). The studies illustrate how negative illness schemas, as explained above, may bias how people process information and in so doing reinforce the unhelpful cycle of cognitions and behaviours. This review builds upon the existing self-report research (i.e. symptom focusing activates the illness schema and primes the individual for making somatic biases) and neuropsychological studies, (i.e. poor attentional control allows attention to be more readily grabbed and maintained by schema congruent information).

These experiential paradigms provide an additional method of studying constructs related to illness representations which occur at more implicit levels of processing. It may be interesting for researchers to explore these constructs in other groups of patients. In terms of CFS, further research is needed, using reliable and standardized methodology and
illness specific materials, in order to identify whether cognitive processing biases are a reliable phenomenon in CFS. If these effects are replicable, future work will need to determine whether there is a causal link with chronic fatigue. To do this, studies are needed which measure biases pre and post treatment and assess the extent to which change in the bias predicts improvement. Manipulation of the bias itself can establish whether it moderates fatigue, which would indicate that the cognitive process has a causal role in the maintenance of CFS. Potentially, once this basic research is carried out, this knowledge could be translated into novel clinical interventions, for example cognitive bias modification training (see Hertel & Mathews, 2011) or attentional control functioning (see Siegle, Ghinassi, & Thase, 2007) to be used alongside existing treatments.
References of Articles in the Systematic Review


Appendix A

The Downs and Black instrument was selected as it was designed to assess non-randomized designs and contained the highest number of relevant items for the needs of this review. However, as not all items were relevant to the studies included in this review (many relating to interventions), a modified version of the checklist was employed with the following items omitted: items 8 and 9 in the reporting scale, items 13, 14, 15, 17 and 19 in the section on bias, items 23, 24 and 26 relating to confounding and item 27 addressing power was replaced with an easier to use item. Item 4 in the reporting scale was modified to assess whether ‘the experimental tasks were clearly described’ as opposed to whether the ‘intervention’ was clearly described. The final checklist was made up of 17 items with a maximum score of 17 points (with higher points indicating superior quality) rather than the original 32 points. The checklist covered the categories of reporting, external validity and internal validity (bias). The checklist was administered by two independent researchers and cross checked for consistency.

17 Item Quality Checklist:

1. Is the hypothesis/aim/objective of the study clearly described? Must be explicit.

2. Are the main outcomes to be measured clearly described in the Introduction or Methods section? If the main outcomes are first mentioned in the results section the answer should be no. All primary outcomes should be described as yes.

3. Are the characteristics of the patients included in the study clearly described? In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.

4. Are the experimental tasks clearly described?

5. Are the distributions of principal confounders in each group of subjects to be compared clearly described? A list of principal confounders is provided.
6. Are the main findings of the study clearly described? Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions.

7. Does the study provide estimates of the random variability in the data for the main outcomes? In non normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported.

8. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?

9. Were the subjects asked to participate in the study representative of the entire population from which they were recruited? The study must identify the source population for patients and describe how the patients were selected.

10. Were those subjects who were prepared to participate representative of the entire population from which they were recruited? The proportion of those asked who agreed should be stated.

11. If any of the results of the study were based on “data dredging”, was this made clear? Any analyses that had not been planned at the outset of the study should be clearly indicated. Retrospective = NO. Prospective = YES

12. Were the statistical tests used to assess the main outcomes appropriate? The statistical techniques used must be appropriate to the data. If no tests done, but would have been appropriate to do = NO

13. Were the main outcome measures used accurate (valid and reliable)? Where outcome measures are clearly Yes/No/UTD described, which refer to other work or that demonstrates the outcome measures are accurate = YES. ALL primary outcomes valid and reliable for YES
14. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? Patients for all comparison groups should be selected from the same hospital. The question should be answered UTD for cohort and case control studies where there is no information concerning the source of patients.

15. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time? For a study which does not specify the time period over which patients were recruited, the question should be answered as UTD. Surgical studies must be <10 years for YES, if >10 years then NO

16. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? In nonrandomised studies if the effect of the main confounders was not investigated or no adjustment was made in the final analyses the question should be answered as no. If no significant difference between groups shown then YES

17. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance <5%
Chapter 4 Developing illness-specific materials for experimental research

4.1 Chapter overview

This chapter is published in the following article:

4.2 Published article

**Title:** Maximizing potential impact of experimental research into cognitive processes in health psychology: A systematic approach to material development

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Statement of contribution

What is already known on this subject?
Cognitive biases (e.g., tendencies to attend to negative information and/or interpret ambiguous information in negative ways) have a causal role in maintaining anxiety and depression.
There is mixed evidence of cognitive biases in physical health conditions and chronic illness; one reason for this may be the heterogeneous stimuli used to assess attention and interpretation biases in these conditions.

What does this study add?
Steps for comprehensive/robust stimuli development for attention and interpretation paradigms are presented.
Illustrative examples are provided from two conditions: chronic fatigue syndrome and breast cancer.
We provide tools to help researchers develop condition-specific materials for experimental studies.
Abstract

Background: There is an abundance of research into cognitive processing biases in clinical psychology including the potential for applying cognitive bias modification techniques to assess the causal role of biases in maintaining anxiety and depression. Within the health psychology field there is burgeoning interest in applying these experimental methods to assess potential cognitive biases in relation to physical health conditions and health-related behaviours. Experimental research in these areas could inform theoretical development by enabling measurement of implicit cognitive processes that may underlie unhelpful illness beliefs and help drive health-related behaviours. However, to date, there has been no systematic approach to adapting existing experimental paradigms for use within physical health research. Many studies fail to report how materials were developed for the population of interest or have used untested materials developed ad-hoc. The lack of protocol for developing stimuli specificity has contributed to large heterogeneity in methodologies and findings. Purpose: In this article we emphasize the need for standardised methods for stimuli development and replication in experimental work, particularly as it extends beyond its original anxiety and depression scope to other physical conditions. Method: We briefly describe the paradigms commonly used to assess cognitive biases in attention and interpretation, then describe the steps involved in comprehensive/robust stimuli development for attention and interpretation paradigms using illustrative examples from two conditions; chronic fatigue syndrome and breast cancer. Conclusions: This article highlights the value of preforming rigorous stimuli development and provides tools to aid researchers engage in this process. We believe this work is worthwhile in order to establish a body of high quality and replicable experimental research within the health psychology literature.
**Introduction**

Several decades of research in clinical psychology have identified that how people process incoming information, specifically having an attentional bias to threatening information (attentional bias) and a bias to interpret ambiguous information in a negative way (interpretation bias), plays a central role in the onset and maintenance of anxiety and depression (Beck, 2002; Beck & Clark, 1997; MacLeod, et al., 1986; Mathews & MacLeod, 2005; Mogg, Mathews, & Eysenck, 1992; Wilson, MacLeod, Mathews, & Rutherford, 2006). Within health psychology, there is burgeoning interest in applying these experimental methods to assess potential cognitive processing biases in physical health conditions, such as chronic pain (Pincus & Morley, 2001; Schoth, Nunes, & Liossi, 2012), chronic fatigue syndrome (Hughes, Hirsch, Chalder, & Moss-Morris, 2016a) irritable bowel syndrome and cancer (Chan, Ho, Tedeschi, & Leung, 2011) as well as health behaviours such as eating, (Beard, Weisberg, & Primack, 2012; Dobson & Dozois, 2004; van Beurden, Greaves, Smith, & Abraham, 2016), smoking (Bradley, Mogg, Wright, & Field, 2003) and alcohol use (Field, Mogg, & Bradley, 2005; Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011). Experimental research in these areas could inform theoretical development by enabling access to levels and types of information processing that may underpin unhelpful illness representations and influence health behaviours (Sheeran, et al., 2016).

To date, health psychology theories have often neglected the role of these less conscious processes in behaviour and coping (Sheeran, Gollwitzer, & Bargh, 2013); assuming behaviour is predominantly driven by conscious processing, for example the theory of planned behaviour (Ajzen, 2011). However, some prominent health psychology models acknowledge a role for more implicit processes. Leventhal’s self-regulatory model (Leventhal, et al., 1997; Leventhal, et al., 1980) proposes that illness representations are
crucial to understanding human adaptation and response to illness and that, importantly, these illness representations can be activated by stimuli at any level. The role of explicit illness representation in adjustment to illness, adherence to treatment, and psychological and clinical outcomes has received vast empirical support across a range of conditions (Hagger & Orbell, 2003; Petrie & Weinman, 2006). However, the role of ‘nonconscious’ or implicit processes that may be activating these illness representations has been lesser explored, particularly in physical health and chronic illness.

These more implicit levels of processing require alternative methods of assessment than self-report questionnaires. Clinical psychologists have led research in this field, developing computerized experimental methods to tap into how people implicitly process salient, emotive and threatening information. The rationale was that salient information to the individual would be preferentially processed above that of neutral information (Riemann & McNally, 1995; Tamir & Robinson, 2007; Yiend, 2010).

These methods have been employed in research into health behaviours and to a lesser degree physical health conditions. The chronic pain literature in particular, has employed these experimental methods to test the role of hypervigilance to pain (Crombez, Van Ryckeghem, Eccleston, & Van Damme, 2013) as well as pain related interpretations of ambiguous information (Schoth & Liossi, 2016). Experimental research has begun to be carried out in other long term conditions such as Chronic Fatigue Syndrome (Hughes, et al., 2016a), Irritable Bowel Syndrome (Afzal, Potokar, Probert, & Munafò, 2006; Chapman & Martin, 2011; Tkalcic, Domijan, Pletikosic, Setic, & Hauser, 2014) and fear of cancer recurrence (Butow, et al., 2015; Custers, et al., 2015; DiBonaventura, Erblich, Sloan, & Bovbjerg, 2010; Miles, Voorwinden, Mathews, Hoppitt, & Wardle, 2009). However, to date, evidence for cognitive biases in these areas has been mixed. One reason
for the heterogeneous findings may be the suboptimal selection of stimuli materials to tap into salient concepts of the target population (Hendrikse, et al., 2015). Some studies have used materials developed for other populations, for example studies of attentional biases in CFS (Hou, Moss-Morris, Bradley, Peveler, & Mogg, 2008; Hou, et al., 2014; Hughes, et al., 2016a) have used materials developed for the general population to tap into health threats (Lees, Mogg, & Bradley, 2005), which may not be integral to the specific concerns of the population. More specific and distinct types of stimuli are needed in order to help refine our models and allow for stimuli specific predictions. Whilst some material development and validation work has been carried out in some studies (Andersson & Haldrup, 2003; Crombez, Hermans, & Adriaensen, 2000; Keogh, et al., 2001; Moss-Morris & Petrie, 2003) many fail to thoroughly address this issue, selecting materials from previous literature without validation (Dehghani, Sharpe, & Nicholas, 2003), gaining ratings of stimuli from unrelated populations (Martin & Alexeeva, 2010; Tkalcic, et al., 2014), or failing to report how materials were selected or categorized (Asmundson, Carleton, & Ekong, 2005; Roelofs, Peters, Fassaert, & Vlaeyen, 2005).

Given that patterns of processing biases are most pronounced for stimuli specifically related to the principle domain of concern that characterizes that particular disorder (Gotlib, Krasnoperova, Yue, & Joormann, 2004), it is essential that preliminary work is conducted to identify clinically relevant stimuli, salient to the particular clinical group and integral to the concepts in which they intend to tap into. We argue that a systematic approach to stimuli development across the experimental literature would enhance the content validity of the stimulus materials and enable further specificity in the conclusions drawn for experimental research in different populations.

In this paper we briefly describe the paradigms commonly used to assess cognitive biases, and then propose a series of steps for developing condition specific salient stimuli for
attention and interpretation paradigms; providing tools to assist this process and illustrative examples from two conditions, CFS and breast cancer. These cases have been chosen as two distinct populations in which some experimental research has been conducted but produced inconsistent results. CFS is a condition of severe, debilitating and enduring fatigue (Fukuda, et al., 1994). Breast cancer is a specific life threatening event that can have an emotional impact of an individuals’ life for years to come (Ganz, et al., 2002). Cognitive processes may play a role in how people with both these conditions cope with on-going symptoms and specific health threats.

**Examples of methods of assessing cognitive processing biases**

**Attentional bias (AB)**

Three paradigms are commonly used to assess AB, the modified emotional Stroop task (Williams, Mathews, & MacLeod, 1996); the visual probe task (MacLeod, et al., 1986) and the exogenous cueing task (Posner, 1980; Posner, Walker, Friedrich, & Rafal, 1984). These tasks use reaction time to neutral versus emotive stimuli to determine an AB score. Emotive stimuli are either words or images relating to the concept of interest and salient to the participant group. For example, previous studies in chronic pain have used words such as ‘aching’ and images of people in pain. These salient, emotive or ‘threatening’ stimuli are paired with control stimuli which are usually neutral and/or positive. Quicker reaction time to threatening stimuli compared to control stimuli is thought to indicate an attentional bias for such information.

**Interpretative bias (IB)**

There are a variety of IB paradigms in use (for review see, Hirsch, Meeten, Krahe, & Reeder, 2016). All require the participant to resolve some form of ambiguous information by inferring an interpretation. A commonly used IB task is ambiguous scenarios task (Mathews & Mackintosh, 2000), whereby participants are presented with real world
scenarios, each starting with a title and ending ambiguously. After reading a selection of scenarios they are presented with a 'recognition test', where they rate four sentences (one positive interpretation, one negative interpretation and a positive and negative foil) to the degree to which they are similar or dissimilar in meaning to the original text. The rationale is that high similarity ratings of the recognition sentence relating to a negative interpretation of the text, is indicative of a more negative interpretation of the ambiguous information. The foil sentences are included to rule out the possibility of participants endorsing any material of a certain valence (positive or negative) without truly interpreting the text.

In this paper we will describe steps involved in developing ambiguous and appropriate IB materials which can be used for any IB task, with specific examples of material development for the ambiguous situations task. IB materials need to be devised to allow for both positive and negative inferences to be generated. In order to assess interpretations that maintain a given problem, IB materials should focus on the type of ambiguity people face in everyday life at times when the central component of interest is operating (Hirsch, et al., 2016). All recognition statements should be realistic but distinctly positive or negative. The interpretation items should be equally credible resolutions to the ambiguous scenario. The foil items should be related to the original text but have an obvious factual inaccuracy. Examples of IB items such as those used in the ambiguous scenarios task are presented in Appendix C.

Selecting appropriate materials to tap into central ambiguous concepts for a given physical health problem (hypothesis development & refinement)

Before embarking upon the development of appropriate materials for experiments, researchers need to identify the salient concept(s) they wish to tap into, based on a sound
theoretical rationale. For example, the fear avoidance model of chronic pain (Vlaeyen & Linton, 2000) proposes that fearful patients become increasingly vigilant to signals of bodily threat, which in turn leads to avoidance behaviour and increased disability. As such experimental research in chronic pain based on this theory have used materials which tap into bodily threat, e.g. words and images relating to the sensory (e.g. throbbing, sharp) and affective (e.g. agonizing, punishing) experience of pain (Crombez, Van Ryckeghem, Eccleston, & Van Damme, 2013; Roelofs, Peters, Crombez, Verschuere, & Vlaeyen, 2005). However, other applications of experimental research in areas of health and physical illness have often poorly defined theoretical concepts and have tended to tap into broadly defined concepts, such as general health anxieties (Hou, et al., 2008) or social threat (Chapman & Martin, 2011). These broader concepts are informative for exploring psychopathology but do not draw or build upon an illness specific theory driven approach. Experimental studies should be guided by a sound rational as to when, how and why cognitive biases may play a role in the specific group of interest. This theory driven approach should guide researchers to identify concepts of experimental interest.

**Stimuli development and testing**

The next step is to develop and pilot relevant materials. Materials need to map directly onto the key concepts pertinent to a given bias that may be central to the clinical problem. Given this may vary between people the materials need to span the main, common themes or aspects of the problem. Here we propose a systematic and robust approach to stimuli development and testing, with associated tools to aid researchers with this process (Figures 1 and 2) and provide illustrative examples of stimuli development for two populations;
**Illustrative example 1 – CFS:** In order to assess whether people with CFS have an AB for CFS-related stimuli and/or an illness related IB, appropriate materials that capture key aspects of CFS were developed. This research builds upon cognitive behavioural models of CFS which propose that physiological factors interact with cognitive and behavioural responses to illness to perpetuate symptoms and disability (Chalder, Butler, & Wessely, 1996; Knoop, et al., 2010; Vercoulen, et al., 1998). Selective attention towards health threatening information and a tendency to interpret ambiguous information in a health threatening way, may also contribute to this vicious circle.

**Illustrative example 2 – Breast Cancer:** In order to determine whether disease-free breast cancer survivors attend to and interpret cancer and symptom related information following treatment, cancer related materials were developed that mapped onto key concerns of this population. The rationale was that a selective processing of threatening cancer information and interpretation of potentially cancer related information in a negative way may have triggered or reinforced distress.
Figure 1. Flow Diagram for Attentional Bias Stimuli Development

- **Research**
  - Relevant theory
  - Are there any experimental studies in the population of interest or related populations?
    - no
      - Qualitative interviews to identify salient concepts
    - yes
      - Extract materials

- **Development**
  - Expand pool of materials across different key aspects of the physical health problem

- **Testing**
  - Survey to rate salience completed by sample of the population (see appendix A)
  - Select stimuli rated as most salient for the attentional bias task

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Are the positive and negative foils related to but factually inconsistent with the scenario?

Are both the positive and negative interpretations realistic in relation to the scenario?

Are the positive and negative interpretations equally likely to be endorsed?

Is the scenario self-referential?

Does the scenario allow for both positive and negative resolutions?

Does the scenario describe a realistic every day situation where key ambiguity may occur?

Identify salient concepts/ themes

Identify relevant theory

Search existing literature

Conduct exploratory interviews and focus groups to identify salient concepts where an interpretation may be generated

Develop test materials

Interpretation items

Foil items

Pilot test materials

Think aloud sessions with sample of population

Pilot IB task with patient population and control groups

Not sufficient for test material

no

Figure 2. Flow diagram for Interpretative Bias Stimuli Development
Step 1: Pooling materials

As with any research, we begin with ‘what is known’ on the subject. Have any experimental studies been conducted in this area before? If so, what materials did they use? How were these materials selected? Are there any experimental studies in areas with some overlap with the area of interest? What explicit measures are used to assess the type of concepts of interest? In order to aid this process, we propose that researchers make materials easily available, to aid information sharing and replication, as well as being transparent about the conceptual model which led to the operationalisation of these stimuli.

Example 1. Attention: As a starting point to developing AB materials to tap into CFS related concerns, we pooled materials from previous experimental studies in CFS (Hou et al., 2008; 2014; Moss-Morris & Petrie, 2003) as well as chronic pain (Schoth et al., 2012) and general health anxiety (Lees, et al., 2005; Owens, Asmundson, Hadjistavropoulos, & Owens, 2004). Interpretation: In order to identify salient topics which may elicit an interpretation bias in CFS, we drew from the Cognitive Behavioural Responses Questionnaire (Cella, et al., 2013; Skerrett & Moss-Morris, 2006) and Illness Perceptions Questionnaire (Moss-Morris, et al., 2002; Weinman, Petrie, Moss-Morris, & Horne, 1996).

Example 2. Attention: Initial AB material was pooled from cognitive biases studies in cancer populations (Butow, et al., 2015; Custers, et al., 2015; Glinder, Beckjord, Kaiser, & Compas, 2007) as well as healthy populations with anxiety about cancer (DiBonaventura, et al., 2010). Interpretation: For the development of ambiguous situations for the IB task, initial topic areas were generated from searching cancer survivorship literature (Costanzo, et al., 2007; Fenlon, et al., 2015; Miles, et al., 2009).
Step 2: Focus groups & interviews

The pooling process results in an accumulation of potentially useful but non-specific materials. The next stage is to use qualitative methods to identify salient illness specific concerns and extract vocabulary or images directly generated by the patient or target group.

Example 1. One to one interviews with CFS participants explored the experience of CFS using open questions and prompted interviewees to recall real-life examples that captured these experiences. A workshop with six clinically trained psychologists and cognitive behaviour therapists who specialize in the treatment of CFS, discussed the ways in which their patients typically described their experience of CFS and recurring themes salient to that experience. Attention: Fifty-six words used to describe CFS were extracted from the interviews and workshop. Interpretation: The real-life examples described by patients and clinicians were used to develop 40 ambiguous test items for the IB task, which tapped into the three overarching themes of (i) perceived effort (ii) catastrophic thinking (iii) misattributions of emotions and sensations. The test materials were short descriptions of an ambiguous scenario which could be interpreted in either a positive or somatic way (Appendix B1).

Example 2. Interviews with six breast cancer survivors explored issues of most concern, with open questions regarding their experiences and worries. Attention: Fifty-eight cancer-related words were identified from previous literature and interviews. Interpretation: Key themes associated with breast cancer survivorship were identified from the interviews; (i) fear of cancer recurrence (ii) symptom attribution (iii) concerns about the future and (iv) adjusting to life after treatment for cancer. Fourteen test materials
for the IB task were developed to tap into these themes. Test materials consisted of descriptions of an ambiguous situation and statements offered a positive or negative interpretation of the situation (Appendix B2). Test materials were piloted in the next step.

**Step 3: Piloting the face validity**

The next step is to pare down the accumulated specific and nonspecific materials by selecting items with the best face validity. Similar to the development of questionnaires, this process involves piloting materials with a sample of the target population and conducting think aloud sessions to examine if instructions are understood and interpreted in the expected way.

*Example 1. Attention:* A survey was conducted to determine which of the 56 illness related words identified in steps 1 and 2 were likely to be of current concern, since this will enhance the likelihood that potential AB in CFS will be identified. Participants rated the salience of each word to their experience of CFS (Appendix A). Fifty-eight CFS participants completed the survey. Mean ratings were calculated per word, with higher scores reflecting a greater emotive valence. Twenty-four highest scoring words were selected for the AB task. Words with the highest ratings broadly related to symptom experience (e.g. ‘shattered’) and associated consequences (‘bedbound’). *Interpretation:* A second pilot survey was set up for the IB task which included patients with CFS and healthy controls. The survey consisted of 40 short ambiguous scenarios, with the last word left blank. Participants had to complete the last word, thus revealing their interpretation of the text (Appendix B1). For example, ‘You have planned to clean the downstairs of your house today and found this easier and quicker than you expected. You think if you carry on you will feel …. In this example potential completions could be exhausted or pleased’. Twenty-six CFS participants and 26 healthy participants
completed the survey. The single word completions were rated by two independent researchers, as CFS-related, generally negative, neutral or positive. Inter-rater reliability was high (97% consensus). The scenarios which demonstrated the biggest difference between the groups in terms of CFS-related interpretations, and the scenarios which resulted in consistent conceptually related interpretations in the CFS group were developed into full text materials for the main IB task (Appendix C1).

**Example 2. Attention:** Stimuli for the AB task were rated for their relevance by 90 breast cancer survivors. Fifty-eight cancer related words, 64 general and 60 neutral words were separately rated on a 5 point scale for (i) the degree of threat (ii) and relevance to cancer. Twenty-four words that were most highly rated in terms of threat and cancer dimensions were selected for the AB task and matched by length and frequency to neutral words.

**Interpretation:** To test the stimuli for the IB task, breast cancer survivors (n=8) were asked to complete a pilot version of the task whilst conducting a think-aloud session with a researcher. This revealed that participants were rating statements according to their own experiences rather than how closely each statement matched the original scenario. Subsequent revisions were made to the instructions of the task and piloted with 51 breast cancer survivors. This piloting demonstrated low internal reliability and frequent endorsement of foil statements; suggesting participants might be forgetting the content of the original scenarios. The task was revised to more clearly differentiate target statements from foils and include expanded titles to make it easier for participants to recall the content of each scenario and piloted with 44 breast cancer survivors. Twelve materials with highest face validity were selected for the final IB task (Appendix C2).

**Hypothesis testing**
In order to test the relevant hypothesis, these illness specific materials need to be paired with control stimuli. The choice of control stimuli is very important as low frequency (unusual) words take longer to process (Moss-Morris, et al., 1996). However, many studies fail to report how control stimuli were decided upon (see Hughes, et al., 2016a for a discussion of this issue). In order to select the control stimuli for the CFS and cancer AB tasks, illness-related and control words were matched in terms of semantic properties that affect reading speed, including word length, number of syllables per word, and frequency of occurrence of each word in the English language. The open source ‘English Lexicon Project’ (Balota, et al., 2007) was used to identify neutral words with matched properties with a paired illness-related word. This is an important step as if words are not matched, one cannot unequivocally interpret differences in reaction time for illness-related and control words as being due to the ‘saliency’ of the words.

In tasks in which pictorial stimuli are used, illness-related and control stimuli should be matched in terms of basic perceptual features, such as overall complexity and brightness, which are likely to influence the allocation of attention, especially the rapid orienting of attention (Egeth & Yantis, 1997). Images should be rated, piloted and validated much in the same way as word stimuli.

In terms of matched materials for the IB tasks, items need to be carefully worded to allow for a positive but realistic interpretation of the earlier text. These positive interpretation items should have similar length and semantic structure to the negative interpretation item. Similarly, to the AB task, if this is not achieved, one cannot rule out the effect of these variables on the phenomenological characteristics observed.
For cross-sectional studies, comparative control groups should be matched to the sample population on variables that may affect their performance on the experimental tasks such as, cognitive ability, age and dexterity. It may be necessary to include an additional clinical control group in order to allow further discrimination between findings being attributed to general clinical characteristics (e.g. pain across different diseases) or findings specific to a particular physical health condition.

**Other conceptual and experimental issues to consider**

*How threatening is too threatening?*

In the real world it is adaptive for people to orientate towards highly threatening stimuli. Research has found that most people orientate towards high threat and away from mild threat (Mathews & Mackintosh, 1998; Mogg & Bradley, 1998); thus for group differences to be identified stimuli need to hold optimal levels of threat intensity for the population.

*Stimulus modality*

The optimal stimuli modality may differ according to the population being studied. For example, studies in CFS have found attentional biases for word stimuli but not images (Hou et al., 2008; Hou et al., 2014) whereas studies of chronic pain have identified an AB for pain related faces and words (Pincus & Morley, 2001; Schoth et al., 2012). This may indicate that in some conditions facial stimuli carry ecological relevance (Dear, Sharpe, Nicholas, & Refshauge, 2011), whereas in other conditions, such as CFS, patients think about their condition and symptoms verbally, thus linguistic stimuli hold greater ecological validity (Hou et al., 2008). However, it may be that these mixed findings are due to procedural variables that affected the presence and magnitude of an AB (Crombez, Van Ryckeghem, Eccleston, & Van Damme, 2013).
Stimuli duration

In AB tasks the duration of stimuli presentation or ‘stimulus onset asynchrony’ (SOA) is manipulated to tap into different stages of processing. Generally researchers have used SOA of 1000ms or more to infer the maintenance of attention and shorter SOA’s of 200ms or less tap into earlier, more ‘automatic’ processing (Koster, De Raedt, Goeleven, Franck, & Crombez, 2005; Mogg, Bradley, De Bono, & Painter, 1997). Similarly, modifications of IB tasks allow researchers to tap into more automatic (e.g. Hirsch & Mathews, 2000) versus controlled processing (e.g. Stopa & Clark, 2000). Researchers should refer to literature in their field to help them decide the stage of processing they wish to tap into (see Hirsch, et al., 2016). However, it is important to note that the distinction between earlier and later stages, or automatic and controlled processing is not clear cut and these paradigms offer only a snap shot of cognitive processing at a given time. Further studies and alternative methodologies are needed to explore the interplay between stages of processing.

Relatedly, these types of reaction time paradigms are restricted to assessing biases for words or images which hold an immediate or salient meaning. However, the concepts under scrutiny are often ones which cannot always be clearly and succinctly defined. For example, people with CFS often use metaphors or ‘as if’ statements to describe their symptoms. If singular words or images do not capture the distinctive sensory qualities of the object of threat they will not elicit a bias. Tasks which allow more vivid representation of the object of threat, such as the primary task paradigm (Crombez, Eccleston, Baeyens, & Eelen, 1998), could explore how the distinctive sensory qualities of the object of threat affects cognitive processing.

Cognitive ability
Cognitive ability affects reaction time (Deary & Der, 2005), recall (Reijnders, van Heugten, & van Boxtel, 2013) and reading ability (Wang & Gathercole, 2013), thus affecting participants’ performance on experimental tasks. Children and adolescents (Burgaleta, Johnson, Waber, Colom, & Karama, 2014) can show meaningful cognitive ability changes within relatively short developmental periods. Other populations such as the elderly (Rebok, et al., 2014) and those on certain medications such as anticholinergic drugs (Fox, et al., 2014), may have reduced cognitive ability. Researchers studying such populations should ensure they consider the level of sophistication of the language and that the SOAs are appropriate for the target population.

**Conclusions**

With experimental research in health psychology growing, there is an exciting opportunity for the field to identify key cognitive processes that may help maintain distress and guide development of novel interventions to target these mechanisms and improve well-being. In order to do this, the key processes need to be assessed with materials that map onto the cognitive processes specific to a given health problem. We believe that adopting the suggested approach detailed here will aid researchers as they begin adapting these paradigms for different populations. Materials used in experimental tasks should be subject to the same rigorous development and validation as self-report questionnaires to ensure materials are reliably tapping into the concept(s) of interest. We encourage researchers to make their materials available alongside published work to aid further transparency about the inferences that can be drawn from the study. This preliminary stimuli development work is essential in order to develop a body of high quality, replicable experimental research.
Traditional health psychology models have largely focused on the role of reflective intentioned action and beliefs (Sheeran, et al., 2013). Experimental research adds another dimension to these models by exploring the more implicit drivers of health behaviours and coping. Extant treatments have principally engaged conscious processes via explicit communication (e.g. persuasive information, problem solving, planning, and implementation intentions). Health psychology interventions may be optimized by additionally targeting these implicit processes. For example, reducing AB to food cues may in turn reduce impulsivity and thereby help regulate impulsive eating (Bongers, et al., 2015). There may also be a role for implicit processing in coping. For example, if survivors of breast cancer have persistent AB for cancer related information and tend to interpret ambiguous information as cancer related, they may consequently experience increased anxiety and fear or recurrence (Glinder, et al., 2007). Modifying these processes with cognitive bias modification (CBM) techniques will enable hypothesis testing and potentially indicate additional treatment targets, paving the way for new interventions.

To date there is no single protocol for consistent and effective CBM. However, there are some promising findings in anxiety which indicate that when CBM is effective in changing an AB associated reductions in anxiety are observed (Linetzky, Pergamin-Hight, Pine, & Bar-Haim, 2015; MacLeod & Clarke, 2015). CBM techniques may benefit from further specificity, identifying and targeting idiosyncratic content that is personalized and tailored to a specific patient. Such an approach could enable testing processing specificity in heterogeneous conditions such as CFS (Wilson, et al., 2001) in which the content of concern may be non-specific and vary markedly across patients.

There are challenges to this material developmental work; it is time consuming, costly, requires additional recruitment and in-depth collaborative work with the population of
interest. Nevertheless, we believe this work is worthwhile in order to establish a body of high quality and replicable experimental research within the health psychology literature. We hope this article highlights the value of preforming rigorous material/stimuli development and aids researchers to engage in this process.
APPENDIX A.
Templates for Attentional Bias stimuli pilot surveys

Template 1.
You will be asked to rate a list of words in terms of how personally emotive or distressing you feel they are. I.e. the degree to which the word brings to mind an unpleasant or distressing emotion related to your INSERT CONDITION.
Recalling a time when you were experiencing your worst symptoms, please rate these words in the degree to which they bring to mind an unpleasant or distressing emotion related to INSERT CONDITION.

<table>
<thead>
<tr>
<th>Word</th>
<th>Not at all distressing</th>
<th>Neutral</th>
<th>Moderately distressing</th>
<th>Quite a bit distressing</th>
<th>Extremely distressing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Template 2.
The following five pages contain lists of words. Some may be related to INSERT CONDITION, others less so. Please indicate on a scale from 1-5 how INSERT CONDITION related each word seems to you. Please give us your first impressions and try to work as quickly and accurately as possible.

<table>
<thead>
<tr>
<th>Word</th>
<th>Not at all related</th>
<th>A little related</th>
<th>Somewhat related</th>
<th>Quite a bit related</th>
<th>Very much related</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

The following five pages contain lists of words. Some may appear threatening, others might not. Please indicate on a scale from 1-5 how threatening each word seems to you. Please give us your first impressions and try to work as quickly and accurately as possible.

<table>
<thead>
<tr>
<th>Word</th>
<th>Not at all threatening</th>
<th>A little threatening</th>
<th>Somewhat threatening</th>
<th>Quite a bit threatening</th>
<th>Very much threatening</th>
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<td>1</td>
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</tr>
</tbody>
</table>
B1. Pilot survey for CFS population

Please imagine yourself in these scenarios and complete the sentences with the first word that comes to mind.

For example: ‘It is winter and you are outside. You notice yourself shivering which is a sign you are …cold”

1. You spent the afternoon shopping and by the time you get home you feel tired. You slept many hours that night and when you wake up you feel...

2. You have planned to clean the downstairs of your house today and found this easier and quicker than you expected. You think if you carry on you will feel...

3. A friend has just asked you to go for a walk with them. You think the walk would be...

4. You are going on holiday tomorrow and have had a busy day packing. When your alarm wakes you up in the morning you feel...

5. You have attended a family occasion and had an enjoyable time. It was a long day and by the end you feel very tired. You think in a couple of days you will feel...

6. You usually get the bus to work but today you are feeling energetic and decided to walk. When you come home from work you feel more tired than usual. You think tomorrow you will feel....

B2. Pilot survey for breast cancer population

Scenario Example

TITLE: Results from a Blood Test

SCENARIO: You completed treatment and go in to have a follow up blood test. The nurse calls to give you the results, but instead tells you that there are further tests that need to be run. You can tell from the tone of her voice if she is concerned.

QUESTION: Did you receive a call from the nurse? (Yes/No)

Recognition Example

TITLE: Results from a blood test

STATEMENT: The nurse seems busy at clinic she speaks quickly and ends the call
QUESTION: How similar is this to THE ORIGINAL DESCRIPTION you read?

- Very similar in meaning
- Fairly similar in meaning
- Fairly different in meaning
- Very different in meaning
APPENDIX C
Example of Interpretative Bias materials

C1. IB materials for CFS population.

Title: Weekend Break
You and your partner booked to go on a weekend break. You stayed for 2 nights and fitted a lot in. You ended up doing a lot of sight-seeing around the city. As you travel home you think about how you found the weekend.
Did you go on a break with a friend?
1. You had an enjoyable and interesting weekend.
2. You found the weekend exhausting.
3. Your partner booked the holiday as a surprise.
4. You had to come home from the holiday early.

Title: Cleaning the House
Last week you spent a day cleaning the house. You hoovered all the carpets in the house and mopped the kitchen floor. A week later you notice the carpets are dirty and need hoovered again. You think about how you felt after the last time you cleaned.
Did you clean the windows?
1. You felt pleased with how nice the house looked after cleaning.
2. You felt stiff and painful for days as you pushed your body too far.
3. You completed the cleaning quicker than you had expected.
4. You were unable to clean last week as you hurt your back.

Title: Cleaning the Windows
You decide to clean inside the windows today. You finish cleaning the windows downstairs quicker than you expected and move on to clean the upstairs windows. While climbing the stairs your notice how your shoulders and arms feel.

Did you clean the inside windows?

1. Your shoulders and arms feel like they have had a good workout.
2. Your shoulders and arms feel stiff and painful after over doing things.
3. You cleaned both the inside and outside windows quicker than expected.
4. You fell off a ladder after cleaning the outside windows.

Title: The exercise class

You have started going to a beginners exercise class once a week at your local leisure centre. After a month you feel fitter and decide to enroll in the intermediate class. After attending the first intermediate class you notice your arms and legs are sore. You think about what this means.

Do you have a personal trainer?

1. Your limbs will be sore until you get used to your new exercise regime.
2. You will be bed ridden for days as you have pushed your body too far.
3. Your arms and legs feel stronger after a week of your new exercise regime.
4. You decrease your exercise regimen as you are not fit enough to exercise twice a week.

C2. IB materials for breast cancer population

Title: Reading the newspaper

You are reading a section of the newspaper and come across a headline about an article on cancer. You hesitate a moment and continue to read the article. The article tells you how likely people are to survive in the long-term if they are diagnosed with breast cancer. This makes you think about your own chances of being cured.
Q: Did you read the entire paper?

1: The article makes you think your risk of being cured after breast cancer is high (Positive target)

2: The article makes you think your risk of being cured after breast cancer is low (Negative target)

3: The article makes you think your risk of being diagnosed with a stroke is high (Negative foil)

4: The article makes you think your risk of being diagnosed with a stroke is low (Positive foil).

Title: One year later

You completed treatment a year ago and are reminded of when you were first diagnosed. You think back to how you felt then and compare this to where you are today. You reflect on how your experience of being diagnosed and treated for cancer has impacted your life as it is today.

Q: Were you thinking about what to prepare for dinner?

1: Cancer has impacted your life and is interfering with your ability to get on with life as usual (Negative target)

2: Cancer affected your life during treatment, but it’s behind you now and you are moving on (Positive target)

3: You remember the weather was very cold and rainy last year and you were often unwell (Negative foil)

4: You remember the weather was good last year and you enjoyed spending time outdoors (Positive foil)

Title: The leaflet
You are being treated for cancer and you pick up a leaflet from the doctor’s about the
disease. You read it and learn about risks and symptoms of breast cancer recurrence. As
you read through the lists you recognise what your own risk might be and consider your
prognosis.

Q: Did you read about cancer on a poster?
1: The leaflet says that most people who get cancer feel well most of the time (Positive
foil)
2: The leaflet says that most people who get cancer feel sick most of the time (Negative
foil)
3: The leaflet says that people who get cancer are likely to die from the disease (Negative
target)
4: The leaflet says that people who get cancer are likely to survive the disease (Positive
target)

Title: The biopsy
You recently had a biopsy to test a lump on your neck for cancer. You are now sitting in
your surgeon’s office and he tells you he has the biopsy report. You think you can tell by
the look on his face what the results of the biopsy show.

Q: Did the surgeon discuss chemotherapy with you?
1: You can tell by the look on your doctor’s face that the result is good news (Positive
target)
2: You can tell by your doctor’s manner that he is relaxed and not rushed (Positive foil)
3: You can tell by your doctor’s tone that he is very busy and in a hurry (Negative foil)
4: You can tell by your doctor’s expression that the results do not look good (Negative
target)
Chapter 5 A cross-sectional study of cognitive biases and deficits in CFS and healthy controls

5.1 Chapter overview

This chapter is published in the following article:

5.2 Published article

Title: An attention and interpretation bias for illness specific information in chronic fatigue syndrome

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Conflict of Interest Statement: TC receives royalties for self-help books on chronic fatigue.

Key words: Attentional bias, chronic fatigue syndrome, cognitive processing, interpretation bias
Abstract

**Background:** Studies have shown that specific cognitions and behaviours play a role in maintaining chronic fatigue syndrome (CFS). However, little research has investigated illness specific cognitive processing in CFS. This study investigated whether CFS participants had an attentional bias for CFS-related stimuli and a tendency to interpret ambiguous information in a somatic way. It also determined whether cognitive processing biases were associated with comorbidity, attentional control or self-reported unhelpful cognitions and behaviours.

**Methods:** Fifty-two CFS and 51 healthy participants completed self-report measures of symptoms, disability, mood, cognitions and behaviours. Participants also completed three experimental tasks, two designed specifically to tap into CFS salient cognitions: (i) Visual-Probe task measuring attentional bias to illness (somatic symptoms and disability) versus neutral words, (ii) interpretive bias task measuring positive versus somatic interpretations of ambiguous information and (iii) the Attention Network Test measuring general attentional control.

**Results:** Compared to controls, CFS participants showed a significant attentional bias for fatigue-related words and were significantly more likely to interpret ambiguous information in a somatic way, controlling for depression and anxiety. CFS participants had significantly poorer attentional control than healthy individuals. Attention and interpretation biases were associated with fear/avoidance beliefs. Somatic interpretations were also associated with all-or-nothing behaviour and catastrophizing. **Conclusions:** People with CFS have illness specific biases which may play a part in maintaining symptoms by reinforcing unhelpful illness beliefs and behaviours. Enhancing adaptive
processing, such as positive interpretation biases and more flexible attention allocation, may provide beneficial intervention targets.
**Introduction**

Chronic Fatigue Syndrome (CFS) is a debilitating condition lasting over 6 months. Symptoms include fatigue, pain, sleep problems and poor concentration and memory (Fukuda, et al., 1994; Sharpe, et al., 1991). No single somatic cause has been identified. Although a virus or work stress may trigger the condition, cognitive, behavioural, affective and physiological factors are thought to perpetuate symptoms and disability (Surawy, et al., 1995; Burgess, et al., 2012; Chalder, 2013; Moss-Morris, et al., 2013). Self-report studies have found that negative illness representations, symptom interpretations and heightened symptom focusing contribute to the maintenance of CFS (White, et al., 1995; Knoop, et al., 2010, Moss-Morris, et al., 2011). Changing such cognitions, in particular fear avoidance beliefs and catastrophizing, have been found to mediate treatment response (Moss-Morris, et al. 2005; White, et al., 2011; Wiborg, et al. 2011; Wearden & Emsley, 2013; Stahl, et al. 2014; Chalder, et al., 2015)

Whilst self-report studies have identified certain cognitions as perpetuating factors, little is understood about the cognitive processes underlying these beliefs. Deary, et al. (2007) have suggested habitual processes, such as attention and misinterpretation, may play a role. For example, selectively attending to somatic information and habitually interpreting ambiguous information as health threatening may precede and perpetuate unhelpful cognitive and behavioural responses, such as fear avoidance beliefs, symptom monitoring and avoidance of activity. If so, targeting these cognitive processes in existing or adjunct treatments may optimize outcomes.
Little experimental research has been conducted in this area. A recent review of cognitive processing biases in CFS found a small number of published studies \((n=5)\), many with methodological limitations including small sample sizes and poorly defined populations (Hughes, et al., 2016a). Results were often conflicting. Studies using a modified Stroop task found threatening content did not interfere with information processing in CFS (Moss-Morris & Petrie, 2003). However, studies using visual probe tasks indicate a selective attention towards health threatening stimuli occurs when stimuli are presented for longer durations (e.g. >500ms; Creswell & Chalder, 2002; Hou, et al., 2008; Hou, et al., 2014) but not when presented briefly (e.g. 100ms; Martin & Alexeeva, 2010). This may indicate that people with CFS have difficulties with attentional processes of disengagement, rather than the initial orientation of attention. Similarly, studies of interpretation biases using on-line tasks, which require participants to make an immediate and spontaneous interpretation of ambiguous information, have not found biases in CFS (Martin & Alexeeva, 2010). Studies that have used off-line interpretative bias tasks which allow participants time to form an interpretation have found biases in CFS (Moss-Morris & Petrie, 2003). This may indicate that people with CFS interpret ambiguous information in a somatic way when they have time to reflect on the material (i.e. off-line tasks) but not when the material is first encountered (i.e., online-tasks). These findings suggest that threat-related processing in CFS occurs at later, elaborative stages of processing.

Furthermore, one study has shown a correlation between increased somatic interpretations of ambiguous information and self-reported somatic focus (Moss-Morris & Petrie, 2003), supporting the hypothesised role for cognitive processing in perpetuating
maladaptive beliefs and behaviours. However, these conclusions are deduced from a small body of evidence, employing different paradigms and subtle methodological variations, tapping into different cognitive content and mechanisms. Further research is needed to establish whether cognitive processing biases are a reliable phenomenon in CFS, the nature of such biases and how they relate to other self-reported cognitions and behaviours factors operationalised in the cognitive behavioural model of CFS.

Most of the previous CFS studies used generic health threatening stimuli, which arguably are not integral to CFS. Some studies recruited participants from support groups, who may have different salient concerns to clinical CFS populations. Given the large heterogeneity in CFS (Cella, et al., 2011a), experimental research would benefit from exploratory work to first identify the salient illness-related concerns before assessing threat-related processing. Content specific processing is evident in depression and anxiety disorders (Fritzsche, et al., 2010; Pergamin-Hight, et al. 2015). Given the high prevalence of comorbid mood disorders in CFS (Cella, et al., 2013) it may be that cognitive biases are a function of depression and/or anxiety in the CFS population, rather than their CFS per se. However, recent research in CFS indicates that these biases are independent of mood and affect (Hughes, Chalder, Hirsch, & Moss-Morris, 2016b). These biases are associated with health related rather than mood related stimuli, suggesting that biases occur for themes central to the disorder. This is in keeping with cognition and emotion research (Mathews & MacLeod, 1994; Hirsch, et al., 2016).
Whether these biases predispose illness or develop as a result of illness is unclear. Prospective and longitudinal studies in the chronic pain literature have associated attentional biases with poorer outcomes (Lautenbacher, et al. 2010; Todd, et al., 2016) and chronicity (Sharpe, et al., 2014). Similarly, it may be that people who have had CFS for some time, living with the ongoing uncertainty of a disabling and poorly explained condition, could reasonably become preoccupied with their illness. Over time this may result in biases in how information is attended to and processed. Research to date has not established whether there is a relationship between illness duration or severity and cognitive biases in CFS (Hughes, et al., 2016b).

Some theories suggest threat-related processing is a result of difficulty in regulation and allocation of attention (Eysenck, et al., 2007). Both self-report and neurological studies suggest that people with CFS have difficulties with general attentional control (Cockshell & Mathias, 2010; Togo et al., 2015). One study (Hou et al., 2014) found that only CFS participants with poor attentional control had an increased attentional bias towards health threat. However, this study was small (n=14) and was likely underpowered to truly detect sub-group effects. Other studies in anxiety and pain have also indicated a moderating role of attentional control in both attentional biases (Heathcote, et al., 2015) and interpretation biases (Salemink & Wiers, 2012). There may be a subgroup of CFS patients who have particularly poor attentional control which may make them more prone to develop biases in cognitive processing. Research would benefit from the assessment of cognitive biases and effortful attentional control in CFS within larger samples to determine whether differences in effortful control may account for observed cognitive biases. If so, training
programs to improve attentional control may be clinically relevant (Jones & Sharpe, 2014; Schoth, et al., 2013; Sharpe, et al., 2012; Sharpe, et al., 2015).

The current study is the largest to date in this area and addresses many of the methodological limitations mentioned above. Stimuli were developed with CFS patients and clinicians to ensure that the tasks were tapping into CFS specific concerns and validated paradigms were selected to assess attention and interpretation biases. The main hypotheses are as follows: 1a) CFS participants, when compared to healthy controls, will have an attentional bias towards fatigue-specific somatic and disability related information presented for 500ms and an interpretive bias towards somatic rather than positive information. 1b) This difference between groups will remain even when controlling for comorbid mood disorders, 2) Attention and interpretation biases in CFS will be associated with/ moderated by deficits in attentional control, 3) Attention and interpretation biases in CFS will be associated with self-reported fear avoidance beliefs, catastrophizing about symptoms, symptom focusing, fatigue, disability and increased illness duration.

Methods

Participants

Participants were included if they were 18 years or older, fluent in English, with normal or corrected-to-normal vision and good manual dexterity. CFS participants were recruited from specialist CFS services in London, Oxford and Dorset. To be included, they had to meet either the Oxford (Sharpe, et al., 1991) or US Centre for Disease Control (Fukuda,
et al., 1994) criteria for CFS, diagnosed by a consultant psychiatrist or experienced cognitive behavioural therapist, and confirmed by self-report questions. CFS participants were excluded if undergoing concurrent Cognitive Behavioural Therapy (CBT) or Graded Exercise Therapy (GET).

Healthy controls were recruited via online advertisements placed on public forums, such as Gumtree, and recruited on the basis that they had similar demographic characteristics of the CFS group. They were included if they had no previous or current diagnosis of CFS (Fukuda, et al., 1994; Sharpe, et al., 1991) ascertained through self-reported medical history and a current score of less than four on the Chalder Fatigue Scale (Chalder, et al., 1993). Participants were excluded if they reported other persistent physical symptoms which may be associated with CFS, including irritable bowel syndrome, fibromyalgia and chronic pain. All participants were paid £20 for taking part.

Sample size was determined by an a priori analysis using the G*Power analysis program (Erdfelder, Faul, & Buchner). Alpha was set at 0.05 with a corresponding power of 0.80 to detect a standard medium effect size of Cohen’s $f^2$ 0.25, resulting in a required sample size of 90 participants in total; 45 per group. This medium effect size was selected based on previous, similar studies, which found medium effect sizes between smaller groups of CFS and healthy controls in terms of attentional bias (Hou, et al., 2008), interpretation ________________

4 Five CFS participants were admitted on the basis of a diagnosis meeting the CDC criteria; 47 were admitted meeting the Oxford CFS criteria depending on the clinical service through which they were recruited. Sensitivity analysis found the diagnostic category did not affect the results.
bias (Moss-Morris & Petrie, 2003) and attentional control (Hou, et al., 2014). We over-recruited by 15% to allow missing or extreme outliers in the data.

**Procedure**

The study was approved by Berkshire-B Research Ethics Committee (14/SC/0172). Following written informed consent, participants completed questionnaires at home and subsequently attended the laboratory to complete the computer tasks. Computer tasks were programmed using E-prime version 2.0 (Psychology Software Tools, Inc., USA). Experiments were conducted in a private room on a Toshiba Satellite-Pro Laptop (screen size 15.6 inches), which was attached to a stand and placed on a table to maintain a 4.0° visual angle for every task. Each task consisted of a practice and test trials which were completed in the absence of the experimenter. All participants completed the Visual Probe Task (VPT), followed by the Attention Network Task (ANT), Interpretative Bias (IB) task and clinical interview.

**Questionnaires**

*Chalder Fatigue Questionnaire (CFQ; Chalder, et al., 1993; Cella & Chlader, 2010).* The CFQ consists of 11 items measuring physical and mental fatigue on a four-point scale, ranging from ‘better than usual’ (0) to ‘much worse than usual’ (3). Items were scored using the continuous method (0, 1, 2, 3). Cronbach’s alpha in the current study was .98.
Work and Social Adjustment Scale (WSAS; Mundt, et al., 2002). This five item scale measures the extent to which fatigue interferes with people’s ability to engage in activities of daily life including work and socialising, rated on a scale from 0 (“not at all”) to 8 (“very severely impaired”). The scale has strong psychometric properties and is a valid and reliable measure in CFS (Cella, et al., 2011b). Cronbach’s alpha in the current study was .97.

Cognitive Behavioural Responses Questionnaire (CBRQ; Skerrett & Moss-Morris, 2006). The CBRQ consists of seven subscales. Five relate to cognitive responses to symptoms: catastrophizing, damage beliefs, symptom focusing, fear avoidance and embarrassment avoidance; rated on a 5-point Likert scale ranging from 1 “strongly disagree” to 5 “strongly agree”, with two items on the fear avoidance scale reverse coded. Two subscales measure behavioural responses to illness: avoidance behaviour and all-or-nothing behaviour, rated on a 5-point scale from 1 “never” to 5 “all the time”. Higher scores indicate proneness to maladaptive responses to symptoms. The CBRQ was included to assess the relationship between self-reported beliefs and behaviours and cognitive biases. Cronbach’s alpha for the 7 subscales ranged from .85 to .97.

Clinical Interview Schedule Revised (CIS-R; Lewis, et al., 1992). The CIS-R is a standardized, highly structured, valid and reliable psychiatric interview which produces depression and anxiety diagnostic categories according to ICD-10 criteria, as well as a continuous total score of psychological distress. A computer version of the CIS-R was
used excluding the fatigue item normally contained within the interview. Cronbach’s alpha in the current study was .76.

**Information processing tasks**

*Stimuli development for the Visual Probe Task (VPT, MacLeod, et al., 1986).* This computerized task measures reaction times to the threatening illness-related words and neutral word pairs matched for length and frequency of use. Faster reaction times to probes replacing (appearing in the location of) CFS-threatenng words relative to probes replacing neutral words, indicates an attentional bias towards threat. In order to ensure illness words were salient to the experience of CFS, we conducted preliminary interviews with 6 CFS patients and a workshop with 6 experienced cognitive behavioural therapists specialising in CFS. The interviews and workshop explored the experience of CFS and elicited real-life examples which captured this experience. From this preliminary work we extracted 56 illness-related words which were subsequently rated for their saliency on an on-line survey by 58 CFS participants. Instructions were ‘Recalling a time when you were experiencing your worst symptoms, please rate these words in the degree to which they bring to mind an unpleasant or distressing emotion related to CFS.’ Ratings were: ‘not at all distressing; neutral; moderately distressing; quite a bit distressing; extremely distressing’. Mean ratings were calculated per word, with higher scores reflecting a greater emotive threat valence. Twenty-four highest scoring words were selected for the VPT (see supplementary material), which broadly related to symptom experience (e.g. ‘shattered’) and associated consequences (‘bedbound’) (Appendix A).
Visual Probe Task (VPT, MacLeod, et al., 1986). Threatening-neutral word pairs were presented in random order for 96 trials. Each trial started with a fixation cross (500ms) followed by two words (Arial point 18), appearing above and below the fixation. After 500ms the words disappeared and one of them was replaced by an arrow. Participants were seated approximately 60cm from the screen and read the following instructions: ‘You will see a fixation cross (+) in the centre of the screen. Please use this fixation cross to focus your vision. Two words will appear, one above and one below the centre of the screen, for a short duration of time. An arrow will appear in either one of the two locations of the previously shown words.’ Participants pressed ‘c’ to indicate the arrow pointing to the left and ‘m’ for the arrow pointing to the right. After reading the instructions participants completed 16 practice trials of neutral-neutral word pairs, before starting the experiment. Inter-trial interval was 500ms. Attentional bias scores were calculated as the standardized residual (i.e. difference score) of the mean reaction time (RT) to probes replacing the illness-related stimuli from the RT to probes replacing the neutral stimuli. To create the standardized residual score a regression analysis was conducted where reaction times to probes replacing neutral stimuli were entered as the dependent variable and reaction times to probes replacing illness related stimuli were entered as the independent variables. Positive values demonstrate an attentional bias to CFS threatening stimuli.
Stimuli development for the Interpretative Bias (IB) task. Scenarios were conceived from the interviews and workshop described above and tested for saliency in a pilot survey. The survey consisted of 40 short ambiguous scenarios, with the last word left blank. Participants had to complete the last word, thus revealing an interpretation of the text (Appendix B). For example, ‘You have planned to clean the downstairs of your house today and found this easier and quicker than you expected. You think if you carry on you will feel (exhausted/ pleased)’. Twenty-six CFS and 26 healthy participants completed the survey. The single word completions were rated by two independent researchers as either CFS-related, generally negative, neutral or positive. The scenarios which demonstrated the biggest different between the CFS and control groups in terms of CFS-related interpretations were selected to be developed into full text materials for the main IB task described above. See Hughes, Gordon, Chalder, Hirsch, & Moss-Morris, 2016c for further details on the development of these CFS specific VPT and IB stimuli.

Interpretative Bias (IB) task (Mathews & Mackintosh, 2000). This computerized task was adapted from Mathews & Mackintosh’s (2000) task used in anxiety. The task comprised of two phases: the initial encoding phase followed by a recognition phase. During the encoding phase, 10 ambiguous descriptions of everyday situations, each headed with a short title, were presented. Participants read all 10 scenarios whilst imagining themselves as the central character. After each scenario participants rated its ‘pleasantness’ and answered a comprehension question. An example scenario and comprehension question follows:

Cleaning the House
Last week you spent a day cleaning the house. You hoovered all the carpets in the house and mopped the kitchen floor. A week later you notice the carpets are dirty and need hoovering again. You think about how you felt after the last time you cleaned.

Did you clean the windows?

After reading all ten scenarios participants are presented with a ‘recognition test’. The recognition phase was designed to test participant’s interpretations of the ambiguous scenarios made during the encoding phase. Participants were presented with the title of each scenario (e.g. ‘Cleaning the Windows’), followed by four sentences, presented individually, to be rated for recognition. For each scenario there were two “target” interpretations, which were possible positive or somatic (negative) interpretations of the scenario; and two foil sentences, one positive and one negative, which were not possible interpretations of the text. Foils were included to assess a potential response bias for endorsing any positive or negative information. Below is an example of the recognition phase which corresponds to the above scenario ‘Cleaning the House’:

1. You felt pleased with how nice the house looked after cleaning. (Positive target/interpretation)

2. You felt stiff and painful for days as you pushed your body too far. (Somatic target/interpretation)

3. You completed the cleaning quicker than you had expected. (Positive foil)

4. You were unable to clean last week as you hurt your back. (Negative foil)

Participants were asked to rate independently how similar in meaning each sentence was from the original encoding description (‘how similar is this sentence to the original
description you read?’), from 1 (very different in meaning) to 4 (very similar in meaning). The scenarios in the encoding and recognition phases were presented in the same order, but the four recognition sentences were randomised for each scenario. For the analyses, mean similarity ratings were calculated for the positive and negative interpretations (targets) and foils separately. To obtain an interpretive bias index, mean similarity scores of positive interpretations were subtracted from mean similarity scores from negative interpretations (higher scores indicate a stronger threat-related interpretive bias).

Attention Network Test (ANT; Fan, et al., 2002, Fan, et al., 2005). The ANT measures three aspects of attention: altering, orientating and attentional control. As a previous study only found differences between CFS and healthy participants on attentional control (Hou et al., 2014), we only included attentional control in this study. The ANT consists of six demo trials, 12 practice trials and 72 experimental trials. Participants are presented with a string of five congruent (→→→→→) or incongruent (→→←→→) arrows and are required to determine the direction of the central arrow. Attentional control is calculated by subtracting the mean RT on congruent flanker trials from the mean RT on incongruent flanker trials. Higher scores indicate poorer attentional control5.

Data preparation and analytical procedure

RT data were excluded from trials with errors and outliers (<200 ms, and >2000 ms) in the VPT and ANT. One CFS participant and two healthy controls were excluded from

5 Attentional control was not correlated with years in education in this study (p>.05)
the VPT analysis due to excessive missing data (>3SD above the group mean) consistent with other studies (Brown, et al., 2014; Hou, et al., 2014). Analysis was performed using the Statistical Package for Social Sciences (SPSS) version 21.

The Kolmogorov-Smirnov test of normality indicated that the distributions of the ANT attention control scores and age were skewed; bootstrapping (set at 1000 resamples) was performed on attentional control data and a Mann-Whitney test was used to assess group differences in age. All other data met assumptions of normality. Gender, employment, education and symptom measures (CIS-R, WSAS and fatigue) were compared between groups using chi-square or t-tests. The CFS group were significantly older than healthy controls so age was controlled for in subsequent analysis. Separate ANCOVAs were run for attentional bias and attentional control scores, with group as the between-subjects factor. The means of the IB task were entered into a three way mixed ANCOVA, with group as between group factor, target type (target sentence v foil sentence) and sentence valence (positive v negative sentence) as within-subjects factors and age as covariate (hypothesis 1a). These ANCOVAs were rerun with total CIS-R scores entered as covariates to identify whether cognitive biases in CFS were independent of comorbidity (i.e. hypothesis 1b). Post hoc ANOVAs and t-tests were used to clarify significant results.

To determine if attentional control acted as moderator of attention and interpretation

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6 There were no differences in results when analyses were conducted without controlling for age.

7 CIS-R total scores were used as a continuous score of psychological distress as opposed to the diagnostic categories to allow a fair comparison with the healthy control group.
biases in CFS, an interaction term was created between centred attentional control scores and group. The interaction term was entered as a criterion variable along with group in separate linear regressions with attentional bias scores and interpretation bias index as the predictor variables (hypothesis 2). Pearson correlations were also carried out between self-reported symptom measures and attention and interpretation bias scores, within the CFS group (hypothesis 3).

**Results**

Eighty people with CFS were invited to participate in the study; 56 agreed (response rate = 70%). After screening for eligibility the final sample consisted of 52 CFS participants and 51 healthy controls.

**Clinical and demographic measures**

Group characteristics and clinical measures are presented in Table 1. CFS participants and controls did not differ with respect to gender, employment, or years in education; however, the CFS group were significantly older than healthy controls. As expected the CFS group had significantly higher rates of comorbid depression and anxiety (CIS-R); and significantly higher scores on all clinical measures compared to controls. Scores and reaction times for the experimental tasks are presented in Table 2.

**Visual Probe Task: attentional bias in CFS versus control group**

The CFS group had slower overall mean RT on the VPT than controls; (614.99 vs. 540.87ms), t(98)=3.97, p<.001. Figure 1 illustrates the standardized attentional bias
scores in both groups; positive scores indicate an attentional bias toward CFS stimuli. The ANCOVA showed a significant main effect of group when controlling for age, $F(1, 97) = 9.98; p = .002; \eta^2_p = .09$; the CFS group had a significant attentional bias towards threat stimuli compared to healthy controls. This effect remained when controlling for CIS-R distress, $F(1, 96) = 4.24; p = .04; \eta^2_p = .04$. Post hoc contrasts of overall mean bias score against zero for each group showed a significant bias towards threat in the CFS group [one-sample $t(50) = 2.13, p = .038$, 95% CI (.62, 21.33)]; while the healthy control group showed a significant bias towards neutral stimuli [$t(48) = 3.7, p = .004$, 95% CI (-21.74, -4.52)].

**Recognition Task: interpretative bias in CFS versus control group**

There was a significant Group x Target x Valence interaction, $F(1, 100) = 20.94, p < .001, \eta^2_p = .17$. To further explore this effect we conducted a mixed model ANCOVA with group as the between-subjects factor, valence (somatic or positive target) as the within-subjects factor and age as covariate for targets and foils separately. The ANCOVA for targets demonstrated a significant Group × Valence interaction, $F(1, 100) = 25.83, p < .001, \eta^2_p = .21$; which remained when controlling for comorbid distress, $F(1, 99) = 4.38, p = .04, \eta^2_p = .10$. Independent samples t-tests showed the CFS group endorsed positive interpretations significantly less than healthy controls, $t(101) = -3.8, p < .001$; and somatic (negative) interpretations significantly more than healthy controls, $t(91) = 2.13, p = .04$. The ANCOVA for foils demonstrated no significant main effects, $F(1, 100) = .05, p = .82$. Within group analyses showed both groups endorsed positive interpretations
significantly more than somatic interpretations; CFS group, $F(1,51) = 39.43, p<.001, \eta_p^2 = .45$, health control group, $F(1,50) = 166.26, p<.001, \eta_p^2 = .78$.

**Attention Network Test: attentional control in CFS versus control group**

The CFS group had slower overall mean RT on the ANT compared to healthy controls (649.33 vs. 556.63ms), $t(101)=3.88, p<.001$. Figure 2 illustrates the mean ANT attentional control scores of both groups. The CFS group had significantly poorer attentional control (i.e. higher ANT scores) than healthy participants, controlling for age; $F(1, 100) =4.05; p=.05; \eta_p^2 = .04$.

**Relationship between attentional control and attention bias**

There was no significant correlation between attentional bias scores and attentional control in either the CFS group, $r(51)=.08, p=.59$; or the healthy control group, $r(49)=.30, p=.12$. To examine if attentional control acted as a moderator of attentional bias in CFS, an interaction term was created between group (CFS, healthy controls) and centred attentional control scores. The interaction term and group were entered as predictor variables in a linear regression with attentional bias as the criterion. There was no significant interaction between attentional bias scores and group; $\beta=.25, t(97)=1.45, p=.15$, 95% CI (-.11, .008).

**Relationship between attentional control and interpretation bias**

In order to assess the relationship between interpretation biases and attentional control an interpretation bias index was calculated by subtracting the mean similarity scores of the
positive interpretations from the mean similarity scores of the negative interpretations from the recognition task. There was no significant correlation between interpretative bias index and attentional control in either the CFS group $r(52)=.12, p=.41$; or the healthy control group, $r(51)=.23, p=.10$. To test the moderating role of attentional control on the relationship between group (CFS and healthy controls) and interpretative bias, a linear regression analysis was performed with the interpretative bias index as the dependent variable and group and the interaction term between group and centred attentional control as the predictors. Attentional control was not a significant moderator of the relationship between group and interpretation bias; $\beta=.17, t(99)=.88, p=.38$, 95% CI (-0.002, .006).
<table>
<thead>
<tr>
<th></th>
<th>CFS (n=52)</th>
<th>Health Controls (n=51)</th>
<th>Inferential statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>37 (45)</td>
<td>32 (46)</td>
<td>$U=1025$, $p=.05$</td>
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<tr>
<td>Female, n (%)</td>
<td>32 (62)</td>
<td>32 (63)</td>
<td>$\chi^2=.02$, df=1, $p=.90$</td>
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<td>Employed, n (%)</td>
<td>36 (69%)</td>
<td>35 (69%)</td>
<td>$\chi^2=.0004$, df=1, $p=.95$</td>
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<td>Years in education (mean, SD)</td>
<td>17.32 (5.33)</td>
<td>17.2 (2.8)</td>
<td>$t(101)=.14$, $p=.89$</td>
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<tr>
<td>Illness duration (months), mean (SD)</td>
<td>67 (88)</td>
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<tr>
<td>CFQ, mean (SD)</td>
<td>26.8 (4.7)</td>
<td>10.7 (3.3)</td>
<td>$t(91.8)^a=20.16$, $p&lt;.001$</td>
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<tr>
<td>WSAS, mean (SD)</td>
<td>23.4 (8.8)</td>
<td>0.5 (2.2)</td>
<td>$t(57.5)^a=18.2$, $p&lt;.001$</td>
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<tr>
<td>Total CIS-R score, mean (SD)</td>
<td>16.87 (8.77)</td>
<td>2.51 (.39)</td>
<td>$t(70.4)^a=10.78$, $p&lt;.001$</td>
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<tr>
<td>CIS-R Anxiety disorders, n (%)</td>
<td>9 (17%)</td>
<td>2 (4%)</td>
<td>$\chi^2=4.84$, df=1, $p=.03$</td>
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<tr>
<td>CIS-R Depression$^b$, n (%)</td>
<td>20 (39%)</td>
<td>0</td>
<td>_</td>
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<tr>
<td>CIS-R Mixed anxiety and depression, n (%)</td>
<td>9 (17%)</td>
<td>1 (2%)</td>
<td>$\chi^2=6.92$, df=1, $p=.01$</td>
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</table>

CFS, Chronic fatigue syndrome; CFQ, Chalder Fatigue Questionnaire; WSAS, Work and Social Adjustment Scale.; CIS-R, Clinical Interview Schedule revised, all CIS-R scores excluded the fatigue scale contained in the interview.

$^a$Degrees of freedom were corrected after Lavene’s test

$^b$Statistics were not computed because all controls scored 0 on this scale
Table 2. Group means and standard deviations of the reaction times and scores on the information processing tasks

<table>
<thead>
<tr>
<th></th>
<th>CFS (n=52) M (SD)</th>
<th>95% CI</th>
<th>Healthy Controls (n=51) M (SD)</th>
<th>95% CI</th>
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<tr>
<td><strong>Visual probe task</strong></td>
<td></td>
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<tr>
<td>Reaction time to threat words (ms)</td>
<td>609.35 (113.76)</td>
<td>577.68 (641.02)</td>
<td>546.89 (61.56)</td>
<td>529.58 (564.21)</td>
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<td>Reaction time to neutral words (ms)</td>
<td>619.24 (124.11)</td>
<td>504.69 (653.79)</td>
<td>538.69 (68.09)</td>
<td>519.54 (557.84)</td>
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<td><strong>Attentional control task</strong></td>
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<tr>
<td>Reaction time on congruent trials (ms)</td>
<td>588.86 (136.58)</td>
<td>550.83 (626.88)</td>
<td>510.25 (80.34)</td>
<td>487.65 (532.84)</td>
</tr>
<tr>
<td>Reaction time on incongruent trials (ms)</td>
<td>722.85 (172.48)</td>
<td>674.83 (770.87)</td>
<td>615.94 (95.81)</td>
<td>588.99 (642.89)</td>
</tr>
<tr>
<td><strong>Interpretative Bias Task</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Similarity rating of somatic interpretation</td>
<td>2.24 (.59)</td>
<td>2.08 (2.41)</td>
<td>2.02 (.41)</td>
<td>1.91 (2.14)</td>
</tr>
<tr>
<td>Similarity rating of positive interpretation</td>
<td>2.75 (.42)</td>
<td>2.63 (2.56)</td>
<td>3.05 (.42)</td>
<td>2.93 (3.17)</td>
</tr>
<tr>
<td>Similarity rating of negative foil</td>
<td>1.46 (.30)</td>
<td>1.38 (1.54)</td>
<td>1.48 (.23)</td>
<td>1.42 (1.54)</td>
</tr>
<tr>
<td>Similarity rating of positive foil</td>
<td>1.54 (.38)</td>
<td>1.45 (1.64)</td>
<td>1.54 (.37)</td>
<td>1.44 (1.65)</td>
</tr>
</tbody>
</table>
Figure 1. Standardised attentional bias scores in CFS and healthy control groups

Figure 2. Mean attentional control scores in CFS and healthy control groups. Higher scores represent poorer attentional control.
**Relationship between cognitive biases and self-reported beliefs, fatigue and disability**

Table 3 shows correlations within the CFS group between self-reported symptoms, beliefs and behaviours, and cognitive biases (attention and interpretation biases). Attentional bias was significantly, positively correlated with fear/avoidance beliefs. Somatic interpretations were significantly positively correlated with all/nothing behaviours, fear/avoidance beliefs and catastrophizing. Positive interpretations were not correlated with any cognitive or behavioural illness responses (CBRQ). There were no significant correlations between self-reported fatigue (CRQ), disability (WSAS) or illness duration and either attentional biases or interpretation biases (positive or somatic).
Table 3. Correlations between cognitive biases and self-report measures in the CFS group.

<table>
<thead>
<tr>
<th></th>
<th>Attentional bias</th>
<th>Somatic interpretation</th>
<th>Positive interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CFS (N=51)</td>
<td>CFS (N=52)</td>
<td>CFS (N=52)</td>
</tr>
<tr>
<td>CFQ</td>
<td>.03</td>
<td>.25</td>
<td>.05</td>
</tr>
<tr>
<td>WSAS</td>
<td>.22</td>
<td>.26</td>
<td>-.01</td>
</tr>
<tr>
<td>Illness duration</td>
<td>-.03</td>
<td>.15</td>
<td>.27</td>
</tr>
<tr>
<td>CBRQ Cognitive sub-scales</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fear/ avoidance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catastrophizing</td>
<td>.08</td>
<td>.42**</td>
<td>.09</td>
</tr>
<tr>
<td>Damage beliefs</td>
<td>-.11</td>
<td>.04</td>
<td>-.19</td>
</tr>
<tr>
<td>Symptom focus</td>
<td>.04</td>
<td>.27</td>
<td>.18</td>
</tr>
<tr>
<td>Embarrassment</td>
<td>.02</td>
<td>.08</td>
<td>.10</td>
</tr>
<tr>
<td>CBRQ Behavioural sub-scales</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All or nothing</td>
<td>.20</td>
<td>.28*</td>
<td>.01</td>
</tr>
<tr>
<td>Avoidance/ rest</td>
<td>.10</td>
<td>.23</td>
<td>.07</td>
</tr>
</tbody>
</table>

CFS, Chronic fatigue syndrome; CFQ, Chalder Fatigue Questionnaire; WSAS, Work and Social Adjustment Scale.; CBRQ, Cognitive Behavioural Responses Questionnaire;

*p<.05; **p<.01; all two tailed
Discussion

This study investigated cognitive processing biases and attentional control, and their relationships with CFS. Our hypotheses, that CFS participants would have an attentional bias towards salient, illness-related information and an interpretive bias towards somatic rather than positive information, were supported. These effects were independent of comorbid anxiety and depression. Although the CFS group had poorer attentional control than healthy participants, this was not related to cognitive processing biases. As hypothesised, somatic interpretations in the CFS group were significantly associated with self-reported fear/avoidance beliefs and catastrophizing, but not symptom focusing. There was also a significant relationship between somatic interpretations and all/nothing behaviours. Attentional bias scores only correlated with fear/avoidance beliefs. Neither bias was significantly associated with fatigue or disability although correlations were in the hypothesised direction.

The finding of an attentional bias for CFS specific (somatic and disability related) information presented for 500ms adds credence to the somewhat ambiguous findings of previous, smaller studies in this area. These attentional biases may reflect a strategy to continually monitor, review and evaluate pertinent threats in the environment as opposed to an initial orientation or hypervigilance to threat (e.g. for stimuli presented for 100ms), as seen in anxiety disorders (Pergamin-Hight, et al., 2015) and other persistent physical symptoms such as irritable bowel syndrome (IBS) (Chapman & Martin, 2011). This attentional strategy may have developed in order to evade further injury or relapse, as evidenced by the association between attentional bias and fear/avoidance beliefs within
the CFS group, or attentional bias may pre-empt such beliefs. These findings parallel similar findings in chronic pain (Crombez, Van Ryckeghem, Eccleston, & Van Damme, 2013; Heathcote, et al., 2015).

Our CFS specific off-line task found people with CFS had a bias to interpret information in a more somatic and less positive way than healthy controls. An advantage of this paradigm is that it allows a broader range of illness-related materials to be used than previous paradigms such as homophones. Furthermore, it is grounded in everyday ambiguous situations, which are more likely to reflect more ‘real-world’ interpretations (Hughes, et al., 2016b; Hirsch, et al., 2016). The groups did not differ in their rejection of false interpretations (foils), thus ruling out the effects of a general threat-based response bias. These findings are consistent with previous off-line tasks (Moss-Morris & Petrie, 2003) suggesting that interpretation biases in CFS occur when there is opportunity for reflection, when the participant has time to draw upon their illness-related schemas.

In the CFS group, somatic interpretations were associated with maladaptive illness responses, which previous research has identified as key mechanisms of change in behavioural treatments for CFS (Stahl, et al., 2014; Chalder, et al., 2015). The relationship between these beliefs/behaviours and cognitive biases highlights the role of implicit processing within the cognitive behavioural model of CFS. This may be a reciprocal relationship. For example, believing that symptoms and activity have serious consequences may encourage biases in cognitive processes to develop. Equally cognitive biases may encourage the person to maintain these beliefs alongside behavioural patterns,
such as overdoing things when symptom free and needing to rest for prolonged periods in response to symptoms (all-or-nothing behaviour) (Moss-Morris & Petrie, 2003); thus contributing to the maintenance of fatigue (Chalder, et al., 1996). The nature of these relationships should be further explored by studies employing longitudinal designs.

We were unable to replicate the finding that attentional bias in CFS is associated with poor attentional control (Hou, et al., 2014). These contradictory findings may be methodological; our CFS and healthy control groups had poorer attentional control than Hou, et al.’s (2014) sample. This, coupled with the fact that people with CFS need more time to process information than healthy adults (Cockshell & Mathias, 2010), may mean that longer exposure conditions are required before effortful attentional control exerts its influence on attentional processing in CFS. A recent pain study showed that self-reported attentional control moderated the relationship between pain catastrophizing and attentional biases in a community sample of adolescents (Heathcote, et al., 2015). It may be that subjective self-reports of attentional control taps into a different construct to the objective and neutral measure (consisting of judging the direction of arrows in an array) of attentional control used in this study.

We were also unable to detect a relationship between interpretation bias and attentional control. Salemink and Wiers (2012) identified a moderating role of objectively measured attentional control in interpretation biases in anxiety, when psychological arousal is temporal and situational (state anxiety), but not when arousal is enduring and dispositional (trait anxiety) in the general population. It may be that objective, general
attentional control (as measured here) moderates threat processing for some individuals when anxiety, pain, or in this case fatigue, is temporary and situational but not necessarily when symptoms are enduring, as is the case with CFS. Perhaps when symptoms are enduring, it is context dependent attentional control that is key to how threatening information is processed. This corresponds to other accounts of threat processing which suggest the threat evaluation process is idiosyncratic and dynamic i.e. people preferentially process information which is salient to their current and specific concerns (Mogg & Bradley, 2016; Pool, et al., 2016; Van Damme, et al., 2010; Riemann & McNally, 1995). Further measures of attentional control are needed which account for context dependent factors, such as saliency of threat and the individual’s current goals/priorities, to fully explore a dynamic relationship between attentional control and threat processing.

Correlations between cognitive biases and self-reported fatigue were not significant, though in the expected direction. There were no significant correlations between cognitive biases and illness duration. Large prospective and longitudinal designs are needed to fully explore how cognitive biases develop and potentially change over time. Cognitive biases did correlate with maladaptive beliefs and behaviours, which other research has identified are proximal treatment outcomes (Chalder, et al., 2015). The potentially maintaining role of these biases should be explored through bias modification studies and pre-post treatment designs. It may be that existing treatments for CFS modify these cognitive biases (Price, et al., 2011; Waters, et al., 2012); or it may be that processing mechanisms are less accessible through extant cognitive behavioural
techniques and treatment outcomes could be optimized by specifically targeting cognitive biases with computer based Cognitive Bias Modification (CBM) techniques.

CBM techniques aim to alter patterns of information processing by means of simple computerized training programmes. Attentional bias modification techniques, for instance, typically use a modified version of the dot-probe task whereby the probe consistently appears in the location of the neutral or positive information (MacLeod et al., 1986). Similarly, interpretative bias modification tasks reinforce positive or neutral interpretations of ambiguous information through repeated training towards positive/negative resolutions of ambiguous information (see Hirsch, et al., 2016 for a recent review). In this way, studies in anxiety have shown an attentional bias towards threat can be reduced, with associated reductions in symptoms (MacLeod & Mathews, 2012).

Recently CBM has been applied with pain patients; one study successfully modified interpretation biases in pain patients and found that those who were trained to interpret information in a threatening way hesitated for longer on a cold pressor task than those who were trained for benign interpretations (Jones & Sharpe, 2014). Studies have also identified some potential in the application of attentional bias modification to pain conditions (Sharpe, et al., 2012). However, the mechanisms of change are still unclear. Further research is needed to understand the mediating and moderating variables for successful modification of biases that could lead to therapeutic benefits in the future. Similar CBM techniques could help elucidate the potential role of cognitive biases in
maintaining key aspects of CFS, and may in time help ameliorate biases in CFS, with potential associated benefits of reduced fear avoidance and catastrophizing.

This study found attention and interpretation biases in the CFS group remained when psychological comorbidity was controlled for, suggesting cognitive biases in CFS are not a function of negative mood or affect but rather intrinsic to the condition itself. These findings are consistent with studies in chronic pain (Crombez, Viane, Eccleston, Devulder, & Goubert, 2013) and IBS (Chapman & Martin, 2011), suggesting that cognitive biases in persistent physical conditions depend on the relevance of the stimuli to the individual's illness concerns and beliefs, rather than anxiety or depression per se. Thus CBM techniques need to be tailored to tap into illness specific concerns (Hughes et al., 2016b; Pergamin-Hight, et al., 2015) and may further benefit from exploring the within-person variability in the temporal expression of attention and interpretational biases (Hirsch & Mathews, 2000; Heeren, et al., 2015).

Although this study has several strengths, including the use of well-established diagnostic, symptom and cognitive processing measures, there are limitations. One limitation is the lack of clinical control group, thus the obtained cognitive biases in CFS may reflect the chronicity of illness generally rather than a unique CFS effect; although the use of CFS specific stimuli makes this unlikely. Secondly, the groups were not adequately matched in age. Age is associated with increased reaction times on cognitive tasks and less cognitive flexibility (Jurado & Rosselli, 2007) thus we controlled for age in all between group analysis. Furthermore, the VPT used here provides a ‘snap shot’ of
attention; we cannot determine whether attention is initially captured (e.g. 100ms) and then maintained for 500ms or whether this occurs later within the 500ms window. Attentional bias may be better understood as a dynamic process in time rather than a static trait (Heeren, et al., 2015). Similarly, though we can conclude interpretative biases occur at later stages of processing in CFS, interpretation biases may also occur at earlier stages than our off-line task can assess. Future research should also employ on-line interpretative bias tasks (Hirsch & Mathews, 2000) and utilize advances in eye tracking technology, which offer more precise methods of measurement than RT alone (Armstrong & Olatunji, 2012).

Conclusions

This is the largest study to date measuring cognitive processing biases in CFS and the first to use materials developed with CFS patients to tap into illness specific concerns. The findings suggest that people with CFS have illness specific biases in how information is attended to and interpreted, which are associated with specific, illness beliefs and behaviours. Cognitive processing biases in CFS may independently play a part in maintaining symptoms by driving and reinforcing maladaptive illness beliefs and behaviours. Enhancing adaptive processing, such as positive interpretation biases and more flexible attention allocation, may provide beneficial intervention targets.
Appendix A

Table 1A. Attentional Bias Task Stimuli

<table>
<thead>
<tr>
<th>Illness related words</th>
<th>Matched Neutral Words</th>
</tr>
</thead>
<tbody>
<tr>
<td>bedridden</td>
<td>buttercup</td>
</tr>
<tr>
<td>collapse</td>
<td>transmit</td>
</tr>
<tr>
<td>immobilised</td>
<td>calligraphy</td>
</tr>
<tr>
<td>fatigue</td>
<td>pockets</td>
</tr>
<tr>
<td>exhausted</td>
<td>messenger</td>
</tr>
<tr>
<td>disabled</td>
<td>calendar</td>
</tr>
<tr>
<td>drained</td>
<td>pitched</td>
</tr>
<tr>
<td>limited</td>
<td>created</td>
</tr>
<tr>
<td>aches</td>
<td>domes</td>
</tr>
<tr>
<td>anxious</td>
<td>whistle</td>
</tr>
<tr>
<td>Incapacitated</td>
<td>infinitesimal</td>
</tr>
<tr>
<td>painful</td>
<td>trumpet</td>
</tr>
<tr>
<td>impaired</td>
<td>polished</td>
</tr>
<tr>
<td>restricted</td>
<td>newspapers</td>
</tr>
<tr>
<td>debilitating</td>
<td>articulation</td>
</tr>
<tr>
<td>housebound</td>
<td>grapevines</td>
</tr>
<tr>
<td>weak</td>
<td>zone</td>
</tr>
<tr>
<td>powerless</td>
<td>triangles</td>
</tr>
<tr>
<td>unwell</td>
<td>russet</td>
</tr>
<tr>
<td>frustrated</td>
<td>settlement</td>
</tr>
<tr>
<td>tired</td>
<td>brief</td>
</tr>
<tr>
<td>disheartened</td>
<td>stewardesses</td>
</tr>
<tr>
<td>feeble</td>
<td>inland</td>
</tr>
<tr>
<td>shattered</td>
<td>brochures</td>
</tr>
</tbody>
</table>
Appendix B

Online pilot survey for the interperative bias task materials.

We would like to know more about how CFS has affected your daily life.
Please imagine yourself in these scenarios and complete the sentences with the first word that comes to mind.

For example: ‘It is winter and you are outside. You notice yourself shivering which is a sign you are …cold’

You have been on your feet more than usual today and when you go to bed you notice that your legs are aching. You think tomorrow your legs will be…

You spent the afternoon shopping and by the time you get home you feel tired. You slept many hours that night and when you wake up you feel...

You have had an argument with your partner and have developed a head ache, which is a sign of...

Recently your job has been so demanding that you have worked straight through your lunch hour. Today is Friday and your boss has asked you to work late. You think at the weekend you will...

Your friend invites you to their birthday party however it doesn't start until 8pm and you have to get up early the next morning, so you decide not to go. This is...

Today you went grocery shopping and bought ingredients for dinner. When you get home you are...

You have planned to clean the downstairs of your house today and found this easier and quicker than you expected. You think if you carry on you will feel...

You have stayed late at work a few evenings this week in order to meet a deadline. Monday is a bank holiday so you have a long weekend ahead. You think next week you will feel...

A friend has just asked you to go for a walk with them. You think the walk would be...

You have had a busy morning and are running late for picking up your children from school. You are rushing to get to school on time and think you might...

You teach at a primary school. This lunch break it was your turn to stand and watch the children in the playground. You sit down for the rest of the afternoon and in the evening your legs are...
You have been invited to a wedding at the weekend. It's not close to home so you would have to travel by car and stay overnight at a hotel nearby. You think the weekend will be...

You are running late for an appointment and have taken public transport to get there. You arrive at your station to find the lifts and escalators are out of order. Passengers have been advised to either get off at the next stop for disabled access or use the stairs. You think if you take the stairs you will probably be...

You have been unable to complete a project in the expected time as you are too...

Your child is the lead in the school play and the school have asked you to make a costume for them. Another parent offers to help you, which makes you feel...

You have been working hard all day to get the house ready for some guests who are coming to stay tomorrow night. You feel...

You are going on holiday tomorrow and have had a busy day packing. When your alarm wakes you up in the morning you feel...

Yesterday you went for a walk with a friend. This morning you notice your legs are stiff. You think today will be...

You used to have 20/20 vision but recently you have had trouble focusing your eyesight. You think it is because you are...

You are chatting with a friend and are having trouble finding the right word. You think this is due to your...

Although you got quite a bit done at work today, you leave work early because you were feeling particularly exhausted. You think to yourself tomorrow will be...

You've had a very busy day at work and even skipped your lunch break. On your way home you begin to feel light-headed because you are...

At the weekend you went to a party and stayed out quite late. By Monday you think you will feel...

You are walking up a hill on a warm sunny day; you get out of breath and feel quite warm. When you get to the top of the hill you are sweaty from the exertion. You think it is probably because you are...

Last night you slept poorly and this morning you are having difficulty concentrating. You think this is a sign you are...
You have had a busy day and when you sit down to watch TV with your family in the evening you fall asleep. You think that this is because you are...

You are walking up the stairs and notice you are out of breath because you are...

You have had an argument with a family member and your heart is racing because of your...

You are in a meeting at work and when you speak you notice you have palpitations because of your...

You are giving a presentation at work and forget some of your words because you are...

You notice your neighbour spraying their roses with insecticide. The next day you have itchy eyes and a runny nose and think this is because...

You have attended a family occasion and had an enjoyable time. It was a long day and by the end you feel very tired. You think in a couple of days you will feel...

Recently you have had more energy than usual and have been able to meet up with people you haven't seen in a quite some time. Yesterday you met up with a friend and went for dinner. The next day you feel...

You are going to a family occasion at the weekend. You think it will be a lot of...

You are meeting up with an old school friend. You ask them if they would meet you locally. They will think you are...

Tomorrow is your son's birthday and you are throwing a birthday party for him. You are preparing the decorations and food. You have to ask your neighbour for help because you are...

You have had a busy day at work and have a number of tasks to get done before the end of the day. You ask a colleague for help because you are...

You used to play a lot of football and your local team has asked you to referee a match for a charity event. You think this is...

In the last few days you have developed a sore throat and are feeling achy. You think these are symptoms of a...

You usually get the bus to work but today you are feeling energetic and decided to walk. When you come home from work you feel more tired than usual. You think tomorrow you will feel....
Chapter 6 A cross-cultural replication study of cognitive biases and deficits in CFS

6.1 Chapter overview

This article is under peer review at the International Journal of Behavioural Medicine
6.2 Submitted article

Title: Cross-cultural study of information processing biases in Chronic Fatigue Syndrome: comparison of Dutch and UK chronic fatigue patients

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Key words: attentional bias, interpretation bias, chronic fatigue syndrome, cross-cultural
Abstract

Purpose: This study aims to replicate a UK study, with a Dutch sample to explore whether attention and interpretation biases and general attentional control deficits in Chronic Fatigue Syndrome (CFS), are similar across populations and cultures.

Methods: Thirty-eight Dutch CFS participants were compared to 52 CFS and 51 healthy participants recruited from the UK. Participants completed self-report measures of symptoms, functioning and mood; as well as three experimental tasks (i) Visual-Probe task measuring atten- tional bias to illness (somatic symptoms and disability) versus neutral words, (ii) interpretive bias task measuring positive versus somatic interpretations of ambiguous information and (iii) the Attention Network Test measuring general attentional control.

Results: Compared to controls, Dutch and UK participants with CFS showed a significant attentional bias for illness-related words and were significantly more likely to interpret ambiguous information in a somatic way. These effects were not moderated by attentional control. There were no significant differences between the Dutch and UK CFS groups on attentional bias, interpretation bias or attentional control scores.

Conclusions: This study replicated the main findings of the UK study, with a Dutch CFS population; indicating that across cultures and populations people with CFS demonstrate biases in how somatic information is attended to and interpreted. These illness-specific biases appear to be unrelated to general attentional control deficits.
Introduction

Self-report studies have identified that how people perceive and respond to symptoms, can play a role in maintaining Chronic Fatigue Syndrome (CFS) (Cella, et al., 2013; Moss-Morris & Chalder, 2003; Silver, et al., 2002; Stahl, et al., 2014). Experimental studies have explored how people with CFS attend to and interpret illness-related information at earlier, more implicit levels of processing (Hou, et al., 2008; Hou, et al., 2014; Hughes, et al., 2016b; Martin & Alexeeva, 2010; Moss-Morris & Petrie, 2003). A recent review of this experimental literature concluded that findings were mixed due to a lack of standardized methodology, small sample sizes, and illness-specific materials (Hughes, et al., 2016a).

Subsequent to this review the authors developed CFS-specific experimental tasks by tailoring materials to tap into concepts central to the disorder (Hughes, et al., 2016c). A large (n=103) cross-sectional study using these tasks, found people with CFS, showed an attentional bias to information related to fatigue and associated consequences; and tended to form less positive and more somatic interpretations of ambiguous information (Hughes, et al., 2016b). Effects were independent of comorbid psychological distress. Contrary to an earlier, smaller study in CFS (Hou, et al., 2014), this larger study found that illness-specific processing biases were not associated with general attentional control deficits.

In order verify these findings they need to be replicated in another CFS population using the same experimental protocol. Replication is a basic requirement for scientific integrity
(Koole & Lakens, 2012), yet a recent, high profile publication found poor rates of replication success across a range of classic psychological research (Collaboration, 2015). Replication in experimental research is particularly pertinent given the range of methodologies employed. Subtle variations in experiments can have implications for the processes which are being tapped into (Hughes, et al., 2016c). Furthermore, experimental methods can be prone to error that can arise from errors in millisecond timing and programming (Hirsch, Meeten, Krahé, & Reeder, 2016; Plant & Quinlan, 2013; Sigurjónsdóttir, Sigurðardóttir, Björnsson, & Kristjánsson, 2015). Thus, exact replication, using the same experimental protocols, is needed to establish whether findings are reliable and can be extrapolated across populations (Hirsch, et al., 2016; Plant & Quinlan, 2013; Sigurjónsdóttir, et al., 2015).

The aim of this study was to determine whether we can replicate the findings from the UK study (Hughes et al., 2016b), with a Dutch CFS cohort to establish whether cognitive processing biases are a reliable finding across populations and cultures (Collaboration, 2015). Experimental data obtained from a newly recruited Dutch CFS cohort were compared to the data from CFS and healthy participants recruited from the UK who took part in our previous study (Hughes, et al., 2016b). No study to date has assessed these cognitive processes in a CFS population from outside the UK. Given that self-report studies have identified Dutch and UK CFS participants have similar symptom profiles (Hickie, et al., 2009), illness beliefs and responses to symptoms (White, et al., 2011b), it was expected that they will also have similar cognitive processing tendencies.
The main hypotheses are: 1) The Dutch CFS group will show significant biases and control deficits compared to the healthy control group but equivalent biases and attentional control to the UK group with CFS 2) Attention and interpretation biases will be independent of levels of anxiety and depression 3) Attentional control will not moderate attention or interpretation biases.

**Methods**

**Participants**

38 Dutch CFS participants were recruited from a specialist CFS treatment service of the Radboud University Medical Centre. Inclusion criteria were, meeting Centre for Disease Control (CDC) criteria for CFS (Fukuda, et al., 1994; Reeves, et al., 2003), being over 18 years old, able to read and write Dutch and not having received psychological treatment for CFS. The 38 Dutch CFS participants were compared to the 52 UK CFS participants and 51 UK healthy controls described in the original study. For details of the UK participant recruitment see the original study (Hughes, et al., 2016b).

**Procedures**

The Dutch CFS group followed the same protocol as that of the UK CFS and healthy controls (Hughes, et al., 2016b). Participants provided demographic information on age, gender and employment status and completed Dutch versions of questionnaires and experiments in the following order.

**Measurements**
Questionnaires

Chalder Fatigue Questionnaire CFQ (Cella & Chalder, 2010; Chalder, et al., 1993) was used as a measure of fatigue severity, consisting of 11 items scored 0-3.

Work and Social Adjustment Scale WSAS (Mundt, Marks, Shear, & Greist, 2002) measured everyday functioning, using 5 items (rated 0–8).8

Hospital Anxiety and Depression Scale HADS (Zigmond & Snaith, 1983) measured levels of depression and anxiety, using 14 items (Norton, Cosco, Doyle, Done, & Sacker, 2013).

Information processing tasks

Materials for the information processing tasks were translated from English to Dutch; back translated to ensure they retained meaning; and piloted with Dutch participants (Appendix A).

1. Visual Probe Task (VPT) (MacLeod, et al., 1986) assessed attentional bias (AB). Participants completed 16 practice trials followed by 96 experimental trials. Each trial starts with a fixation cross in the centre of the screen (500ms), followed by two words (illness-related v. neutral), appearing above and below the fixation. After 500ms the words disappear and one is replaced by an arrow. Participants identify the direction of the arrow by pressing ‘C’ for left and ‘M’ for right. AB scores are calculated as the standardized residual (difference) between reaction times (RT) to probes replacing the

8 Both English and Dutch versions of the CFQ (Cella & Chalder, 2010; Chalder, et al., 1993a) and WSAS have been validated for use with CFS populations (Cella, et al., 2011b; Mundt, et al., 2002; Worm-Smeitink, et al.).
illness-related stimuli and RT to probes replacing neutral stimuli. Positive values demonstrate an AB to CFS-threating stimuli.

2. **Recognition task (Mathews & Mackintosh, 2000)** assessed interpretation bias (IB). Participants read 10 ambiguously phrased scenarios, followed by a short comprehension question. After reading all 10 scenarios participants are presented with the title of each scenario in turn and asked to rate 4 new sentences in terms of how similar or dissimilar they are to the original text (1= not at all similar - 4= very similar). The sentences contain a positive interpretation and an illness-related interpretation of the original scenario. Recognition items also include two ‘foils’ or false statements. Foils are included so that not all items are related to the original text, thereby providing greater face validity for the task. For the purpose of this study we analysed mean scores on the interpretation items only. An IB index was also calculated as mean similarity ratings of illness-related interpretations minus positive interpretations. Higher scores indicate an increased somatic interpretation.

3. **Attention Network Task (ANT) (Fan, McCandliss, Sommer, Raz, & Posner, 2002)** assessed general attentional control. Participants are presented with a string of five congruent (→→→→→) or incongruent (→→←→→) arrows. Participants’ identify the direction of the central arrow by pressing different keys. Attentional control is calculated

9 The Attention Network Task measures three aspects of attention: orientation, altering and attentional control. For the purpose of this study we have reported only the trials which correspond to the attentional control score.
by subtracting the mean RT on congruent trials from the mean RT on incongruent trials. Higher scores indicate poorer attentional control.

**Analysis**

To test whether there was a main effect between groups, separate one-way ANOVAs were conducted with group (Dutch CFS, UK CFS and healthy controls) as the between-subjects factor and AB and attentional control scores as the dependent variables. The means of the IB task were entered into a two-way ANOVA, with group as the between-subjects factor and valance (positive and somatic interpretation scores) as the within-subjects factor. Post-hoc ANOVAs and t-tests were used to clarify significant results (hypothesis 1). ANOVAs were rerun with HADS anxiety and depression scores separately as co-variates (hypothesis 2). To examine if attentional control acted as a moderator of AB or IB, an interaction term was created between group and centred attentional control scores. The interaction term and group were entered as predictor variables in separate linear regressions with AB scores and IB index as the criterion (hypothesis 3).

**Results**

**Sample**

Table 1 shows the Dutch and UK CFS groups had equivalent levels of fatigue (CFQ), functioning (WSAS) and depression. The Dutch CFS group had significantly lower levels
of anxiety compared to the UK CFS group, $t(87)=-3.71, p<.001^{10}$. UK and Dutch CFS patients did not differ from healthy controls in terms of gender$^{11}$ and employment (all $p>.05$). Healthy participants were significantly younger than either UK CFS participants, $U=1025, p=.05$; and Dutch CFS participants, $t(63.83)=2.09, p=.04$. Age was not correlated with any of the main outcomes so was not controlled for in subsequent analyses. As expected, UK and Dutch CFS groups had significantly higher rates of anxiety, depression and disability compared to healthy participants (all $p<.05$).

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$^{10}$ Sensitivity analysis found no effect of controlling for HADs anxiety in subsequent analyses.

$^{11}$ Though gender was not significantly different across groups, the Dutch CFS group had 21% more females than the UK CFS group. Sensitivity analysis found no effect of controlling for gender in the subsequent analyses.
Table 1. Demographic variables and scores on self-report measures and information processing tasks for the Dutch and UK CFS patients and UK healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Dutch CFS group</th>
<th>UK CFS group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=38</td>
<td>n=52</td>
<td>n=51</td>
</tr>
<tr>
<td>Age (years M, SD)</td>
<td>40 (13)</td>
<td>39 (12)</td>
<td>34 (10)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>16 (42%)</td>
<td>32 (62%)</td>
<td>32 (63%)</td>
</tr>
<tr>
<td>Employed, n (%)</td>
<td>24 (65%)</td>
<td>36 (69%)</td>
<td>35 (69%)</td>
</tr>
<tr>
<td>CFQ, M (SD)</td>
<td>24.97 (4.05)</td>
<td>26.83 (4.71)</td>
<td>10.7 (3.3)</td>
</tr>
<tr>
<td>WSAS, M (SD)</td>
<td>23.6 (7.29)</td>
<td>23.38 (8.81)</td>
<td>0.5 (2.2)</td>
</tr>
<tr>
<td>HADS anxiety, M (SD)</td>
<td>6.41 (3.86)</td>
<td>9.96 (4.84)</td>
<td>4.69 (3.43)</td>
</tr>
<tr>
<td>HADS depression, M (SD)</td>
<td>9.0 (4.28)</td>
<td>8.44 (4.0)</td>
<td>2.04 (2.38)</td>
</tr>
<tr>
<td><strong>Visual probe task, M (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attentional bias score</td>
<td>.28 (1.16)</td>
<td>.22 (.90)</td>
<td>-.20 (.82)</td>
</tr>
<tr>
<td><strong>Interpretation bias task, M (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic interpretations</td>
<td>2.28 (.51)</td>
<td>2.24 (.59)</td>
<td>2.02 (.41)</td>
</tr>
<tr>
<td>Positive interpretations</td>
<td>2.69 (.39)</td>
<td>2.74 (.49)</td>
<td>3.05 (.42)</td>
</tr>
<tr>
<td><strong>Attentional control task, M (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT to congruent trials</td>
<td>652.95 (222.05)</td>
<td>588.86 (136.58)</td>
<td>510.25 (80.34)</td>
</tr>
<tr>
<td>RT to incongruent trials</td>
<td>793.20 (236.38)</td>
<td>722.85 (172.48)</td>
<td>615.94 (95.81)</td>
</tr>
<tr>
<td>Attentional control score</td>
<td>140.25 (104.02)</td>
<td>133.62 (73.58)</td>
<td>105.70 (50.4)</td>
</tr>
</tbody>
</table>

12 One Dutch CFS participant had excessive missing data due to errors and outliers (>3 SD from the group mean) on both the VPT and ANT, this participant was excluded from both these analysis, consistent with other studies. One UK CFS participant was removed as an outlier on the VPT.
VPT: Attentional bias in UK and Dutch CFS groups and healthy controls

A one-way ANOVA with AB scores showed a significant main effect of group, $F(2, 136) = 3.46; p = .03; \eta^2_p = .05$. Compared to healthy controls the Dutch CFS group had a significant AB towards illness-related stimuli, $F(1, 84) = 4.98; p = .03; \eta^2_p = .06$. There were no differences in AB scores between Dutch and UK CFS groups, $F(1, 86) = .07; p = .80; \eta^2_p = .001$. The main effect remained when controlling for anxiety, $F(3, 136) = 3.25; p = .04; \eta^2_p = .05$, but disappeared when controlling for depression, $F(3, 136) = 1.17; p = .31; \eta^2_p = .02$.

Recognition task: Interpretation bias in UK and Dutch CFS groups and healthy controls

There was a significant group x valence interaction $F(2, 138) = 16.84, p < .001, \eta^2_p = .20$, which remained significant when controlling for anxiety, $F(3, 136) = 12.60, p < .001, \eta^2_p = .16$; and depression $F(3, 136) = 10.44, p < .001, \eta^2_p = .13$. The Dutch CFS group endorsed positive interpretations significantly less than healthy controls, $t(87) = -4.17, p < .001, 95\% CI (-54, -19)$; and somatic interpretations significantly more than healthy controls, $t(87) = 2.61, p = .01, 95\% CI (.06, 45)$. There was no significant differences between the CFS groups in ratings of somatic, $t(88) = .36, p = .72, 95\% CI (-.19, .28)$ or positive interpretations, $t(88) = -.71, p = .48, 95\% CI (-.23, .11)$.

ANT: Attentional control in UK and Dutch CFS groups and healthy controls
There was a non-significant trend towards a main effect of group on attentional control scores, $F(2, 138)=2.72$, $p=.069$, $\eta^2_p=.04$. Separate ANOVAs indicated the Dutch CFS group had significantly poorer attentional control than healthy participants, $F(1, 87)=4.29$, $p=.04$, $\eta^2_p=.05$; but equivalent attentional control to the UK CFS group, $F(1, 88)=.126$, $p=.72$, $\eta^2_p=.001$.

*Moderating role of attentional control on attention and interpretation biases*

A linear regression with AB scores as the criterion and the interaction term and group as predictor variables, found attentional control did not moderate the relationship between group and AB; $b=<.02$, $SE_b=.001$, $\beta=.31$, $t(136)=.1.58$, $p=.12$, 95% CI (-.00, .004). A separate linear regression with IB index as the criterion found attentional control was not a significant moderator of the relationship between group and IB; $b=-3.85$, $SE_b=.001$, $\beta=-.01$, $t(140)=-.05$, $p=.96$, 95% CI (-.002, .001).

**Discussion**

This is the first CFS study to show replication of illness-specific cognitive biases in a population outside of the UK. These findings indicate cognitive biases in CFS are evident across different cohorts and cultures when using illness-specific materials [12]. In line with our previous study (Hughes, et al., 2016b) attentional control did not moderate AB or IB, suggesting, attentional control is not a mechanism through which these processes occur. In this study, differences between groups in AB disappeared when controlling for depressed mood using the HADS. This is atypical of depression, where AB is found at longer stimuli presentation durations than used here (Mogg & Bradley, 2005).
Furthermore, the original study found AB was independent of comorbid distress (Hughes, et al., 2016b), as measured by a clinical interview schedule (Lewis, Pelosi, Araya, & Dunn, 1992). These differences may be a reflection of the HADS capturing fluctuating mood whereas the CIS-R assessed clinical psychological comorbidity.

By carefully conducting a replication of previous experimental research this study offers protection against false positives (Collaboration, 2015). Replication in this area is particularly pertinent given that a recent systematic review of experimental studies in CFS found mixed results due to a range of methodologies and unspecific materials (Hughes, et al., 2016a). Furthermore, large heterogeneity has been identified in CFS (Cella, et al., 2011a). The successful replication of the original findings indicates that cognitive processing biases are a robust finding in CFS populations and furthermore can be extended across cultures.

This study adds to existing literature by comparing populations with CFS from the UK and Netherlands (Worm-Smeitink, et al., 2016). Findings indicate cognitive and behavioural factors, including cognitive processing biases, have a role to play in CFS, across cultures. However, the current study is limited by a lack of Dutch healthy control group. In addition, a clinical comparison group would be enlightening to further explore whether attention and interpretation biases occur in other fatigued populations or are due to the chronicity of illness. Replication studies such as this pave the way for progress in theory and treatment development. Longitudinal studies should build upon this basic
research to explore whether these cognitive processes change over time, following interventions and in comparison to other chronic conditions.
Appendix A

Table 1. Rated Dutch stimuli for the visual probe task

<table>
<thead>
<tr>
<th>Threat word</th>
<th>Neutral word</th>
</tr>
</thead>
<tbody>
<tr>
<td>vermoeidheid</td>
<td>videobeelden</td>
</tr>
<tr>
<td>onuitgerust</td>
<td>bezighouden</td>
</tr>
<tr>
<td>uitgeput</td>
<td>vertaald</td>
</tr>
<tr>
<td>belasting</td>
<td>afdrukken</td>
</tr>
<tr>
<td>Slap</td>
<td>pijl</td>
</tr>
<tr>
<td>verzwakt</td>
<td>schuilen</td>
</tr>
<tr>
<td>Afgemat</td>
<td>gebraad koolsla</td>
</tr>
<tr>
<td>moedeloos</td>
<td>omstreken motorblok</td>
</tr>
<tr>
<td>Sloom</td>
<td>place mails</td>
</tr>
<tr>
<td>Slopend</td>
<td>lengtes</td>
</tr>
<tr>
<td>Strijd</td>
<td>blanke gratis</td>
</tr>
<tr>
<td>hoofdpijn</td>
<td>speelgoed</td>
</tr>
<tr>
<td>uitputting</td>
<td>platenzaak sleutelgat</td>
</tr>
<tr>
<td>Futloos</td>
<td>trommen cijfers</td>
</tr>
<tr>
<td>Beperkt</td>
<td>cheques portier</td>
</tr>
<tr>
<td>Slaperig</td>
<td>voorruit</td>
</tr>
<tr>
<td>Bekaf</td>
<td>poppy depot</td>
</tr>
<tr>
<td>lusteloos</td>
<td>honingbij</td>
</tr>
<tr>
<td>Zwak</td>
<td>kies</td>
</tr>
<tr>
<td>gefrustreerd</td>
<td>statistieken</td>
</tr>
<tr>
<td>instorten</td>
<td>negentien</td>
</tr>
<tr>
<td>tekortschieten</td>
<td>studievrienden</td>
</tr>
<tr>
<td>Zwakte</td>
<td>herder</td>
</tr>
<tr>
<td>insepanning</td>
<td>prototype</td>
</tr>
</tbody>
</table>
Chapter 7 Cognitive predictors of treatment outcomes in Chronic Fatigue Syndrome

7.1 Chapter overview

This article has been submitted to Behaviour Research and Therapy.
Title: Cognitive predictors of treatment outcomes in Chronic Fatigue Syndrome: Attentional bias, attentional malleability and interpretation bias

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Conflict of Interest Statement: TC receives royalties for self-help books on chronic fatigue.

Key words: attentional bias, attentional malleability, prediction of outcome, interpretation bias, treatment response, chronic fatigue syndrome
Highlights

- Illness-specific biases in attention and interpretation have been identified in CFS.
- Attentional biases pre-treatment predicted greater improvement in physical functioning after CBT or GET.
- Attentional malleability pre-treatment also predicted better functional outcomes in CFS post-treatment.
- Interpretation biases pre-treatment did not predict change in functioning pre to post treatment.
Abstract

This study investigates whether cognitive processes of attentional bias, attentional malleability and interpretation bias, predicts response to treatments for Chronic Fatigue Syndrome (CFS). Patients with CFS who received either Cognitive Behavioural Therapy (CBT) or Graded Exercise Therapy (GET) for CFS completed measures of fatigue and physical functioning pre- and post-treatment. Patients also completed experimental tasks to assess attentional bias towards CFS information, (visual-probe task), malleability of attentional bias (assessed via extent of change on attentional bias over a brief attentional bias training) and interpretation bias of ambiguous material (recognition task), pre-treatment. Cognitive processing variables were entered as predictors in regression analyses, with post-treatment fatigue or functioning scores as the outcome variables, and pre-treatment scores as covariates. Fatigue and functioning significantly improved after both CBT and GET. Pre-treatment attentional bias and an increased attentional malleability predicted better functioning, but not fatigue, post-treatment. Interpretation bias did not predict either fatigue or functioning outcomes. These findings suggest both attentional biases towards CFS material, and attentional malleability, are important factors in predicting treatment outcomes in CFS. This knowledge can help us understand the cognitive characteristics of those most likely to benefit from current treatment protocols for CFS and guide further research to tailor treatments.
Introduction

Chronic fatigue syndrome (CFS), also known as myalgic encephalitis (ME) is a debilitating condition, defined as severe mental and physical fatigue persisting for 6 months or more (Fukuda, et al., 1994; Sharpe, et al., 1991). Secondary symptoms include muscle pain, multi-joint pain, headaches and poor concentration and memory (Fukuda, et al., 1994). Although no single somatic cause has been identified, biological as well as cognitive and behavioural factors are thought to contribute to the aetiology of the condition (Burgess, et al., 2012; Cella, et al., 2013; Deary, et al., 2007; Knoop, et al., 2010; Surawy, et al., 1995).

Current recommended treatments for CFS are Cognitive Behavioural Therapy (CBT) and Graded Exercise Therapy (GET) (NICE, 2007). These treatments focus on changing precipitating factors, such as reducing all-or-nothing behaviours and increase activity levels; alongside cognitive changes such as changing beliefs about the harmfulness and controllability of symptoms, in order to reduce levels of fatigue and disability (Chalder, et al., 2015; Price, et al., 2008; Stahl, et al., 2014). Several systematic reviews have identified both CBT and GET are the most promising treatments for CFS in secondary care (Chambers, et al., 2006; Edmonds, et al., 2004), with comparable treatment effects (White, et al., 2011b). A large randomized control trial found compared to standard medical care alone, CBT and GET moderately improved fatigue and physical functioning in CFS (White, et al., 2011b). Non-randomized studies have also found CBT and GET are effective in routine clinical practice (Flo & Chalder, 2014); however, effects can be slightly less than in randomized control trials (Quarmby, et al., 2007).

Although these treatments seem to be effective for some people with CFS, around 40% of patients do not show clinically significant improvements (Malouff, et al., 2008; White,
et al., 2013). Unfortunately, we still know little about why certain people respond well to current treatments for CFS whilst others do not. The aim of this study is to explore facets of cognitive processing as potential predictors of response to cognitive and behavioural based treatments for CFS (GET and CBT). Specifically, we will assess the role of key cognitive processes that differentiate those with and without CFS, namely attentional biases and interpretation biases. Identifying cognitive processes that predict treatment outcome may also elucidate ways in which CFS treatments can be developed, tailored or optimized for people who do not respond well to current treatment protocols.

A small body of experimental research has identified cognitive processing biases in how people with CFS attend to and interpret information (Hughes, et al., 2016a; Hughes, et al., 2016b). Hughes, et al. (2016b) found that people with CFS preferentially attend to illness related information (attentional bias) and tended to interpret ambiguous information as less positive and more illness related (interpretation bias), compared to healthy individuals. Interestingly, these cognitive biases were associated with self-reported cognitive and behavioural responses to symptoms (catastrophizing, fear avoidance and all-or-nothing behaviours); factors which previous studies have identified as predicting increased fatigue and disability (Moss-Morris, 2005) and moderating treatment outcomes (Flo & Chalder, 2014). These relationships suggest that cognitive processes may have a role to play in precipitating or perpetuating cognitive and behavioural factors in CFS (Hughes, et al., 2016b). Exploring whether cognitive processing biases predict treatment outcomes may provide further understanding about who will respond best to current treatments.

Several studies within the anxiety literature have explored whether attentional biases predict response to current treatments for anxiety. The pattern of findings suggest that an
attentional vigilance towards threat or a difficulty disengaging from threatening information, predicts reduced anxiety following CBT (Barry, Sewart, Arch, & Craske, 2015; Calamaras, Tone, & Anderson, 2012; Niles, Mesri, Burklund, Lieberman, & Craske, 2013; Waters, Mogg, & Bradley, 2012). One potential reason for this finding is that an attentional vigilance to threat is a key maintaining factor in anxiety. If treatments are able to target and modify the problematic attentional bias, participants will show associated anxiety reduction. Another hypothesized mechanism is that an attentional vigilance pre-treatment facilities engagement with certain aspects of treatment; for example, extinction learning which requires a sustained attention on a feared stimuli in order to challenge the anticipated adverse event associated with it (Waters & Kershaw, 2015). A similar pattern of findings may be observed in CFS; an attentional vigilance to illness-related information could be maintaining core illness beliefs and behaviours; thus treatments which modify this bias would be helpful. Additionally, an attentional vigilance may be beneficial when engaging with some aspects of treatment for CFS, for example behavioural experiments which aim to test out beliefs and encourage alternative coping responses.

Not only is attentional bias potentially important in predicting treatment outcomes, it has also been shown that changing an attentional bias can reduce distress. A task developed by McLeod MacLeod, et al., (2002)- the Attentional Bias Modification task (ABM)- has been used to modify attentional biases. Using this paradigm, studies in anxiety disorders have found that when an attentional bias towards benign information is successfully induced, greater reductions in anxiety are observed (Linetzky, et al., 2015; Mobini, Reynolds, & Mackintosh, 2013). For example, Schmidt, Richey, Buckner, and Timpano (2009) investigated the impact of ABM training on patients with diagnoses of generalised social anxiety disorder (SAD). Those who were trained to avoid threatening information
(thus reducing their attentional bias to threat), exhibited significantly greater reductions in social anxiety compared to patients who received a placebo training procedure. Furthermore, ABM studies have also shown that there are individual differences in the degree to which people alter their attentional bias over the course of ABM, with some individuals showing greater levels of attentional malleability than others. Studies have now begun to assess, not just attentional bias, but the role of attentional malleability in anxiety disorders and treatment outcome.

Attentional malleability is defined as the ability or readiness to adopt an attentional bias (Clarke, et al., 2008). It is measured in terms of the degree of change of attentional biases from before, to after, brief ABM training. Using this approach, Clarke, et al. (2008) found those with more malleable attention (measured as an ability to adopt an attentional bias towards threatening information), were more likely to naturalistically develop an attentional preference for threat when exposed to extended mild stress (i.e. the first semester at university); which in turn predicted an elevation of trait anxiety. In another study, Clarke, et al. (2012) showed that higher attentional malleability (again measured toward threatening information) predicted a better response (i.e. larger reductions in anxiety) to a course of group CBT for people with SAD. Thus, people with high attentional malleability may be more at risk of developing attentional biases and anxiety in response to stressful environments. However, these same people may also be more likely to benefit when exposed to environments (i.e. treatment) which promote the adoption of a reverse processing bias. This supports the bias plasticity account of cognitive processing (Clarke, et al., 2012), which suggests that an increased attentional malleability is adaptive when undergoing treatment.
However, these studies have only assessed malleability towards threatening information. Measuring the degree of malleability towards neutral information would be informative to assess whether facilitating more benign processing has associated benefits. The bias plasticity account (Clarke, et al., 2012) suggests that malleability is a non-valenced construct; it is the ‘malleability’ of attention that is important, not the direction attention is trained in. This is further supported by a genetic study which mapped attentional malleability onto a genetic marker, they termed a ‘plasticity gene’ (a serotonin transporter gene, 5-HTTLPR) (Fox, et al., 2011). This ‘plasticity gene’ was associated more malleable attention, both towards and away from threatening information. There were also some tentative indications that those with this ‘plasticity gene’ are more responsive to, and therefore get more benefit from environments that provide the opportunity to change their attention; for example ABM (Fox, et al., 2011). Thus, the finding that increased attentional malleability predicts better treatment response should hold true regardless of the whether malleability is measured towards threatening or neutral stimuli.

In order to test malleability as a non-valenced construct within CFS, participants in the current study were randomized to conditions whereby attention was briefly trained towards either a threatening or neutral stimuli. Consistent with the bias plasticity account we hypothesized that higher attentional malleability would be associated with better response to treatments for CFS.

Another cognitive bias evident in individuals with CFS, is the tendency to interpret ambiguous information in a particularly negative, illness-related way (interpretation bias) (Hughes, et al., 2016a; Hughes, et al., 2016b) The degree of interpretation bias may predict response to treatment for CFS, but to our knowledge no study to date has assessed this. Previous findings in CFS indicate that interpretation bias is associated with unhelpful responses to illness; such as fear and avoidance of activity, all-or-nothing behaviours,
catastrophic thinking styles and symptom focusing (Hughes, et al., 2016b; Moss-Morris & Petrie, 2003). Given this, we might expect interpretation bias predicts how an individual will respond to treatments which target these cognitive and behaviourial responses to symptoms. It could be that negative interpretation bias reinforces cognitive and behaviourial responses to symptoms, thus making them more resistant to change through current treatments. Alternativly, it could be that patients who have a negative interpretation bias prior to treatment may have a better response to treatment given the opportiity to modify their bias; e.g. through behavioural experiments. If so, having interpretation bias pre-treatment may predict better treatment outcome.

The current study was designed to identify cognitive processes that predict outcome of treatments for CFS (CBT and GET). Measuring ‘habitual’ cognitive characteristics using experimental paradigms will establish whether these processes are associated with change in fatigue and functioning post treatment. This may provide information about why some patients with CFS respond to treatments, whereas others do not. This is the first study to test whether illness-specific biases in cognitive processing predict response to treatment for CFS. It is also the only study to assess the concept of attentional malleability in this population. From the previous literature we expected to find that individual differences in these facets of cognitive processing predict how an indivdiual will respond to treatment. Specifically, we hypothesise that in CFS, the extent of attentional biases towards illness specific information would predict better fatigue and functioning post treatment. Furthermore, greater attenional malleability would also predict a better response to treatment (i.e. reduced fatigue and increased functioning post treatment). We expect that individual differences in interpretation biases pre-treatment will predict treatment response (i.e. levels of fatigue and physical functioning post treatment). However, as it is unclear at this stage whether having a strong interpretation bias would
help or hinder treatment response, our hypotheses regarding interpretation biases are exploratory and non-directional.

Methods

Participants

Participants were those that had previously been included in our cross-sectional study (Hughes, et al., 2016b) in which just their pre-treatment attention and interpretation bias scores were reported. Participants recruited from consecutive outpatient clinics between October 2014 and August 2015. They were selected in accordance with the Oxford (Sharpe, et al., 1991) criteria for CFS, which was diagnosed by a consultant psychiatrist or experienced cognitive behavioural therapist, and confirmed by self-report questions. Routine blood tests (NICE, 2007) indicated that there were no other medical condition that would explain the fatigue.

To be eligible for this follow-up study, participants needed to have received at least three sessions of either CBT or GET at one of three specialist CFS services in London or Oxford, and to have completed pre and post treatment assessments. Twenty-six people were included in this follow-up study. All participants were aged 18 or older, fluent in English, with normal or corrected-to-normal vision and good manual dexterity. The study was approved by Berkshire-B Research Ethics Committee (14/SC/0172).

Outcome variables

The outcome variables were self-reported levels of fatigue and day-to-day functioning. Fatigue was measured with the Chalder fatigue questionnaire (Likert scoring 0, 1, 2, 3; range 0–33; lowest score is least fatigue) (Chalder, et al., 1993) and physical functioning with the short form-36 physical functioning subscale (McHorney, Ware Jr, Lu, &
Sherbourne, 1994) (version 2; range 0–100; highest score is best function). These two primary outcome measures are valid and reliable and have been shown to be sensitive to change in previous RCTs in CFS (Edmonds, et al., 2004; Malouff, et al., 2008; Price, et al., 2008; White, et al., 2011b).

**Predictor Variables**

For the current analyses, attentional bias, attentional malleability and interpretation bias at baseline were assessed as predictors of treatment outcome. This data was collected pre-treatment. Pre-treatment attention and interpretation bias scores are reported in Hughes, et al. (2016b).

**Visual Probe task** (MacLeod, et al., 1986)

The visual probe task (VPT) is a computerised measure of attentional bias. Each trial begins with a 500ms fixation point followed by two simultaneously presented words (one neutral and one illness-related) above and below the fixation for 500ms. One word is then replaced with an arrow (probe) for 500ms. Participants are asked to indicate the direction of the arrow by pressing keys ‘c’ for left and ‘m’; for right, as quickly as possible while avoiding mistakes. The arrow appeared in the prior location of the neutral and illness-related word an equal number of times. For details of the material and experimental procedure see Hughes, et al. (2016b). Attentional bias is calculated as the standardized residual (difference score) of reaction times (RT) to probes replacing neutral words minus the RT’s to probe replacing CFS-related words. Positive values indicate an attentional bias to CFS-threatening words.

13 To create the standardized residual score a regression analysis was conducted where reaction times to probes replacing neutral stimuli were entered as the dependent variable and reaction times to probes replacing illness related stimuli was entered as the independent variable.
Malleability (MacLeod, et al., 2002)

The VPT described above was adapted to assess attentional malleability using the same design as Clarke, et al. (2008) and Clarke, et al. (2012). This involves assessing attentional bias after a brief period of training to determine the extent to which participants are able to adopt the designated attentional bias. For this purpose, the VPT was extended to include two additional blocks; a training block of 192 trials and post-training block of 48 trials. Participants were randomized to receive either training towards neutral words or training towards threatening words. For those trained towards neutral/benign stimuli, probes consistently appeared in the prior location of the neutral word for the 192 trials. For those trained towards threatening stimuli, probes consistently replaced threatening/illness-related words. In the post-training block the probe appeared in the prior location of the threatening or neutral word an equal number of times. The purpose of the post contingency block was to assess the attentional bias post training. Consistent with MacLeod, et al., (2002) the stimuli for the training block was the same as that in the VPT (see above). A new set of stimuli were used for the post-training block in order to assess generalisation of training to new, novel stimuli (see supplementary material).

To assess the degree to which participants’ attention is malleable to change via training, we calculated an attentional malleability index. As we are interested in malleability per se and not malleability in relation to valence of training, we calculated attention malleability scores separately for those in the threat training and neutral training conditions. Scores were calculated as follows:

Malleability scores for those in the threat training condition = post training RT to neutral - post training RT to threat
Malleability scores for those in neutral training condition= post training RT to threat- post training RT to neutral
Higher scores, regardless of the training condition (threat or neutral), are indicative of greater malleability of attentional biases.

*Interpretative bias task* (Mathews & Mackintosh, 2000)
The interpretative bias task is an ambiguous scenario recognition task (Mathews & Mackintosh, 2000) which has two phases, the encoding phase and the recognition phase. During the encoding phase participants are presented with ten ambiguous scenarios, each beginning with a title. Participants are asked to read each scenario as though they are the main protagonist. After reading the scenario they are then asked to rate how pleasant the scenario was (scale of 1-10) and answer a brief comprehension question to ensure the text has been read and understood.

After reading all ten scenarios the recognition phase begins. Participants are presented with the title of a given scenario and asked to rate four new sentences to the degree to which they are similar in meaning to the original text (1=, very different in meaning, to 4= very similar in meaning). The four sentences relate to (i) a positive interpretation of the scenario (ii) an illness related interpretation of the scenario (iii) a positive sentence which is factually incongruent to the scenario (positive foil) (iv) a negative sentence which is factually incongruent to the scenario (negative foil). Foils were included to make the purpose of the task more obscure. The foils were not analysed. For the analysis, mean similarity ratings for the interpretation items were calculated. Higher scores indicate increased endorsement of that type of interpretation. For details of the stimuli and experimental procedure see Hughes, et al. (2016b).
**Procedure**

After obtaining written informed consent, participants completed questionnaires at home and then attended the laboratory to complete the cognitive processing tasks on a laptop computer. This data is reported in Hughes, et al. (2016b). For the current follow-up study participants completed questionnaires up to two weeks after their final treatment session. Primary outcomes were also assessed at the time of drop-out, and used when no other outcome data were available.

**Treatments**

All treatments were provided as part of routine clinical practice at specialist CFS services in the UK. Treatments were administered by trained Cognitive Behavioural Therapists, Clinical Psychologists or Physiotherapists. Patients were allocated CBT or GET based on the patient preference, assessor recommendation and local authority funding. All treatment centres followed standardized CBT and GET treatment protocols (White, et al., 2011b), which are designed to be delivered over 14 sessions over 24 weeks. Most treatments were delivered face-to-face but some were provided by telephone. Treatment was provided individually, although participants could be accompanied if they wanted.

**Cognitive Behavioural Therapy**

The aim of CBT for CFS is to change the behavioural and cognitive factors assumed to play a role in the perpetuation of the participant’s symptoms and disability (White, Sharpe, Chalder, DeCesare, & Walwyn, 2007).

The behavioural component of CBT includes setting a baseline of current activity levels and sleep/wake patterns and using these to set goals to develop more consistent patterns, with the view to increasing activity. The cognitive component has a number of elements.
First – unhelpful thoughts in relation to fatigue such as catastrophizing and fear-avoidance beliefs are identified and patients are taught methods of challenging these and coming up with alternatives. Second- symptom focusing is discussed, linking the patient’s thoughts, feelings (physical and emotional) and behaviour, using their own examples. Third- other factors which may negatively influence the patient’s ability to cope with their illness, such as low self-esteem or beliefs about perfectionism, are identified and addressed. Where applicable patients complete ‘sleep diaries’, ‘unhelpful thoughts diaries’ and ‘alternatives to unhelpful thoughts diaries’; as well as writing out a plans for each week in an ‘activity programme’ and recording their activities in a ‘weekly activity diary’. These are reviewed with their therapist during treatment sessions.

CBT treatment for CFS is usually structured as course of 10-14, one to one sessions between the person with CFS and a trained health professional (NICE, 2007).

*Graded Exercise Therapy*

The aim of GET in relation to CFS is to help the participant gradually engage and participate in physical activity and aerobic exercise. Emphasises is on reducing fear of exercise through systematic desensitisation and reverse muscle and fitness depletion (i.e. deconditioning), that is assumed to be perpetuating the fatigue and disability. (Edmonds, McGuire, & Price, 2004). The rational is that reversing deconditioning and improving fitness and physical functioning will alter the persons perception of effort and enable the body to gain fitness and strength; leading to a reduction in symptoms and an increase in activity capacity (Fulcher & White, 1997).

Therapeutic strategies consist of establishing a baseline of achievable exercise, followed by a negotiated, incremental increase in the duration of time spent physically active. After
an assessment of the patient’s current physical capacity, and mutual negotiation of meaningful and functional physical goals, a baseline of physical activity is agreed upon and commenced, at a manageable low level of intensity. The duration of physical activity/exercise is then increased slowly, once every 1–2 weeks. Intensity is increased by encouraging the patient to speed up the pace of their walk, increase the resistance on exercise machines or do an activity faster, using their heart rate monitor (HRM) as a guide. If increased symptoms occur after an increment, the patient is encouraged to stick at the current level until symptoms reduce, and then increase afterwards. However, activity is mutually reviewed on a regular basis, and plans may be adjusted depending on the patient’s general health and symptoms. Patients are encouraged to see symptoms as temporary and reversible, as a result of their current physical weakness, and not as signs of progressive pathology (White, et al., 2007).

GET is usually delivered on a one to one basis by a trained exercise therapist, usually a physiotherapist (NICE, 2007). The number of sessions vary according to the treatment protocols used. The GET protocol used at the specialist CFS clinics in this study provided a course of 10-14 sessions (White, et al., 2007).

**Analytic strategy**

To assess the effect of treatment on primary self-reported outcomes, paired t-tests within the CBT and GET groups were conducted with pre and post treatment fatigue (CFQ) and functioning (SF-36) scores. To examine whether cognitive processes assessed at the start of therapy served to positively or negatively predict improvement in fatigue and/or functioning in response to specialist CFS treatments (CBT and GET), multiple linear regressions were conducted. Separate linear regressions were conducted with the criterion variables of post therapy fatigue (CFQ) and functioning (SF-36). For each linear
regression, predictor variables included: the type of treatment; pre-treatment scores of the criterion measure in order to account for “baseline” levels; and the pre-treatment cognitive processing score of interest (attentional bias, attentional malleability or interpretation bias).

Results

Treatment outcome

Figure 1 illustrates the recruitment into the study. Fifty-two CFS participants were recruited into the cross-sectional study (Hughes, et al., 2016b), of these 40 were eligible for the current study as they were assigned either CBT or GET at one of the three recruitment sites, based in London or Oxford. Of the 40 participants eligible to participate, 4 dropped out of treatment before completing the minimum of 3 treatment sessions; 3 were still in treatment at the time of analysis; and 7 were lost to follow up. There were no significant differences in demographics (age, t(50)=-.65, p=.52; gender; χ²=.33, df=1, p=.57) or illness factors (illness duration, t(50)=.24, p=.81; fatigue, t(50)=.33, p=.76; functioning, t(50)=.13, p=.90; distress, t(50)=.68, p=.50) between those who were included in the final analysis (n=26) and those who were not (n=26). The group characteristics and clinical measures of the final sample (n=26) are presented in Table 1. There were no significant differences between CBT and GET groups at baseline, in terms demographics (age, gender, employment), clinical variables

14 Sensitivity analysis found no difference in effects when treatment centre or number of treatment sessions were entered as predictor variables in the linear regression analyses; therefore, these variables were not included in the regression models. Treatment type was included in the regression models but was not a significant predictor of fatigue or functioning in any of the models.

15 The three recruitment sites were chosen for the follow-up study as they had comparable treatment protocols.
(illness duration, distress, fatigue or functioning) or number of treatment sessions received.
CFS Participants
\((n=52)\)

**Complete baseline questionnaires and experimental/cognitive tasks**

**Attending treatment clinics outside of the study recruitment sites \((n=7)\)**
**Did not receive funding for treatment \((n=5)\)**

**Participants assigned treatment at the clinic \((n=40)\)**
**CBT \((n=27)\)**
**GET \((n=13)\)**

**Dropped out after < 3 sessions \((n=4)\)**
**Still on waitlist \((n=3)\)**
**Lost to follow-up \((n=7)\)**
  - 4 unable to contact
  - 3 declined to participate

**Post treatment questionnaires \((n=26)\)**
**CBT \((n=19)\)**
**GET \((n=7)\)**

Figure 4 Flow chart of study design
Table 1. Comparisons between CBT and GET groups on demographic variables and pre-treatment clinical variables

<table>
<thead>
<tr>
<th></th>
<th>CBT</th>
<th>GET</th>
<th>Inferential statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), M (SD)</td>
<td>39 (12)</td>
<td>34 (5)</td>
<td>t(22.79) = 1.53, p = .28</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>13 (68%)</td>
<td>4 (57%)</td>
<td>( \chi^2 = .29, df = 1, p = .59 )</td>
</tr>
<tr>
<td>Employed, n (%)</td>
<td>12 (63%)</td>
<td>6 (86%)</td>
<td>( \chi^2 = 1.22, df = 1, p = .27 )</td>
</tr>
<tr>
<td>Years in education, M (SD)</td>
<td>15 (5)</td>
<td>15 (3)</td>
<td>t(24) = .03, p = .97</td>
</tr>
<tr>
<td>Illness duration (months), M (SD)</td>
<td>70.59 (89.78)</td>
<td>45.29 (62.08)</td>
<td>t(24) = .69, p = .50</td>
</tr>
<tr>
<td>HADS distress</td>
<td>20.37 (7.18)</td>
<td>16.42 (6.45)</td>
<td>t(24) = 1.27, p = .22</td>
</tr>
<tr>
<td>CFQ, M (SD)</td>
<td>27.26 (5.28)</td>
<td>26.14 (1.12)</td>
<td>t(19.37) = .679, p = .60</td>
</tr>
<tr>
<td>SF-36, M (SD)</td>
<td>47.11 (2.97)</td>
<td>45.71 (15.12)</td>
<td>t(24) = .14, p = .89</td>
</tr>
<tr>
<td>Number of treatment sessions, M (SD)</td>
<td>9.63 (4.07)</td>
<td>10.71 (4.11)</td>
<td>( \chi^2 = 8.42, df = 1, p = .30 )</td>
</tr>
</tbody>
</table>

CFS, Chronic fatigue syndrome; CFQ, Chalder Fatigue Questionnaire; SF-36, Short-Form 36 physical functioning scale; HADS, Hospital Anxiety and Depression Scale.

*aDegrees of freedom were corrected after Lavene’s test

In order to assess the predictors of treatment efficacy it was necessary to first test whether treatments did indeed result in decreases in fatigue and increases in functioning. In order to do so, paired t-tests were conducted with participants’ fatigue and functioning scores pre and post treatment. Table 2 shows that both CBT and GET resulted in significant improvements in fatigue (CBT; \( t(18) = 6.31, p < .001, 95\% \) CI 6.91, 13.86; GET; \( t(6) = 2.66, p = .017, 95\% \) CI .45, 10.93), as measured by the Chalder fatigue scale (Chalder, et al., 1993) and functioning (CBT; \( t(18) = -.266, p = .04, 95\% \) CI -20.93, -2.40; GET; \( t(6) = 3.49, p = .01, 95\% \) CI -28.0, -4.91) measured by the SF-36 (McHorney, et al., 1994) from beginning to end of treatment. However, participants showed considerable individual
difference in the size of fatigue reduction and improvements in functioning across the course of treatment.

Table 2. CFS patients means and standard deviations for the outcome variables at baseline and after completing treatment

<table>
<thead>
<tr>
<th></th>
<th>CFQ</th>
<th>SF-36</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td>CBT (n=19)</td>
<td>27.00</td>
<td>16.61</td>
</tr>
<tr>
<td></td>
<td>(5.30)</td>
<td>(6.91)</td>
</tr>
<tr>
<td>GET (n=7)</td>
<td>26.14</td>
<td>20.46</td>
</tr>
<tr>
<td></td>
<td>(2.97)</td>
<td>(5.43)</td>
</tr>
</tbody>
</table>

CBT, Cognitive behavioural therapy; GET, graded exercise therapy; CFQ, Chalder Fatigue Questionnaire; SF-36, Short-Form 36 physical functioning scale

Predictors of treatment outcome

Pre-treatment scores on the attentional bias task, malleability task and interpretation bias task are presented in Table 3. Linear regressions of predictors of post-treatment fatigue are presented in Table 4; and linear regressions of predictors of post-treatment physical functioning are presented in Table 5.

Table 3. Reaction times and scores on the cognitive tasks (CBT and GET groups combined)

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=26</td>
</tr>
<tr>
<td>Visual Probe Task</td>
<td></td>
</tr>
<tr>
<td>RT to threat pre-training block</td>
<td>611.04 (94.39)</td>
</tr>
<tr>
<td>RT to neutral pre-training block</td>
<td>615.12 (92.76)</td>
</tr>
<tr>
<td>Malleability score</td>
<td>.75 (64.22)</td>
</tr>
<tr>
<td>Recognition Task</td>
<td></td>
</tr>
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</table>
Table 3. Continued…

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n=26</td>
</tr>
<tr>
<td>Positive interpretation</td>
<td>2.75 (.44)</td>
</tr>
<tr>
<td>Somatic interpretation</td>
<td>2.32 (.57)</td>
</tr>
<tr>
<td>Positive foil</td>
<td>1.55 (.31)</td>
</tr>
<tr>
<td>Negative foil</td>
<td>1.45 (.22)</td>
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</table>

RT, reaction time

Table 4. Summary of linear regression analyses of predictors of post treatment fatigue

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE (B)</th>
<th>β</th>
<th>t</th>
<th>p</th>
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<tbody>
<tr>
<td>Treatment type</td>
<td>3.69</td>
<td>2.95</td>
<td>.25</td>
<td>1.25</td>
<td>.22</td>
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<tr>
<td>Pre-treatment fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attentional bias</td>
<td>.54</td>
<td>.28</td>
<td>.38</td>
<td>1.96</td>
<td>.06</td>
</tr>
<tr>
<td></td>
<td>-.46</td>
<td>1.36</td>
<td>.07</td>
<td>-.34</td>
<td>.74</td>
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<table>
<thead>
<tr>
<th>Variable</th>
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<th>SE (B)</th>
<th>β</th>
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<tbody>
<tr>
<td>Treatment type</td>
<td>3.74</td>
<td>2.86</td>
<td>.25</td>
<td>1.31</td>
<td>.20</td>
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<tr>
<td>Pre-treatment fatigue</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Attentional malleability</td>
<td>.52</td>
<td>.27</td>
<td>.36</td>
<td>1.89</td>
<td>.07</td>
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<tr>
<td></td>
<td>-.02</td>
<td>.2</td>
<td>-.15</td>
<td>-.81</td>
<td>.43</td>
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<table>
<thead>
<tr>
<th>Variable</th>
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<th>t</th>
<th>p</th>
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<tbody>
<tr>
<td>Treatment type</td>
<td>2.84</td>
<td>3.08</td>
<td>.19</td>
<td>.92</td>
<td>.37</td>
</tr>
<tr>
<td>Pre-treatment fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive interpretation bias</td>
<td>.29</td>
<td>.28</td>
<td>.21</td>
<td>1.02</td>
<td>.32</td>
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<tr>
<td></td>
<td>2.22</td>
<td>3.16</td>
<td>.15</td>
<td>.70</td>
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<th>p</th>
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</thead>
<tbody>
<tr>
<td>Treatment type</td>
<td>2.74</td>
<td>3.15</td>
<td>.19</td>
<td>.86</td>
<td>.40</td>
</tr>
<tr>
<td>Pre-treatment fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic interpretation bias</td>
<td>.21</td>
<td>.29</td>
<td>.21</td>
<td>.97</td>
<td>.34</td>
</tr>
<tr>
<td></td>
<td>-.033</td>
<td>2.43</td>
<td>-.03</td>
<td>-.14</td>
<td>.89</td>
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Table 5. Summary of linear regression analyses of predictors of post treatment physical functioning

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<th>p</th>
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</thead>
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<tr>
<td>Treatment type</td>
<td>1.80</td>
<td>7.33</td>
<td>.03</td>
<td>.25</td>
<td>.81</td>
</tr>
<tr>
<td>Pre-treatment functioning</td>
<td>.84</td>
<td>.16</td>
<td>.71</td>
<td>5.28</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Attentional bias</td>
<td>9.83</td>
<td>3.39</td>
<td>.40</td>
<td>2.90</td>
<td>.008</td>
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<table>
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<th>β</th>
<th>t</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Treatment type</td>
<td>7.71</td>
<td>7.13</td>
<td>.14</td>
<td>1.08</td>
<td>.29</td>
</tr>
<tr>
<td>Pre-treatment functioning</td>
<td>.881</td>
<td>.16</td>
<td>.74</td>
<td>5.52</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Attentional malleability</td>
<td>.16</td>
<td>.05</td>
<td>.40</td>
<td>2.99</td>
<td>.007</td>
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<th>p</th>
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<tbody>
<tr>
<td>Treatment type</td>
<td>8.67</td>
<td>7.87</td>
<td>.17</td>
<td>1.10</td>
<td>.28</td>
</tr>
<tr>
<td>Pre-treatment functioning</td>
<td>.81</td>
<td>.18</td>
<td>.72</td>
<td>4.65</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Positive interpretation bias</td>
<td>2.64</td>
<td>8.01</td>
<td>.05</td>
<td>.75</td>
<td>.50</td>
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</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE (B)</th>
<th>β</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment type</td>
<td>9.30</td>
<td>7.74</td>
<td>.18</td>
<td>1.20</td>
<td>.24</td>
</tr>
<tr>
<td>Pre-treatment functioning</td>
<td>.45</td>
<td>.18</td>
<td>.67</td>
<td>4.12</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Somatic interpretation bias</td>
<td>-6.15</td>
<td>6.24</td>
<td>-.16</td>
<td>-.98</td>
<td>.34</td>
</tr>
</tbody>
</table>

1. Does attentional bias prior to treatment predict fatigue and physical functioning post treatment?

To assess whether attention bias pre-treatment predicts improvement in fatigue post treatment a multiple linear regression was conducted with treatment type, pre-treatment fatigue and pre-treatment attentional bias entered as predictors, and post treatment fatigue
entered as the dependent variable. Attentional bias at the start of therapy did not predict change in fatigue, $b=-.46$, $SE_b=1.36$, $\beta=.07$, $t(25)=-.34$, $p=.74$, 95% CI (-2.35, 3.28).

To assess whether attention bias predicted change in functioning pre to post therapy a separate linear regression was conducted with SF-36 measured post-therapy as the criterion and treatment type, pre-treatment SF-36 score, and attentional bias as the predictors. Pre-treatment attentional bias significantly predicted functioning post therapy, over and above the other variables; $b=-9.83$, $SE_b=3.39$, $\beta=.40$, $t(25)=2.90$, $p=.008$, 95% CI (2.79, 16.86).

2. Does attentional malleability prior to treatment predict fatigue and physical functioning post treatment?

The degree to which individuals changed their pattern of attention as observed on the malleability index (M=.71, SD=64.22) was highly variable, suggesting that, as expected, there was considerable individual difference in attentional malleability. To examine whether attentional malleability at the start of treatment predicts symptom change across therapy, separate linear regressions were conducted with treatment type, baseline fatigue or functioning and malleability scores as predictors of the fatigue and functioning post treatment. Malleability pre-treatment did not predict change in fatigue pre to post therapy, $b=-.02$, $SE_b=.02$, $\beta=-.15$, $t=-.81$, $p=.43$; but did predict change in functioning pre to post therapy, $b=.16$, $SE_b=.05$, $\beta=.40$, $t=2.99$, $p=.007$, 95% CI (.05, .26).

To rule out any possibility that this finding is a result of the relative contribution of the pre-training attentional bias, the linear regression predicting change in functioning was re-run including both attentional bias and malleability scores as predictors. Treatment
type was not included as this variable did not have a significant impact on the previous model. The model remained significant, $F(3,22) = 19.52$, $r = .85$, $p = .001$. Malleability remained a significant predictor of change in functioning pre to post treatment, over and above that of attentional bias, $b=.14$, $SE_b=.04$, $\beta = .35$, $t = 3.11$, $p = .005$, 95% CI (.05, .23). Furthermore, attentional bias did not serve to significantly predict the malleability score, $r(24) = .41$, ns.

3. Does interpretation bias prior to treatment predict fatigue and physical functioning post treatment?

To investigate whether interpretation bias pre-treatment predicted improvement in fatigue or functioning post treatment, separate linear regressions were conducted with post treatment fatigue (CFQ) and functioning (SF-36) as the criterion, and treatment type, pre-treatment scores and pre-treatment interpretation bias scores entered as predictors. There was no significant effect of pre-treatment positive interpretation bias scores on fatigue $b=2.22$, $SE_b=3.16$, $\beta = .15$, $t(25) = .70$, $p = .50$, 95% CI (-4.35, 8.78); or functioning, $b=2.64$, $SE_b=8.01$, $\beta = -.05$, $t(25) = .33$, $p = .75$, 95% CI (-14.01, 19.29). There was also no significant effect of pre-treatment negative interpretation bias scores on fatigue, $b=-.33$, $SE_b=2.43$, $\beta = -.03$, $t(25) = -.14$, $p = .89$, 95% CI (-5.39, 4.72); or functioning, $b=-6.15$, $SE_b=6.24$, $\beta = -.16$, $t(25) = -.98$, $p = .34$, 95% CI (-19.12, 6.83).

**Discussion**

The aim of the present study was to examine facets of cognitive processing, specifically attentional bias, attentional malleability and interpretation bias, as predictors of response to specialist treatments for CFS, namely CBT and GET.
Attentional bias emerged as a significant predictor of physical functioning post-treatment, with those who have greater illness-related attentional biases showing greater improvement in functioning over the course of treatment. This reflects similar findings reported in the anxiety literature which has found that an attentional bias towards threat predicts better response to CBT (Reinholdt-Dunne, Mogg, Vangkilde, Bradley, & Esbjørn, 2015; Tobon, Ouimet, & Dozois, 2011). Attentional malleability was also a predictor of improved functioning pre- to post- treatment, even when controlling for attentional bias. This is consistent with Clarke, et al. (2012) which identified attentional malleability predicted treatment response in social anxiety disorder; suggesting that individual differences in the readiness to adopt a different pattern of attention (i.e. malleability) is associated with individual differences in response to therapy. In keeping with the non-directional account of plasticity, the current study trained attention both towards threatening and neutral stimuli. By operationalising malleability in this way, this study has indicated that malleability, irrespective of training direction, is an important predictor of treatment outcome in CFS. This supports findings by Fox, et al. (2011) who also measured malleability both towards and away from threat and found tentative evidence that people with anxiety who had more malleable attention benefited more in terms of reductions in anxiety following ABM than those with low malleability. Interestingly Fox, et al. (2011) also identified genetic markers that map on to attentional malleability.

Considering the findings of interpretation bias, contrary to our hypothesis interpretation bias did not predict changes in fatigue or functioning over the course of treatment. This corresponds with cross-sectional study data, which found that somatic interpretations were not related to fatigue or physical functioning in CFS (Hughes, et al., 2016b). However, they did correlate with self-reported and unhelpful responses to symptoms.
Previous studies have identified that changing these unhelpful symptom responses are key mediators of effective treatments for CFS (Chalder, et al., 2015; Moss-Morris, et al., 2005; Stahl, et al., 2014; Wearden & Emsley, 2013). Given this, it would be interesting to know if interpretation biases have a casual role in maintaining some of these cognitive and behavioural responses in CFS. Future research should consider whether interpretation biases help mediate treatment responses in CFS, and examine the relationship between interpretation bias and other key mechanisms of change.

Returning to consider attentional bias and the broader implication of these significant findings, the fact that attentional processes predicted post-treatment functioning, may be indicative of a mutually reinforcing relationship. It may be that an attentional bias to threat is maintaining disability (i.e. reduced physical functioning) for some people with CFS. Thus, engaging in techniques which modify this bias in turn reduces disability. It may be that over the course of the illness people with CFS have learnt a fearful and avoidant response to activity and fatigue triggering stimuli (Nijs, et al., 2013), which in turn reduces every-day functioning (Knoop, et al., 2010; Moss-Morris, 2005; Silver, et al., 2002). For some people, this fear and avoidance of activity may be extrapolated to a strategy of attentional vigilance for feared, illness-related information, which people engage in to pre-empt and circumvent further injury (Hughes, et al., 2016b). If treatments for CFS address the underlying mechanisms that are sustaining the unhelpful fear avoidance responses, associated reductions in attentional bias may be observed; which in turn may reduce fear and increase activity and in so doing improves levels of functioning. Alternatively, those with an increased attentional bias may more readily be able to engage in behavioural techniques that require an attentional focus on the threat (e.g. extinction learning), thus gain larger benefit from treatment (Waters & Kershaw, 2015). Further
studies are needed to explore whether changing these biases are a mechanism of treatment for CFS.

This study identified that in CFS people have differing degrees of attentional malleability. Furthermore, similar to findings in the anxiety literature, the more malleable attention, the more benefit is gained from treatment (Fox, et al., 2011; Clarke, et al., 2012) Why might attentional malleability be important in treatment? One hypothesis is that the more malleable the individuals’ attention, the more ability they have to shift an attention or interpretation bias. If these biases are problematic, i.e. they are maintaining some core aspect of the condition, then attenuating the bias would produce therapeutic effects. This assumes that current treatment protocols for CFS provide the conditions under which cognitive biases change. Clarke, et al. (2012) showed that people with SAD who were more malleable pre-treatment, had greater reductions in attentional biases and anxiety following CBT. Given this, it may be the case that those with CFS who have higher attentional malleability are more able to reduce unhelpful attentional biases through current cognitive and behavioural based treatments for CFS (i.e. GET and CBT), and may also benefit more from treatment. Since attentional malleability has been identified as an important predictor of outcome in CFS, research is needed to establish whether current treatments can be optimised for those with poor malleability and/or whether certain treatments are more effective for those with poor versus greater attentional malleability.

The nature of this non-randomized study includes the potential for a number of confounding variables (e.g. numerous treatment centres, different therapeutic approaches). However, sensitivity analysis found no effect of treatment centre or treatment type. Furthermore, consistent with previous studies (White, et al., 2011b), CBT and GET showed similar treatment effects. However, previous research suggests that
CBT and GET may engage different mechanisms to achieve these treatment effects. For example, Chalder, et al. (2015) found that fear avoidance beliefs were the strongest mediator for both CBT and GET for CFS, but more so for GET. This may be a result of GET engaging with fear-avoidance more directly through behavioural techniques. Given this, cognitive processes in CFS could influence treatment outcomes differently depending on the specific treatment received. Indeed, a previous study found that attentional vigilance to threat predicted better outcomes in CBT for anxiety, but not ACT (Niles, et al., 2013). The current study lacked the sample size to explore differences between treatments (CFS=19, GET=7). It may be that one treatment targets cognitive biases whereas the other does not. If this is the case, there may be important implications for how patients are assigned to different treatments. For instance, an individual who has an attentional bias that maintains some core aspect of their condition may benefit from a treatment that specifically targets this problem. Cognitive processing characteristics could be one way to match patients to the most personally efficacious treatment.

This study identified cognitive characteristics that predicted increased physical functioning. This is an important outcome for CFS, a condition defined by its debilitating effects (Fukuda, et al., 1994; Sharpe et al., 1991). However, the facets of cognitive processing studied in this research did not predict improvements in fatigue. Further research is needed to establish what factors can predict fatigue outcomes in CFS and whether cognitive processes play a role. Whilst cognitive biases may not have a direct relationship with fatigue, they may interact with other mechanisms of treatment; for example, self-reported cognitions and behaviours.

This study is the first to experimentally assess whether cognitive processing can predict response to treatment in patients diagnosed with CFS. The findings support the efficacy
of current treatments provided in routine clinical practice in improving fatigue and functioning in CFS (Quarmby, et al., 2007; Stahl, et al., 2014); and importantly indicate that facets of cognitive processing, namely attentional bias and attentional malleability, predict some of these treatment effects. Further work is needed to explore whether these cognitive processes mediate treatment outcomes in CFS.
Table 1. Materials for the VPT (MacLeod et al., 2002)

<table>
<thead>
<tr>
<th>Illness related words</th>
<th>Neutral Words</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Set 1.</strong></td>
<td></td>
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<tr>
<td>bedridden</td>
<td>buttercup</td>
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<tr>
<td>collapse</td>
<td>transmit</td>
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<tr>
<td>immobilised</td>
<td>calligraphy</td>
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<td>fatigue</td>
<td>pockets</td>
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<tr>
<td>exhausted</td>
<td>messenger</td>
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<tr>
<td>disabled</td>
<td>calendar</td>
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<tr>
<td>drained</td>
<td>pitched</td>
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<tr>
<td>limited</td>
<td>created</td>
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<td>aches</td>
<td>domes</td>
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<tr>
<td>anxious</td>
<td>whistle</td>
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<tr>
<td>Incapacitated</td>
<td>infinitesimal</td>
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<tr>
<td>painful</td>
<td>trumpet</td>
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<tr>
<td><strong>Illness Related Words</strong></td>
<td><strong>Neutral Words</strong></td>
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<td><strong>Set 2</strong></td>
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<td>impaired</td>
<td>polished</td>
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<td>restricted</td>
<td>newspapers</td>
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<td>debilitating</td>
<td>articulation</td>
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<td>housebound</td>
<td>grapevines</td>
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<td>weak</td>
<td>zone</td>
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<td>powerless</td>
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<td>unwell</td>
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<td>frustrated</td>
<td>settlement</td>
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<td>tired</td>
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<td>disheartened</td>
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<td>feeble</td>
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<tr>
<td>shattered</td>
<td>brochures</td>
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Chapter 8 Do cognitive processes change over the course of treatment?

8.1 Chapter overview

This chapter reports on preliminary follow-up data of participants who took part in the nested longitudinal study. The chapter assesses whether cognitive biases and attentional control capacity changed over the course of treatment for CFS (CBT or GET); and the extent to which changes in these domains relates to treatment outcomes.

8.2 Introduction

Our previous studies have established that people with CFS have illness-specific attention and interpretation biases, compared to healthy individuals (Chapter 5 and Chapter 6). Associations between cognitive biases and factors which perpetuate fatigue and disability, suggest these cognitive processes maybe important in the autopoietic cycle of symptom maintenance in CFS. Our previous study (7) illustrated that certain cognitive processes also predict how an individual will respond to treatments for CFS. Having pre-existing attentional vigilance towards illness-related information (attentional bias) and more malleable attention, predicted larger reductions in disability post-treatment. Interpretation bias did not predict treatment outcomes. These findings may indicate that having an attentional vigilance towards illness-related information is a maintaining factor of disability for some people with CFS. Thus, by engaging in treatments which modify this bias, disability is reduced. Those with more malleable attention may be more able engage in treatments which modify their attentional habits and thus show better treatment responses. An underlying assumption of these hypotheses is that treatments for CFS target and modify attentional biases.
The finding that interpretation biases were not related to treatment outcomes indicate that an individual’s pre-exiting interpretation habits are not important for predicting fatigue or disability. Does this mean interpretation biases are not an important factor to address during treatment? Our earlier cross-sectional findings suggest otherwise; illness-related interpretations were associated with more negative responses to illness, indicating that interpretation biases may be important for changing these proximal treatment outcomes.

While pre-existing illness-related interpretation biases may not predict treatment outcome (Chapter 7) it may still be important to change these interpretation biases in therapy, as the ability to make a range of interpretations of ambiguity is thought to be adaptive (Clarke, Nanthakumar, Notebaert, Holmes, Blackwell & MacLeod, 2014; Koole, Schwager, & Rothermund, 2015; Troy, Wilhelm, Shallcross, & Mauss, 2010).

Consistent with other research, our previous studies also showed that people with CFS had poorer attentional control compared to healthy individuals (Cvejic, Birch, & Vollmer-Conna, 2016; Hou, et al., 2014; Hughes, et al., 2016b; Togo, et al., 2015). Attentional control is an individual’s capacity to direct and control the focus of their attention (Fan, et al., 2002). Previous studies have shown that those with CFS who have poorer attentional control, show increased disability (Schmaling & Betterton, 2016) and mental fatigue (Capuron, et al., 2006). Although attentional control was not associated with symptoms or disability in our CFS sample improving attentional control may still be an important outcome in treatment for CFS. One experimental study with CFS participants successfully improved working memory and restored general attention control back to average normative levels (Maroti, Westerberg, Saury, & Bileviciute-Ljungar, 2015), illustrating that attentional control in this population is
indeed malleable. However, the degree to which changes in attentional control may relate to improvements in other domains (e.g. symptoms) is unclear.

It could be that existing CFS treatments, directly or indirectly, modify these cognitive processes. Indeed, modifying habitual cognitive processing may be a mechanism through which CFS treatments are effective. To date, no study has experimentally assessed whether treatments for CFS shift biases in cognitive processing. However, experimental studies in the psychopathology literature, and in anxiety in particular, provide some promising indications. The following section will highlight some of the key findings in these areas.

8.2.1 Modification of cognitive processing in cognitive and behavioural treatments for anxiety

Several studies have assessed whether CBT augments attentional biases in anxiety disorders. Findings indicate that over the course of CBT patterns of attention shift; starting with a bias towards threat at baseline and shifting attention away from threat after treatment (Reinholdt-Dunne, et al., 2015; Tobon, et al., 2011). Some studies have found that this shift in attentional biases is associated with larger improvements in symptoms post treatment (Legerstee, et al., 2010; Mogg, Bradley, Millar, & White, 1995; Pishyar, Harris, & Menzies, 2008; Waters, et al., 2012). However, this is not always the case; some studies show no change in attentional bias following psychological therapies; whilst others find even when psychological treatments do reduce attentional biases, this is not necessarily correlated with improved outcomes (Tobon, et al., 2011). Perhaps some treatment protocols tap into and modify these biases whereas others do not. For example, Niles, et al. (2013) found attentional biases in a socially anxious population predicted response to CBT, however, it did not predict response
to acceptance and commitment therapy (ACT); though both treatments were effective at reducing anxiety. The authors supposed that these treatments operated via different treatment mechanisms. Whereas, CBT may facilitate attentional focus away from anxiety-provoking information, the therapeutic effect of ACT may operate through different mechanisms, for example it may focus on more flexible attention rather than changing an attentional bias.

Fewer studies have experimentally measured whether interpretation biases change over the course of psychological treatments. Those that have, have been conducted in the anxiety literature, using a range of methodologies and treatment protocols. Broadly, findings suggest that anxious patients who receive treatments such as CBT and group anxiety management, make fewer negative interpretations of ambiguous information post treatment (Bowler, et al., 2012; Eysenck, et al., 1991; Franklin, Huppert, Langner, Leiberg, & Foa, 2005; McNally & Foa, 1987). Several authors have also found that computerized cognitive behavioural therapy (cCBT) can significantly reduce negative interpretations in populations with high social anxiety (Bowler, et al., 2012; Butler, Mobini, Rapee, Mackintosh, & Reynolds, 2015). Bowler, et al. (2012) also included a treatment arm which specifically aimed to modify interpretation biases via computerized training called cognitive bias modification for Interpretation biases (CBM-I). The findings indicated that both cCBT and CBM-I modified people’s interpretation of ambiguous information. Interestingly, however, when participants were under increased mental load, those who had received CBM-I maintained the change in interpretation biases, whereas those who received cCBT did not. This suggests that, whilst cognitive and behavioural treatments can successfully reduce interpretation biases, this change may not be maintained when under increased stress.
Another key cognitive process is attentional control (Fan et al., 2002); the capacity to execute goal directed attentional deployment. People vary in the extent to which they can control their attention, which importantly is amenable to change (Derryberry & Reed, 2002). Studies with healthy and anxious populations indicate that attentional control can be accessed and enhanced by a range of psychological therapies and therapeutic techniques, including cognitive behavioural therapy (Hadwin & Richards, 2016), mindfulness (Chambers, Lo, & Allen, 2008) and exercise (Colcombe & Kramer, 2003; Colcombe, et al., 2006); although, how these diverse treatments achieve these effects is still unclear. Nevertheless, it seems likely, that CBT and GET for CFS would show similar improvements in attentional control capacity. Indeed, an fMRI study with CFS patients observed that following CBT participants had significant increases in grey matter volume localized in the lateral prefrontal cortex; (De Lange, et al., 2008) an area associated with attentional control functions (Miller & Cohen, 2001). This raises the possibility that current evidenced treatments for CFS may improve attentional control, with associated neuroplastic changes.

Given that psychological treatments for anxiety are successful in modifying cognitive biases and attentional control, it is conceivable, that cognitive and behavioural treatments for CFS, may too modify these processes.

8.2.2 Do changes in cognitive processing relate to changes in symptoms?

Cognitive processes appear to be malleable via psychological treatment. However, are changes in cognitive processing a benign bi-product of treatment or do they reflect meaningful change in the experience of the patient? In order to answer these questions studies
need to explore whether changes in cognitive processing are related to changes in core symptoms and associated disability.

Studies which experimentally manipulate cognitive biases through computerized training—cognitive bias modification (CBM)—have been fundamental in addressing these questions. CBM techniques are specifically designed to target and alter patterns of information processing (i.e. attention and interpretation biases) by means of consistently training attention or interpretation in a certain way. For example, CBM techniques to reduce attentional biases (CBM-A) typically use a modified version of the visual probe task (MacLeod, et al., 2002) (which the current research used to assess attentional biases in previous chapters), whereby a selective attention towards neutral over threatening information is repeatedly reinforced. Similarly, CBM for interpretation biases typically use a version of the ambiguous scenarios/recognition task (Mathews & Mackintosh, 2000) (which the current research used to assess interpretation biases in previous chapters), whereby positive or benign interpretations of ambiguity are consistently reinforced through repeated training towards positive/neutral resolutions of ambiguity. (For recent reviews see (Amir & Conley, 2014; Hirsch, et al., 2016b). Using these CBM methodologies, converging evidence in the anxiety literature indicates that reducing attention and interpretation biases has associated benefits of symptom reduction for people with clinical and non-clinical anxiety disorders (Linetzky, et al., 2015; Mobini, et al., 2013). Similar effects have been observed for mood disorders (Gold, Montana, Sylvia, Nierenberg, & Deckersbach, 2016). For example, a CBM-A study with people with clinical depression found a reduced attentional bias to negative emotive information, was associated with a reduction in depressive symptoms, which was maintained at 3 months follow-up (Yang, Ding, Dai, Peng, & Zhang, 2015). In a CBM-I study Williams, et al. (2013)
found that depressed participants who had been trained to interpret ambiguous situations positively, demonstrated clinically significant reductions on measures of anxiety, repeated negative thoughts, and disability; which were partially mediated by the change in interpretation bias. Thus, it seems changing these cognitive biases can have some associated benefits in symptom reduction in anxiety and depression.

However, CBM techniques are not always effective at shifting the bias, and even when they do, associated symptom reduction is not always observed (Menne-Lothmann, et al., 2014; Price, et al., 2016b). This suggests a more complex relationship between cognitive biases and symptoms, which is likely to be dependent on a range of factors. One contributing factor to these inconsistencies may be the diverse range of methods utilized in CBM protocols. For example, CBM-A is more likely to be effective at reducing an attentional bias under laboratory conditions (Clarke, Notebaert, & MacLeod, 2014; Linetzky, et al., 2015; Mogoașe, et al., 2014) and when conducted with clinical populations (Bar-Haim, et al., 2007). Similarly, CBM-I training is thought to be effective only when ambiguity is evoked (Clarke, Nanthakumar, Notebaert, Holmes, Blackwell & MacLeod, 2014) during ‘active’ training (i.e. the individual is required to resolve the ambiguity) (Hoppitt, Mathews, Yiend, & Mackintosh, 2010), and is more likely to be effective when the training involves imagery (Hirsch, et al., 2016b; Holmes, Lang, & Shah, 2009). Thus, while CBM has shown that cognitive biases are malleable constructs and may have some causal/ maintaining roles to play in psychopathology, CBM has not yet established the optimal conditions in which change in cognitive biases can be elicited and importantly, how precisely these changes equate to meaningful improvements for the patient.
A more diverse range of methods have been used to modify general attentional control (Tang & Posner, 2009) (as discussed earlier in this chapter, section 8.5.1). Studies have found that not only is attentional control plastic (i.e. malleable) and trainable but that improvements in executive attentional control transfer to other general cognitive abilities (such as, fluid intelligence and working memory) (Posner, Rothbart, & Tang, 2015; Rueda, Rothbart, McCandliss, Saccomanno, & Posner, 2005; Shipstead, Redick, & Engle, 2012). These cognitive abilities are important for everyday functioning (Royall, et al., 2002), such as multitasking (Diamond, 2013). Thus, improved attentional control is itself a clinically relevant outcome.

Several studies have also shown that improved attentional control is related to other self-reported improvements. For example, Fox, Dutton, Yates, Georgiou, and Mouchlianitis (2015) conducted a computerized attentional control training task and found that as attentional control improved, so did the ability to suppress worry-related intrusive thoughts. In another study using a different attentional control training design, increased attentional control when processing emotional information, was associated with reduced rumination and associated depressed mood (Cohen, Mor, & Henik, 2015). These studies suggest improvements in attentional control may reduce emotional reactivity. However, both studies were conducted with unselected samples and Fox, et al. (2015) failed to significantly improve attentional control at the population level. Larger studies with clinical samples are needed to assess whether changes in objective attentional control correspond with improvements that are perceived and reported by patients.
In the anxiety and depression literature at least, changing cognitive biases and enhancing attentional control, appears to be associated with some reduction in symptoms and emotional reactivity. These findings suggest that cognitive biases and attentional control may play a causal role in the maintenance of anxiety and depression (Cisler & Koster, 2010; MacLeod & Mathews, 2012; Mogg & Bradley, 2016). Thus, specifically targeting these cognitive processes is important for reducing symptoms and improving outcomes in emotional disorders. However, this may not be the case for CFS. Our previous studies found no relationship between cognitive biases or attentional control and primary symptoms and disability (Chapter 5, Chapter 6 and Chapter 7), though we did find some relationships between attentional biases and mood in CFS (Chapter 5). Nor were cognitive biases associated with improvements in fatigue or functioning post treatment (Chapter 7). Thus, shifting cognitive biases and improving attentional control in CFS may not necessarily directly result in better outcomes for the patient. In physical health conditions (such as CFS and pain), cognitive biases are more closely associated with other precipitating or perpetuating factors (e.g. fear and avoidance of activity) or proximal treatment outcomes (e.g. changes in unhelpful cognitions and behaviours).

8.2.3 Do changes in cognitive processing relate to changes in other maintaining factors?

Theoretical models of pain (e.g. the fear-avoidance model of pain and threat-interpretation model) hypothesise that cognitive biases play a role in maintaining some key aspects of pain; specifically, fear avoidance beliefs and catastrophizing (Crombez, et al., 2012; Leeuw, et al., 2007; Todd, et al., 2015). Cross-sectional studies go some way in supporting this hypothesis. For example, several studies have found that those who catastrophize and who are highly fearful about pain also demonstrate increased attentional interference by pain stimuli,
difficulty disengaging from pain stimuli, and more negative pain/illness related
interpretations of ambiguity (Asmundson, et al., 1997; Heathcote & Jacobs, 2015; Heathcote,
2015; Vancleef & Peters, 2006). Experimental pain research using CBM techniques is just
beginning. Several CBM-A studies with people with chronic pain suggests that training
patients to habitually avoid pain-related information (i.e. training attentional avoidance) is
associated with reduced anxiety sensitivity and pain related fear (Carleton, et al., 2011;
Schoth, et al., 2013; Sharpe, et al., 2012). This may indicate that there are mutually
reinforcing relationships between cognitive factors which maintain pain (e.g. pain related
fear) and pain specific cognitive processing biases (e.g. attentional bias towards pain stimuli).
Thus, when one of these factors is modified it is accompanied by changes in the other. A
similar cyclical relationship may be occurring in CFS. Indeed, Chapter 5 showed that illness-
specific processing biases in CFS were associated with fear and avoidance of activity,
catastrophizing and all-or-nothing behaviours; factors which previous research has indicated
are maintaining factors of fatigue and disability in CFS (e.g. Edwards, et al., 2001; Heijmans,
1998; Moss-Morris, et al., 1996)

Given this association between cognitive biases in CFS and self-reported cognitions and
behaviours, it follows, similar to findings in the pain literature, that a change in one domain
would be mirrored by a change in the other. That is, changes in self-reported, unhelpful
cognitions and behaviours would be associated with changes in habitual cognitive
processing. We know that self-reported cognitive and behavioural responses to symptoms
change over the course of treatment for CFS (Chalder, et al., 2015; Heins, et al., 2013; Moss-
Furthermore, changes in these cognitive and behavioural responses, such as changing fearful beliefs about the consequences of activity and reducing symptom focusing, have been highlighted as key mechanisms of treatment outcomes (Chalder, et al., 2015; Moss-Morris, et al., 2005; Stahl, et al., 2014; Wearden & Emsley, 2013; Wiborg, et al., 2011) (as discussed in Chapter 1, section 1.5.8). It may be that during treatment, changes also occur at a more habitual level. Changes in how an individual habitually attends to and interprets incoming information, may be driving or supplementing changes in how an individual copes with and responds to their symptoms. Indeed, treatments for CFS claim to target some of these more habitual processes; a stated aim of CBT for CFS is to reduce hypervigilance to symptoms (NICE, 2007) and help participants interpret symptoms differently (White, et al., 2007). However, thus far studies have relied on self-report measures to tap into these constructs. Not only are these methods subject to demand but they are also only able to reflect explicit ‘top-down’ cognitions and behaviours, which participants can recognize and report on. In order to assess more habitual or ‘bottom-up’ processes, such as how an individual selects and processes incoming information, experimental measures are needed.

As discussed in Chapter 2 (section 2.3) theoretical models propose a nuanced interaction between ‘bottom-up’ cognitive processes (e.g. attention and interpretation biases), and ‘top-down’ cognitions and behaviours (Clark & Beck, 2010; Everaert, Koster, & Derakshan, 2012; Hirsch, et al., 2006), whereby cognitive processing (i.e. how a person selects and encodes incoming information at a habitual level) interacts with and shapes cognitive and behavioural products (i.e. explicit, self-reported beliefs and behaviours). In CFS, for instance, believing that symptoms are damaging and must be avoided (i.e., a person’s ‘illness schema’; as discussed in Chapter 2, section 2.3) may encourage bottom-up processing biases to
develop; such as, a hypervigilance for illness related information (attentional bias), or habitually interpreting ambiguous information as illness related and threatening (interpretation bias). These biases may reinforce the already salient concern that symptoms are pervasive, uncontrollable and damaging, and thus shapes how the individual responds to symptoms (e.g. symptom focusing, fear and avoidance of activity). In this way, attention and interpretation biases in CFS may have a bidirectional or mutually reinforcing relationship with unhelpful cognitions and behaviours. Alternatively, these relationships may be sequential; i.e. cognitive biases may encourage unhelpful responses to symptoms; or unhelpful responses may encourage the development of cognitive bias heuristics—information processing shortcuts derived from experience, to make processing salient information more efficient.

If changes in one domain (i.e. illness beliefs and behaviours) are reflected in changes in another (i.e. cognitive processing biases), it would support the hypothesis of a dynamic, interwoven relationship between top-down and bottom-up processing in CFS. Exploring whether more habitual or ‘bottom-up’ cognitive processes also change over treatment, may illuminate other mechanisms of treatment and provide further insight into how identified self-reported treatment mechanisms (e.g. changing fear avoidance beliefs, catastrophizing and symptom focusing) may operate.

8.2.4 Aims
This study is an extension of the follow-up study reported in Chapter 7. The previous study assessed whether pre-treatment cognitive biases and general malleability of attention, predicted how an individual would respond to treatment for CFS. In the current chapter I
investigate whether current treatments for CFS (CBT and GET) are able to change cognitive biases (attention and interpretation) or improve an individual’s attentional control capacity. These concepts were chosen for investigation as previous literature had identified that they were amenable to change (as reviewed above). I will also assess whether changes in these cognitive processes are associated with treatment outcomes of fatigue, functioning and mood as well changes in self-reported cognitive and behavioural illness responses. Changes in cognitive processing that accompany reduced symptomology would support the theory that biases in cognitive processing and deficits in general attentional control play a role in maintaining some core aspects of CFS. Changes in cognitive processing that accompany changes in self-reported cognitions and behaviours would support the interwoven relationship between explicit top-down coping responses and habitual bottom-up information processing.

8.2.5 Hypotheses

The main hypothesis are as follows:

1) Cognitive biases will be reduced and attentional control will improve pre to post treatment (CBT or GET) for CFS

2) Changes in cognitive biases will be associated with

   a. changes in fatigue, functioning, and mood, as well as

   b. changes in cognitive and behavioural responses to symptoms.
8.3 Methods

8.3.1 Participants

Participants were those that had been included in the follow-up study detailed in Chapter 7. To be included in this follow-up analysis participants were required to have completed both questionnaires and experimental measures at two time points, pre and post treatment. This resulted in the loss of six participants who had completed post-treatment questionnaires but could not attend the laboratory to complete the post-treatment cognitive tasks (Figure 4). The current study therefore includes 20 participants. All participants had a diagnosis of CFS and received at least 3 sessions of either CBT or GET within routine clinical practice. Details of the recruitment procedure and inclusion criteria are provided in Chapter 5 and a description of the CBT and GET treatments in Chapter 7.
Complete pre-treatment baseline questionnaires and experimental/cognitive tasks (n=52)

Attending treatment clinics outside of recruitment sites (n=7)
Did not receive funding for treatment (n=5)

Participants assigned treatment at the clinic (N=40)
CBT (n=27)
GET (n=13)

Received < 3 sessions (n=4)
Still on waitlist (n=3)
Lost to follow-up (n=7)
– 4 unable to contact
– 3 declined

Complete post treatment questionnaires (N=26)
CBT (n=19)
GET (n=7)

Unable to travel (n=6)

Complete post treatment experimental/cognitive tasks in the lab (N=20)
CBT (n=13)
GET (n=7)

Figure 5 Flow diagram of inclusion into study
8.3.1.1 Measures

The full list of questionnaires can be found in Appendix B. For this study change scores on self-reported measures of fatigue functioning; anxiety and depression as well as change in cognitive and behavioural responses to symptoms were analysed. Fatigue was measured with the Chalder Fatigue Questionnaire, (CFQ) (Chalder, et al., 1993). Anxiety and depression were measured with the Hospital Anxiety and Depression Scale, (HADS) (Zigmond & Snaith, 1983). Maladaptive responses to symptoms were measured with the subscales on the Cognitive Behavioural Responses to illness Questionnaire, (CBRQ) (Skerrett & Moss-Morris, 2006), subscales included; catastrophizing, damage beliefs, symptom focusing, fear avoidance and embarrassment avoidance, avoidance behaviour and all-or-nothing behaviour. These measures have been described in detail in preceding Chapter 5 and Chapter 7.

Change in physical functioning was measured by change scores on the Short-form Health Survey, SF-36 (McHorney, et al., 1994). The SF-36 was used in both follow-up analysis (the previous Chapter 7 and the current Chapter 8). It was chosen as it is a valid and reliable measure, that has been shown to be sensitive to detecting change in functioning in CFS in previous randomized control trails (Edmonds, et al., 2004; Malouff, et al., 2008; Price, et al., 2008; White, et al., 2011b). It was also the routine measure of functioning used across all the recruitment sites, and thus allowed for a direct comparison between this data and others collected at these treatment centres. The SF-36 is a self-rating questionnaire measuring functioning in everyday life. It consists of eight subscales: (1) physical functioning, (2) role limitations due to physical problems, (3) bodily pain, (4) general health perceptions, (5) vitality, (6) social functioning, (7) role limitations due to emotional problems, and (8)
emotional well-being. Subscale scores range from 0 to 100 with higher values representing better functioning.

8.3.1.1.1 Cognitive tasks

Experimental cognitive tasks, attentional bias, interpretation bias and attentional control were conducted on a laptop computer in a private testing room. A brief summary of the key methods is provided here as the tasks have been presented in detail in Chapter 5.

A Visual Probe Task (McLeod, et al., 1998) (VPT) assessed attentional biases for illness-related words, relative to neural words. An attentional bias score was calculated as the difference in reaction times in responding to probes (arrows) replacing illness-related words and probes replacing neutral words. Faster reaction times to probes replacing illness-related stimuli relative to neural stimuli, is indicative of an attentional biases towards illness-related information. Higher scores indicate an increased attentional bias.

An ambiguous recognition task (Mathews & Mackintosh, 2000) assessed positive and negative interpretation biases. Participants read 10 ambiguous scenarios, imaging themselves as the main protagonist. Later in the task participants are presented with positive and negative/illness-related resolutions of these ambiguous scenarios and asked to rate how similar they are in meaning (1= very different, 4= very similar) to the original text. Mean similarity ratings were calculated separately for positive and negative/illness-related interpretation biases. Higher scores indicate an increased endorsement of positive and negative/illness-related interpretations (respectively).
The materials for the above cognitive bias tasks were developed to tap into CFS relevant concerns. The development process is described in detail in Chapter 4. As participants in this study completed these tasks twice, different sets of materials were used in each testing session. The sets of material were randomized for each participant, as to avoid order effects, should one set of materials be superior to the other\textsuperscript{16}. The full sets of materials for both the attention and interpretation bias tasks are available in Appendix C.

The \textit{Attention Network Test} (Fan \textit{et al.}, 2002; 2005)\textsuperscript{17}(ANT) assessed general attentional control ability. Attentional control is represented by the latency between reaction times to correctly identify the direction of a central arrow, in a string of 5 congruent or incongruent arrows. Higher attentional control scores indicate greater difficulty in screening out the flanking arrows, and thus poorer attentional control.

\textbf{8.3.2 Procedure}

Participants completed questionnaires at home and subsequently (within 5 days) attended the laboratory to complete the cognitive tasks. All participants completed the questionnaires and cognitive tasks at two time points; up to 3 weeks before starting treatment (pre) and up to 2 weeks after finishing treatment (post). Participants received either CBT or GET for CFS as part of routine clinical practice. The CFS treatments were described in Chapter 5.

\textsuperscript{16} Controlling for stimuli sets had no effect on the attention or interpretation bias analyses.
\textsuperscript{17} The \textit{Attention Network Test} (Fan \textit{et al.} 2002; 2005) measures three facets of attention: altering, orientating and attentional control. For the purposes of this study only the attentional control scores were analysed.
8.3.3 Data preparation and analytical procedure

On the VPT and ANT reaction time data were excluded from trials with errors and outliers (<200 ms, and >2000 ms). One CFS participant and two healthy controls were excluded from the VPT analysis due to excessive missing data (>3SD above the group mean) consistent with our previous studies (Chapter 5 and Chapter 6) and in-line with others (Brown, et al., 2014; Hou, et al., 2014). Analysis was performed using the Statistical Package for Social Sciences (SPSS) version 21 (USA).

To investigate change in cognitive processes over the course of treatment, paired t-tests within the CFS groups were conducted with pre and post treatment scores on the attentional bias, interpretative bias and attentional control tasks (hypotheses 1). To investigate whether changes in treatment outcomes were related to changes in cognitive processing, bivariate Pearsons’ correlations were conducted with change scores from pre to post treatment on self-report measures (hypotheses 2). Effect sizes are interpreted following Cohen (1988); an \( r \) of .1 represents a 'small' effect size, .3 represents a 'medium' effect size and .5 represents a 'large' effect size. Due to the small and unequal sample sizes of those receiving CBT and GET, comparisons between treatment groups would not have been meaningful. Thus, for hypothesis testing participants receiving either CBT or GET were analysed as one group.

8.4 Results

Participants (\( n = 20 \)) had a mean age of 38 (SD=10). Seventeen (85%) were female. The mean illness duration was 6 years (SD=7.8). Participants received an average of 10 treatment sessions (SD= 4.03).
8.4.1 Does attentional bias, interpretation biases and attentional control change following CFS treatment?

Paired t-tests (Table 3) found attentional control scores significantly reduced pre to post treatment \((p=.003)\), indicating an improvement in general attentional control over the course of treatment, consistent with our hypothesis (hypothesis 1). However, contrary to our hypothesis none of the illness-specific processing biases significantly changed over the course of treatment (all \(p>.05\)). There was a slight decrease in attentional biases pre to post treatment \((M=-.09, \ SD=.87)\) as hypothesised, though this was not significant \((p=.68)\). Positive interpretations remained relatively stable \((M=-.01, \ SD=46)\) showing no significant change pre to post treatment \((p=.91)\). Whereas, there was a slight increase in illness-related interpretations \((M=.08, \ SD=.64)\), indicating a non-significant change \((p=.60)\) in illness-related interpretations in the opposite direction than expected. However, there were large standard deviations in the degree to which these processes changed over the course of treatment, indicating heterogeneity in the malleability of these processes in this sample of CFS participants.
Table 3: Means and standard deviations on the cognitive tasks at baseline and follow up (n=20).

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>Average change</th>
<th>Lower 95%CI</th>
<th>Upper 95%CI</th>
<th>t-score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attentional Bias score</strong></td>
<td>.29 (.84)</td>
<td>.21 (.93)</td>
<td>-.09 (.87)</td>
<td>-.50</td>
<td>.33</td>
<td>-.42</td>
</tr>
<tr>
<td><strong>Illness-related interpretation</strong></td>
<td>2.27 (.57)</td>
<td>2.35 (.52)</td>
<td>.08 (.64)</td>
<td>-.22</td>
<td>.38</td>
<td>.53</td>
</tr>
<tr>
<td><strong>Positive interpretation</strong></td>
<td>2.73 (.45)</td>
<td>2.72 (.41)</td>
<td>-.01 (.46)</td>
<td>-.23</td>
<td>.21</td>
<td>-.11</td>
</tr>
<tr>
<td><strong>Attentional control score</strong></td>
<td>138.85 (54.23)</td>
<td>101.50</td>
<td>-37.35 (49.65)</td>
<td>-60.59</td>
<td>-14.12</td>
<td>-3.36**</td>
</tr>
</tbody>
</table>

Standard deviation given in parentheses; **p<.01
8.4.2 Are changes in cognitive processing related to primary outcomes and mood?

Before assessing whether the degree of change in cognitive processing are associated with changes in fatigue, functioning and mood (hypothesis 2a), it first needs to be established whether treatments were effective at improving these primary treatment outcomes. Paired t-tests showed significant improvements in fatigue, functioning, anxiety and depression pre to post treatment (all \( p<.05 \)), indicating treatments were effective for this sample of patients Table 4.
Table 4 Change in CFS patients (n= 20) self-report measures pre to post treatment

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment M (SD)</th>
<th>Post-treatment M (SD)</th>
<th>Average change M (SD)</th>
<th>95% CI Lower</th>
<th>Upper</th>
<th>t-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFQ</td>
<td>26.69 (4.98)</td>
<td>18.50 (6.82)</td>
<td>-8.19 (7.44)</td>
<td>5.18</td>
<td>18.89</td>
<td>-5.62**</td>
</tr>
<tr>
<td>SF-36</td>
<td>45.77 (21.85)</td>
<td>57.80 (24.13)</td>
<td>12.03 (16.97)</td>
<td>-11.19</td>
<td>-5.19</td>
<td>3.62**</td>
</tr>
<tr>
<td>HADS depression</td>
<td>9.00 (4.53)</td>
<td>6.43 (4.81)</td>
<td>2.57 (4.50)</td>
<td>.52</td>
<td>4.62</td>
<td>2.62*</td>
</tr>
<tr>
<td>HADS anxiety</td>
<td>11.25 (5.26)</td>
<td>940 (4.83)</td>
<td>1.85 (3.80)</td>
<td>.07</td>
<td>3.63</td>
<td>2.17*</td>
</tr>
</tbody>
</table>

**CBRQ cognitive responses**

| Fear avoidance beliefs  | 20.68 (5.50)         | 17.60 (4.32)         | -3.08 (4.27)          | -4.84        | -1.32  | -3.61** |
| Catastrophizing         | 20.08 (5.20)         | 16.68 (5.15)         | -3.40 (4.61)          | -5.30        | -1.50  | -2.87** |
| Damage beliefs          | 15.76 (2.83)         | 13.64 (4.25)         | -2.12 (3.69)          | -3.64        | -.60   | -2.87*  |
| Symptom focusing        | 20.48 (6.51)         | 17.40 (5.56)         | -3.08 (5.53)          | -5.36        | -.80   | -2.79*  |
| Embarrassment avoidance | 18.52 (5.13)         | 17.32 (5.51)         | -1.20 (5.03)          | -3.28        | .88    | -1.19   |

**CBRQ behavioural responses**

| All-or-nothing behaviour| 13.60 (4.93)         | 12.08 (5.51)         | -1.52 (4.77)          | -3.49        | .45    | -1.59   |
| Avoidance and rest     | 20.44 (5.13)         | 17.20 (4.73)         | -3.24 (4.76)          | -5.20        | -1.28  | -3.41*  |

CFQ, Chalder Fatigue Questionnaire; SF-36, Short-form Health Survey; HADS, Hospital Anxiety and Depression Scale; CBRQ, Cognitive Behavioural Responses to Symptoms Questionnaire; *p<.05; **p<.01
To assess whether these changes in self-reported outcomes related to changes in cognitive processing (hypotheses 2) bivariate Pearson’s correlations between change scores were conducted (Table 5).

There were no significant correlations between improved fatigue (CFQ) and functioning (SF-36) and the degree of change on any of the cognitive processing measures; attentional bias, interpretation biases (positive or illness-related) or attentional control (all \( p > .05 \)). However, there were small to medium non-significant correlations between fatigue (CFQ) and changes in positive interpretations (\( r = .29, p = .27 \)) and attentional control (\( r = .20, p = .43 \)), suggesting that the degree to which participants’ positive interpretations increased and attentional control improved was associated with reductions in fatigue. There were also small to medium sized non-significant correlations between functioning (SF-36) and changes in interpretations; with reduced illness-related interpretations (\( r = -.36, p = .29 \)) and increased positive interpretations (\( r = .27, p = .27 \)) associated with larger improvements in functioning.

In terms of mood, reductions in anxiety and depression, as measured by the HADS, were associated with some cognitive processing changes (Table 5). Though all correlations were in the expected directions, the only significant finding was between changes in anxiety and attentional control, \( r = -.47, p = .04 \); indicating that as attentional control improved, anxiety decreased. There were also non-significant, small to medium sized correlations between increased positive interpretations and reduced anxiety (\( r = -.31, p = .24 \)) and depression (\( r = -.39, p = .11 \)). There was also a small non-significant relationship between reduced attentional biases and reduced anxiety (\( r = .25, p = .29 \)).
8.4.3 Are changes in cognitive processing related to self-reported cognitive and behavioural changes?

Before assessing whether the degree of change in cognitive processing was associated with changes in cognitive and behavioural responses to symptoms (CBRQ), (hypothesis 2b) it first needs to be established that treatments do indeed modify these cognitions and behaviours. Paired t-tests found significant reductions in fear avoidance beliefs (\(p=.001\)), catastrophizing (\(p=.001\)), damage beliefs (\(p=.008\)), symptom focusing (\(p=.01\)) and avoidance/rest behaviours (\(p=.002\)) pre to post treatment. There were no significant changes in embarrassment avoidance beliefs or all-or-nothing behaviours (both \(p<.05\)), though both reduced pre to post treatment (Table 4). To assess whether changes in these secondary outcomes are related to changes in cognitive processing, Pearson’s correlations between change scores were conducted.

8.4.3.1 Changes in attentional bias and self-reported cognitions and behaviours

There were significant medium sized, positive correlations between changes in attentional biases, all-or-nothing behaviours, \(r=.44, p=.03\) and embarrassment avoidance, \(r=.43, p=.03\) (respectively). There was also a moderate non-significant correlation between attentional bias and catastrophizing, \(r=.32, p=.12\); indicating that, the degree to which attentional biases decreased, correlated with a reduction in these unhelpful cognitive and behavioural responses.

8.4.3.2 Changes in interpretation biases and self-reported cognitions and behaviours

There were significant, medium to large, negative correlations between changes in positive interpretations, catastrophizing (\(r=-.49, p=.03\)) and symptom focusing (\(r=-.49, p=.03\))
(respectively); indicating that as positive interpretations increased these negative cognitive responses to symptoms decreased. There were no other significant relationships between positive interpretations and changes on the CBRQ, though trends were in the expected direction; with medium correlations between increased positive interpretations and reduced fear-avoidance ($r = -0.40, p = 0.09$) and damage beliefs ($r = -0.38, p = 0.11$).

In terms of negative, illness-related interpretations, there were no significant correlations between changes in illness-related interpretations and the CBRQ. However, there was a small, non-significant negative relationship between changes in illness-related interpretations and changes in symptom focusing, $r = -0.29, p = 0.24$; suggesting that as illness-related interpretations decrease, symptom focusing increases. This is an unexpected finding in the opposite direction than anticipated. However, the relationship was non-significant and whilst some people showed reduced illness-interpretations others showed an increase (range=min change -1.08, max change 1.17). Furthermore, symptom focusing had the largest standard deviation in change across all of the CBRQ sub-scales (mean change=3.08; SD=5.53), and whilst some participants showed a reduction in symptom focusing, others increased (range= min change -20.00, max change 7.0).

### 8.4.3.3 Changes in attentional control and self-reported cognitions and behaviours

There was a significant positive correlation between changes in attentional control and symptom focusing ($p = 0.04$); indicating that as attentional control improved, symptom focusing reduced. There was also a small, non-significant correlation between increased attentional control and reduced catastrophizing ($p = 0.19$). There were no other correlations between changes in attentional control and the CBRQ.
Table 5 Correlations in CFS group (n=20) between change in self-reported outcomes and changes in cognitive processing

<table>
<thead>
<tr>
<th></th>
<th>Attentional bias</th>
<th>Illness-related interpretation</th>
<th>Positive interpretation</th>
<th>Attentional control</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFQ</td>
<td>-.07</td>
<td>-.11</td>
<td>-.29</td>
<td>.23</td>
</tr>
<tr>
<td>SF-36</td>
<td>.11</td>
<td>-.36</td>
<td>.27</td>
<td>-.01</td>
</tr>
<tr>
<td>HADS depression</td>
<td>.23</td>
<td>.02</td>
<td>-.39</td>
<td>.20</td>
</tr>
<tr>
<td>HADS anxiety</td>
<td>.25</td>
<td>.004</td>
<td>-.31</td>
<td>.47*</td>
</tr>
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</table>

**CBRQ cognitive responses**

<p>| | | | | |</p>
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<tr>
<th></th>
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<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Fear avoidance</td>
<td>.03</td>
<td>.15</td>
<td>-.40</td>
<td>.08</td>
</tr>
<tr>
<td>Catastrophizing</td>
<td>.32</td>
<td>.23</td>
<td>-.49*</td>
<td>.29</td>
</tr>
<tr>
<td>Damage beliefs</td>
<td>.21</td>
<td>-.10</td>
<td>-.38</td>
<td>.25</td>
</tr>
<tr>
<td>Symptom focusing</td>
<td>-.13</td>
<td>-.29</td>
<td>-.49*</td>
<td>.47*</td>
</tr>
<tr>
<td>Embarrassment avoidance</td>
<td>.43*</td>
<td>.07</td>
<td>-.23</td>
<td>.06</td>
</tr>
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</table>

**CBRQ behavioural responses**

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<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All-or-nothing</td>
<td>.44*</td>
<td>.19</td>
<td>.10</td>
<td>.03</td>
</tr>
<tr>
<td>Avoidance and rest</td>
<td>.01</td>
<td>.18</td>
<td>-.26</td>
<td>.17</td>
</tr>
</tbody>
</table>

CFQ, Chalder Fatigue Questionnaire; SF-36, Short-form Health Survey; HADS, Hospital Anxiety and Depression Scale; CBRQ, Cognitive Behavioural Responses to Symptoms Questionnaire; *p<.05
8.5 Discussion

This study hypothesized that current treatment treatments for CFS (CBT and GET) would shift people’s illness-specific attention and interpretation biases and improve general attentional control capacity. We also anticipated that changes in these measures of cognitive processing would be related to positive changes in self-reported outcomes. The findings only partially support our hypotheses. In terms of change in the three experimental cognitive tasks, only general attentional control capacity significantly improved over the course of treatment. Neither illness-specific attention nor interpretation biases changed significantly in this sample. However, there were large variations in the degree and direction in which cognitive processing biases changed, which may have obscured effects at the group level.

As expected, treatments significantly improved self-reported fatigue, functioning and mood (depression and anxiety). Contrary to hypothesis 2a, improvements in fatigue, functioning and depression seemed unrelated to experimentally measured attentional bias, interpretation biases (both positive and negative), or general attentional control; though there were some non-significant correlations in the expected direction. In particular, there were moderate, non-significant relationships between improved outcomes and increased positive interpretations. Interestingly, improved anxiety was significantly associated with an increased attentional control capacity.

Treatments also significantly reduced patients’ unhelpful cognitive and behavioural responses to symptoms, as measured by self-report. Consistent with hypothesis 2b, this change in symptom responding, was associated with changes in experimentally measured cognitive biases and attentional control capacity. Specifically, the degree to
which participant’s attentional biases reduced (i.e. attention is less readily grabbed by illness-related information) and positive interpretation biases increased (i.e. more positive interpretations of ambiguity are inferred), was related to fewer unhelpful cognitive and behavioural responses to symptoms. Interestingly improved attentional control was most closely related to a reduction in symptom focusing.

8.5.1 Can cognitive and behavioural treatments for CFS modify cognitive processing?

It seems CBT and GET for CFS can improve people’s general attentional control capacity. This mirrors findings in fibromyalgia, which found, using this same objective measure, attentional control improved over the course of CBT (Miró, et al., 2011). These findings correspond with neurological changes observed following CBT for CFS (De Lange, et al., 2008) and chronic pain (Seminowicz, et al., 2013), indicating increases in grey matter volume in brain regions associated with attentional control functions.

Illness-specific attention and interpretation biases did not change across the treated sample. This null finding may indicate that current treatments for CFS fail to tap into these more ingrained cognitive processing habits. If, for some people with CFS, these cognitive habits or biases contribute to the maintenance of unhelpful cognitions and behaviours, as indicated by our cross-sectional study in CFS (Chapter 5) and similar studies in pain (Crombez, et al., 1998; Heathcote & Jacobs, 2015; Van Damme, Crombez, & Eccleston, 2004a; Vancleef & Peters, 2006), the lack of change or ‘shift’ in these biases may result in less therapeutic benefit for these individuals (De Raedt & Koster, 2010; Schäfer, et al., 2015).

The current treatment size is too small to draw conclusions about the effects of treatment on these processes. However, if it is the case that current treatment protocols for CFS do
not modify these illness-specific biases as a mechanism of treatment; yet for some people these biases are maintaining some core aspect of the condition; then the lack of change on attention and interpretation biases may explain some of the variance of treatment effects for CFS. Around 40% of people with CFS do not show a clinically significant improvement following CBT or GET (Knoop, et al., 2007; White, et al., 2013). Heterogeneity within CFS has been identified as a moderator of treatment outcomes. Cognitive biases may represent another heterogeneous aspects of CFS, with potential implications for treatment response (Cella, et al., 2011a). Indeed, Chapter 7 identified that attentional biases pre-treatment predicted a better response to treatment in terms of improved functioning. Perhaps for some people in the sample there was a meaningful change on attentional biases but this was obscured by the null group effect. Some people may be more likely to shift their attentional biases than others. This was demonstrated in Chapter 7, which found that people with CFS had varying degrees of attentional malleability (i.e. an ability to adopt an attentional bias); and those with higher attentional malleability responded better to treatment. Thus, whilst there was no change in attentional biases across this small treated sample, there may have been individual differences, not just in the existence of the bias, but also how malleable the bias is.

Even for those that do improve or recover following treatment, a lack of change in these more habitual attention and interpretation processes could be a possible risk factor for later symptom deterioration and relapse. For example, converging retrospective and prospective evidence suggests that residual attentional biases in people recovered from depression, significantly increases the risk of recurrence (Woody, Owens, Burkhouse, & Gibb, 2015). This may be particularly pertinent when mental load is high and an individual’s ability to regulate their thought processes are reduced (Bowler, et al., 2012). In CFS, for instance, when under increased stress a person may not be able to employ
effortful control in order to regulate their cognitive and behavioural responses to symptoms, thus they may rely instead on their more habitual or ‘implicit’ cognitive processing tendencies. If residual cognitive biases are reactivated they may precede or precipitate former negative and unhelpful illness-schemas, thus contributing to worse outcomes. Thus, for some people with pervasive cognitive biases, additionally targeting these processes directly, could enhance the resilience of treatment effects (Schäfer, et al., 2015; Troy & Mauss, 2011).

8.5.2 Are changes in cognitive processing related to changes in primary symptoms in CFS?

The only significant relationship between measures of cognitive processing and primary self-reported outcomes was between changes in general attentional control and anxiety; with increased attentional control capacity, relating to reduced symptom focusing. The relationship between anxiety and attentional control is well documented in the anxiety literature (Berggren & Derakshan, 2013; Derakshan & Eysenck, 2009; Eysenck & Derakshan, 2011; Eysenck, et al., 2007), however, like these authors we cannot determine the direction of this relationship. It is unclear whether treatments directly target and strengthen attentional control or whether improved attentional control is a bi-product of changes in other domains. For example, this study found improved attentional control was associated with reduced anxiety and self-reported symptom focusing. Evidence suggests worry and rumination takes up working memory capacity and thus reduces attentional control ability (Hayes, Hirsch, & Mathews, 2008; Liston, McEwen, & Casey, 2009; Owens & Derakshan, 2013). It may be that treatments reduce illness-related worry and the ruminative processes of symptom focusing, which in turn frees-up working-memory capacity and improves general attentional control. Alternatively, it may be that when attentional control is restored participants are better able to deploy their attention
to non-illness related information; thus reducing symptom focusing. To further explore these relationships mediation and moderation analysis are required with larger sample sizes and additional time-points of assessment.

Though there were no other significant relationships between changes in primary symptoms and experimental variables, there were some non-significant trends in hypothesised directions. Most notably, increased positive interpretation biases were consistently associated with improved outcomes; in particular reduced anxiety and depression. This corresponds with findings in the anxiety and depression literature which indicate that making positive interpretations of ambiguity is a driver of emotional well-being (Fredrickson & Joiner, 2002; Gander, Proyer, Ruch, & Wyss, 2013); and people with mood disorders lack this beneficial positive interpretation bias (Hirsch & Mathews, 2000) Some authors have suggested that boosting positive interpretations, rather than attempting to reduce negative ones, can be therapeutically beneficial (Menne-Lothmann, et al., 2014). Indeed, boosting positive interpretations has been described as a ‘cognitive vaccine’ against low mood (Holmes, et al., 2009).

It is interesting that in this study increased positive interpretations were associated with more self-reported change than illness-related interpretations. Perhaps this is reflective of treatments enhancing a range of alternative resolutions of ambiguity, including the potential for positive resolutions. For example the use of thought diaries in CBT encourages the person to generate a range of alternative thoughts to counter an unhelpful one, and to then weigh up these thoughts in terms of how realistic and balanced they are. This process may lead to less fixed habitual interpretation biases, and increase the likelihood that positive interpretations may be generated; which in turn is associated with more therapeutic change. Thus, for some people with CFS boosting positive
interpretations of ambiguity may be therapeutically beneficial, and potentially important for addressing associated mood disorders.

However, this hypothesis is hampered by the fact that, across this treated sample, there was no significant change in positive biases; in fact they remained relatively stable. It could be speculated that this indicates treatments for CFS do not change habitual interpretations. However, from a clinical perspective this seems unlikely. One of the core aims of treatments for CFS is to reduce misinterpretation of information and catastrophic thinking styles (White, et al., 2007); factors which must be closely related to how an individual interprets ambiguity. Perhaps the ambiguous scenarios task used in the current study was not sensitive enough to detect change in these processes. Indeed, this is the first study to my knowledge that has used the ambiguous scenarios task to assess interpretation biases in a pre-post design. It may be that simple change scores on a 0-4 Likert scale cannot adequately assess change in these processes.

Much larger sample sizes are needed to get a clearer picture of the relationship between cognitive processing and response to treatments in CFS. The lack of significant change at group level, small sample size and inherently heterogeneous sample is likely to have reduced the power of this study to detect significant change. It may be that, where treatments to significantly change cognitive biases, associated changes in fatigue and functioning would be observed.

8.5.3 Are changes in cognitive processing related to changes in self-reported cognitions and behaviours?

It seems illness-specific attention and interpretation biases are not related to primary treatment outcomes of fatigue and functioning. This is consistent with our previous
cross-sectional findings (Chapter 5). It seems that attention and interpretation biases are more closely related to how an individual responds to their symptoms; for example whether they are fearful and avoidant of activity or jump to catastrophic conclusions when a symptom is observed. It may be that these experimental measures are tapping into the more habitual component of these explicit cognitions and behaviours. Of particular note is that, increased positive interpretations were consistently associated with a reduction in unhelpful/ negative responses to symptoms; i.e. catastrophizing, symptom focusing and some non-significant associations with reduced fear avoidance and damage beliefs. These relationships suggest increasing positive interpretations may be an important therapeutic target.

Reduced attentional bias to illness-related stimuli was associated with reduced embarrassment avoidance and all-or-nothing behaviours. Interestingly, these were the only two cognitive and behavioural responses that did not significantly change within this treated sample. It may be that for some people in this sample, these responses to illness were more resistant to change as they are underpinned or associated with more implicit attentional processes, which current treatments do not modify. It may be that attentional biases are associated with different processes for different people, depending on idiosyncratic illness beliefs and concerns. For example, someone who has high levels of embarrassment about their symptoms may have an increased sensitivity to the detection of illness-related, potentially embarrassing, information (attentional bias), which in turn may reinforce or maintain embarrassment avoidance. Specifically targeting illness-related attentional biases in CFS may be an additional way to tap into and target these cognitive and behavioural responses to symptoms.
These findings are in-line with studies in chronic pain which have identified that, for some individuals, cognitive biases of attention and interpretation play a role in maintaining some core aspects of the condition; namely catastrophizing and fear avoidance (Crombez, et al., 1998; Crombez, et al., 2012; Keogh, et al., 2001; Van Damme, Crombez & Eccleston, 2004a; Vancleef & Peters, 2006). However, the exact nature and direction of these relationships are unclear. It may be a reciprocal process of change, or one change may precede the other. For example, in CFS an increased positive interpretation of ambiguous information may in turn reduce catastrophic thinking styles and symptom focusing; or, reducing these explicit, self-reported beliefs and behaviours, may in turn influence more positive interpretations of ambiguity. In order to explore these directional hypothesis, studies are needed which can isolate these components (i.e. attentional biases/ interpretation biases/ explicit cognitions and behaviours) and assess whether modifying one component has an impact upon the other. One method in which this has been achieved in psychopathology is via CBM. The potential use of CBM to explore these hypotheses in CFS is discussed in the subsequent section in this chapter ‘future avenues’ (8.5.5).

8.5.4 Limitations

This study is limited by a small and heterogeneous sample. Therefore, we should not place too much emphasis on the specific factors which were identified as statistically significant. Furthermore, the lack of significant change in cognitive biases at group level could reflect other limitations. The null finding may indicate that these measures are not adequate to assess change in cognitive processing over time. Indeed the visual-probe task, in particular, has been described as unreliable (Schmukle, 2005) and exhibiting only modest reliability even under the best circumstances (Britton, et al., 2013). Future studies
should include a wait list control group to further explore the comparable fluctuations and rigidity of cognitive biases in clinical and healthy populations.

Other methodological limitations should also be considered. For example, because of participant burden the timing of post treatment assessments varied; occurring anywhere from 0 to 2 weeks after the last treatment session. This variability could further reduce the sensitivity of the visual probe and recognition tasks. Additionally, the current study assessed only two time points; pre and post treatment. It may be that cognitive processing biases are more related to longer term outcomes and relapse. Larger, longitudinal studies are needed to explore these possibilities.

Given that this is a non-randomized study, there were a number of inherent confounding variables; including the combined CBT and GET treatments, as well as multiple treatment centers and therapists. Importantly, previous studies have found that whilst both CBT and GET are effective at reducing fatigue and improve functioning, they may operate via different mechanisms of change (Chalder, et al., 2015). Cognitive processes of attention and interpretation may be an important mechanism of change for one treatment but not the other (Niles, et al., 2013). The small sample size in the current study, particularly of the participants receiving GET, prevented us from investigating differences between treatments. Future studies should explore whether different treatments for CFS are related to different cognitive processing changes. Identifying specific, efficacious ingredients of therapy can help assign patients to treatments which are most appropriate for their needs.

Though the current study did not find CFS treatments change these attention and interpretation biases, there were large individual differences in pre-existing biases as well as the magnitude and direction of change in biases over the course of treatment. It may
be that, given the large heterogeneity in CFS (Williams, et al., 2017), some individuals
did have a clinically significant change in cognitive biases; however, these changes were
obscured by the null group effect. Future research should explore these individual
differences in cognitive processing, with the potential to utilize this information for
tailoring and customizing treatments to greater efficacy. If it is the case that current
treatments already go some way in modifying biases for some individuals, as has been
shown with other studies (Bowler, et al., 2012; Reinholdt-Dunne, et al., 2015; Tobon, et
al., 2011), research needs to identify the mechanism through which this change occurs
and secondly whether it can be enhanced.

8.5.5 Future avenues
An alternative, potentially less confounded way to assess the relationship between
cognitive processing and CFS, is to utilize CBM techniques. CBM research can establish
if cognitive processing biases play a causal role in CFS and furthermore whether changing
cognitive biases has a therapeutic benefit. If so, there may be benefit in tailoring CBM
techniques to target illness-specific cognitive biases in CFS. Though CBM techniques are
in their relative infancy, they have shown some promise as a clinical tool (Hakamata, et
al., 2010) and as an adjunct to conventional forms of psychological interventions
(Williams, et al., 2013). Future CBM techniques, designed to tap into CFS relevant
content, may provide a useful ‘add-on’ to current CFS treatments for some people with
CFS. For example, for patients who have unhelpful biases in attention and/or
interpretation, adjunct CBM may be able to target these attention and interpretation biases
and thus facilitate the adoption of more adaptive responses to symptoms (such as reducing
symptom focusing).
Further avenues of research should also consider individual differences in cognitive processing. Whilst our previous studies have shown that illness-specific attention and interpretation biases are a consistent finding in CFS populations (Chapter 5 and Chapter 6), the degree to which these cognitive biases are a problem may vary at an individual level. There may also be heterogeneity in the degree to which cognitive processes are amenable to change. For some, cognitive and behavioural treatments may be sufficient to access and change these processes. For others, these biases may be more ingrained and hard to shift. Large, longitudinal randomized control trials, employing experimental methods are needed to fully explore the causal role of cognitive biases in CFS and the effects of changing cognitive biases on longer-term outcomes.

8.5.6 Conclusions

In sum, in this sample, treatments did not significantly shift habitual, illness-related attention and interpretation biases. Despite the lack of change on these experimental measures patients showed significant improvements in fatigue, functioning and mood pre to post treatment. Furthermore, these improvements seemed unrelated to any change in attention or interpretation (positive or negative) biases. This could lead to the conclusion that changing cognitive biases are not important for effective treatment of CFS. However, this may be premature. Lack of cognitive processing change across this treated sample may have been due to the small and heterogeneous sample. If significant changes in cognitive biases had occurred, associated changes in treatment response may have been revealed. Alternatively, these findings may suggest that cognitive and behavioural treatments for CFS cannot modify these biases. Using CBM techniques to experimentally manipulate cognitive biases would allow a cleaner assessment of the causal role of cognitive biases in CFS.
Importantly, though changes in cognitive biases were not observed across this treated sample, the degree to which individuals did shift their cognitive biases was associated with positive changes in cognitions and behaviours. Consistent with our previous research (Chapter 5), these relationships suggest that illness-specific cognitive processing biases may precede, precipitate or perpetuate unhelpful responses to symptoms. Prospective and mediation studies are needed to explore the specific nature and timing of these relationships.
Chapter 9 Discussion

9.1 Chapter overview

This final chapter concludes the thesis by considering the contributions of the research programme as a whole. The first section summarises the work conducted in this thesis, pulling out key findings and new contributions. The following section reflects upon the strengths and limitations of this work, and the final section highlights avenues for future research and potential clinical implications.

9.2 Major findings and conclusions from the thesis

Chapters 3, 4 and 5 sought to empirically establish whether people with CFS have illness specific cognitive biases in attention and interpretation and to determine the nature of such biases. The systematic review in Chapter 3 (Hughes, et al., 2016a) summarised the experimental work conducted in CFS to date, describing the methodologies commonly used. The review found tentative evidence of attention and interpretation biases for health threatening and illness-specific information in CFS, occurring at later stages of ‘elaborative’ processing. However, studies were limited in number and rigor, and varied markedly in their methodological approach. Studies of interpretation biases in particular were lacking and employed diverse paradigms, tapping into different stages of information processing. Of particular concern was the fact that studies used a variety of ‘threatening’ materials, assumed to tap into illness-related concerns, but largely developed ad-hoc and poorly validated, if at all. This lack of stimuli specificity, not only limited the conclusions drawn from the data, but also may have explained some of the mixed findings. The review concluded that, to assess whether cognitive biases occur in CFS work was needed to establish reliable and empirically valid, illness-specific materials to assess cognitive biases in CFS.
Chapter 4 provided an exemplar systematic approach to material development, undertaken to address this issue. The published article briefly summarized the most recent, up-to-date experimental paradigms used to assess attention and interpretation biases and outlined steps for comprehensive/robust stimuli development for such paradigms. The article provided illustrative examples for material developing for attention and interpretation bias paradigms for two conditions; CFS (used in the current research) and breast cancer. The latter group was chosen to illustrate the methods can be generalised to other illness groups. Three core steps to stimuli development were described; (i) pooling materials (ii) focus groups and interviews (iii) piloting the face validity of the materials. Tools were provided to assist researchers in this process. This work was important for the development of valid, illness-specific materials for the subsequent studies.

Having conducted this developmental work, I sought to assess whether cognitive biases in CFS transpired when using these validated, illness-specific materials. The cross-sectional study in Chapter 5 identified that, consistent with our hypothesis, people with CFS showed an attentional bias towards illness-related information and an interpretation bias favouring negative/illness-related resolutions of ambiguity, compared to healthy controls. The use of CFS specific materials within a large and well-defined population of CFS participants, allowed this study to clarify cognitive biases that had eluded other previous research.

I hypothesised that, similar to findings in chronic pain, illness-specific biases would be associated with unhelpful cognitive and behavioural responses to symptoms (Asmundson, et al., 1997; Roelofs, Peters, Fassaert, & Vlaeyen, 2005; Yang, Jackson, & Chen, 2013). Consistent with our hypothesis there were some significant relationships
In Chapter 2, I highlighted attentional control as a potential moderator of cognitive biases. The systematic review (Chapter 3) found some support for this hypothesis; one CFS study found an attentional biases in CFS were more pronounced for those with poor attentional control (Hou, et al., 2014). The study in Chapter 5 sought to replicate this finding and employed the same attentional control and attentional bias paradigms as Hou, et al. (2014). In line with Hou et al. (2014) the study confirmed that people with CFS have poor attentional compared to healthy populations. However, the study did not replicate poor attentional control as a moderator of either attention or interpretation biases. Several explanations for these contradictory results were proposed. It may simply be that this larger more robust study revealed a spurious finding in a smaller data set. Alternatively, attentional control, a ‘top-down’ process, may not be able to modify cognitive biases that are occurring at more ‘bottom-up’ stages of processing. It is not entirely certain as to whether this attentional bias task tapped into more ‘bottom-up’ or ‘top-down’ stages of attentional biases, as stimuli were presented for 500ms (considered a ‘mid-range’ in information processing). Certainly, however, the interpretation bias task allowed time for ‘top-down’ processing to have an effect. Thus, while methodological differences may explain the null effect between attentional bias and attentional control, it is unlikely to be the reason for the lack of relationship between interpretation bias and attentional control. Another explanation may be that cognitive biases form part of a strategic coping response between increased cognitive biases and unhelpful responses to symptoms. Interestingly, cognitive biases were most strongly associated with fear avoidance beliefs, catastrophizing about symptoms and all-or-nothing behavioural responses to symptoms; factors identified in previous research as perpetuating CFS and mediating treatment outcomes (e.g. Chalder, et al., 2015; Stahl, et al., 2014; Wearden & Emsley, 2013; Wiborg, et al., 2011; discussed in Chapter 1, section 1.5.8).
in CFS, with associated meta-cognitive beliefs about the helpfulness of behaviours such as symptom monitoring and activity avoidance in response to symptoms. This is consistent with the relationship between self-reported unhelpful cognitive and behavioural responses to symptoms and these cognitive biases. Whilst we can only speculate as to the reasons why this may be the case, the findings from this study suggest that cognitive biases in CFS are not moderated by attentional control.

In order to verify these findings, I conducted a replication study with a Dutch CFS population (Chapter 6). The findings were consistent with those reported from the UK data; indicating that cognitive biases were evident across different cohorts and cultures when using illness-specific materials. In line with the previous study, attentional control did not moderate attentional bias or interpretation bias, indicating that in CFS attentional control is not likely to be the mechanism through which these processes occur. However, a major limitation of this study was that no Dutch healthy control group were recruited; the implications of this will be discussed further in the ‘limitations’ section (9.4).

Chapters 3-6 established that people with CFS have CFS-specific cognitive biases and deficits in attentional control when compared to healthy people. The next chapters sought to build a more nuanced picture of cognitive processing in CFS and explore whether facets of cognitive processing predicted how an individual responded to treatments for CFS (Chapter 7), and whether current treatment protocols for CFS modified these cognitive processes (Chapter 8).

Chapter 7 assessed whether attention and interpretation biases, identified in Chapter 5, predicted how people responded to treatments for CFS. Findings indicated that interpretation biases pre-treatment did not significantly predict treatment response.
However, an increased attentional bias pre-treatment significantly predicted larger improvements in daily functioning post-treatment. Chapter 7 also measured the additional concept of ‘attentional malleability’ (introduced in Chapter 2). Previous research had indicated that attentional malleability predicted how people with social anxiety disorder responded to group CBT (Clarke, et al., 2012). Therefore, I hypothesized that people with CFS who had higher attentional malleability would respond better to treatments for CFS; this hypothesis was supported. Increased attentional malleability predicted larger improvements in functioning post-treatment for CFS. However, it did not predict changes in fatigue.

There were several hypothesised mechanisms for these findings. Firstly, it may be that these cognitive characteristics (i.e., attentional bias and a high attentional malleability) facilitated engagement with certain aspects of treatment, such as, extinction type learning, which require an attentional focus on the threatening information in order to challenge and re-evaluate it (Waters & Kershaw, 2015). Thus, people with increased attentional bias and a more malleable attention gained more from these aspects of treatment, than those without attentional biases. Secondly, it may be that, for some people, attentional biases helped to maintain disability in CFS, thus engaging in treatment that modified the bias to some degree, had a therapeutic effect. Secondly, having higher attention malleability allowed more change in the biases when engaging in these treatments, thus boosting treatment efficacy. This fits with the ‘plasticity account’ of cognitive biases, discussed in Chapter 2; and adds to the small but promising literature on attentional malleability (Clarke, et al., 2008; Clarke, et al., 2012; Fox, et al., 2011). The fact that change in fatigue was not predicted by any of the cognitive variables indicates that fatigue may be underpinned by other mechanisms. These hypotheses assume that, to some extent, current treatment protocols for CFS were able to tap into and modify attentional biases.
Chapter 8 explored this hypothesis with a small, longitudinal study with people who have completed a course of treatment for CFS (either CBT or GET).

Contrary to the hypothesis, Chapter 8 found treatments for CFS (CBT and GET) did not shift illness-specific attention or interpretation biases. This may indicate that current treatment protocols for CFS do not modify these habitual cognitive processes. Alternately, it may be that the small sample size (n=20) and heterogeneity in the magnitude and direction of change in this variables, obscured any significant effects. General attentional control capacity, however, significantly improved over the course of treatment. Interestingly the degree of change on attentional control was associated with a reduction in anxiety and symptom monitoring.

Whilst illness-specific attention and interpretation biases did not change across the treated sample, the degree of change in these processes at an individual level was associated with self-reported changes in cognitions and behaviours. In particular, increased positive interpretations were consistently associated with the attenuation of unhelpful symptom responses, such as catastrophizing and symptom focusing. Perhaps by engaging in certain therapeutic techniques (e.g. thought records in CBT) people begin to expand their range of interpretations of ambiguity, to include those that are more positive. These findings, though tentative, indicate that illness-specific cognitive biases have some relationships with self-reported symptom responding.

9.3 Contributions to the literature

The different studies contained in this thesis produced multiple insights and specific results that make a distinct contribution to the literature. Firstly, by employing experimental methods this thesis adds another dimension to cognitive behavioural
literature in CFS, which has largely relied on self-reports to date. Secondly, the thesis identified novel insights into cognitive characteristics and deficits in CFS. Thirdly, this thesis contributes to the currently sparse but burgeoning, experimental research within health psychology. These contributions are discussed below.

9.3.1 Contribution of experimental research to the CFS literature

Self-report methodologies in CFS have been employed across a range of study designs including cross sectional studies (e.g. Edwards, et al., 2001; Heijmans, 1998; Moss-Morris, et al., 1996) predictors of onset of CFS (e.g. Candy, et al., 2003; Moss-Morris, et al., 2011) and mediators of change following treatments (e.g. Chalder, et al., 2015; Wearden & Emsley, 2013; Wiborg, et al., 2011). Consistent findings emerge that negative illness and symptom interpretations, as well as behaviours (particularly all-or-nothing and fear avoidance) are associated with fatigue and disability in CFS. By using experimental methods this thesis has identified that similar and related constructs are activated at more habitual levels of processing. For example, if self-reports of physical symptoms and fatigue are taken to reflect a somatic pre-occupation; an attentional vigilance for illness related information in the environment may represent pre-occupation for illness stimuli at earlier, habitual levels of processing. Similarly, a tendency to interpret ambiguous information as negative/illness-related may over-lap with self-reported catastrophic thinking styles and fearful beliefs regarding activity. Thus, these experimental findings validate self-report studies in CFS and further demonstrate that illness-specific cognitions are also present at habitual levels of processing.

Experimental methods have several advantages over self-report; they are not subject to demand (e.g. social desirability or recall bias) and they can tap into levels of processing that are outside of the individuals ‘conscious’ awareness. A particular advantage of using
experimental measures in CFS populations is that they avoid reinforcing the stigma that is often associated with psychological assessments (Looper & Kirmayer, 2004). Using experimental measures alongside self-report measures can build a more comprehensive picture of cognitions and behaviours involved in CFS.

This experimental research also adds to the literature discriminating between cognitive profiles of CFS and psychiatric disorders. Moss-Morris and Petrie (2001) found distinct cognitive profiles which appear to distinguish between CFS and depression. Similarly, this research found illness-specific cognitive biases in CFS were independent of co-morbid depression and anxiety. These findings are consistent with studies in chronic pain (Crombez, Viane, Eccleston, Devulder, & Goubert, 2013) and irritable bowel syndrome (Chapman & Martin, 2011), suggesting that cognitive biases in somatic based conditions depend on the relevance of the stimuli to the individual’s illness concerns and beliefs, rather than anxiety and depression per se. However, conclusions from this data are limited by the use of only one category of stimuli, as well as the lack of clinical control group. It would be interesting to assess whether biases for other categories of information occur for stratified groups of patients; or indeed, whether people with other chronic health conditions show similar cognitive biases.

Whilst these biases appear to be independent of comorbid psychiatric disorders, (measured by a structured clinical interview) they may be dependent on fluctuating mood. Chapter 6 found that across both the UK and Dutch CFS populations, attentional biases disappeared when distress, measured by the HADS (Zigmond & Snaith, 1983), was partialled out. So, why might attentional biases in CFS be affected by mood but not psychiatric comorbidity? One potential reason may be that low mood in CFS reflects a core aspect of living with this debilitating and chronic condition. Thus, by partialling out
mood the difference between people with CFS and healthy controls was obscured. Whereas, comorbid depression, whilst prevalent in CFS, is not a core aspect of the condition; rather it reflects an additional but distinct psychiatric comorbidity (Cella, et al., 2013). The fact that group differences on attention and interpretation biases remained significant when controlling for comorbidity, suggests that these factors are not driving the cognitive bias. Alternatively, this discrepancy may be due measurement error within the HADS. A psychometric analysis found the use of the HADS to assess anxiety and depression in CFS, was ‘fundamentally compromised’ by the presence of a threedimensional underlying factor structure (McCue, Martin, Buchanan, Rodgers, & Scholey, 2003). However, others have disputed this (Cella, et al., 2011b) and the HADS remains the most widely used research measure of anxiety and depression in CFS populations (Bjelland, Dahl, Haug, & Neckelmann, 2002; Cella, et al., 2011b). The levels of HADS anxiety and depression demonstrated in this CFS sample were similar to that reported in other studies.

It may not be surprising that people with CFS preferentially process illness-related information. Experiencing pervasive, debilitating and unpredictable fatigue would understandably make fatigue related cues salient; thus lowering the threshold for their perception and subsequent processing (Verkuil, Brosschot, & Thayer, 2007). Indeed, we all preferentially attend to information that is most personally meaningful or temporarily salient (Pool, et al., 2016). However, interestingly, cognitive biases in CFS, were not moderated by attentional control (Chapters 5 and Chapter 6); though attentional control was impaired; and were associated with unhelpful responses to symptoms. These findings may indicate that cognitive biases represent a coping strategy, which alert the individual to signs of potential fatigue inducing stimuli and thus helps them evade further injury. Treatments may challenge the perceived helpfulness and necessity of these coping
strategies and thus modify unhelpful responses and cognitive biases. Thus, cognitive biases may have a role to play in the CB model of CFS. However, the direction of these relationships is unclear; it could that cognitive biases are driving more explicit illness beliefs and behaviours, or it could be that repeatedly engaging in certain responses to symptoms may create heuristics (cognitive biases) in information processing. Alternatively, the relation between cognitive biases and symptom responses in CFS may be maintaining, or mutually reinforcing, as has been proposed with anxiety (Van Bockstaele, et al., 2014). To unpick these relationships longitudinal, mediation studies are required.

9.3.2 Cognitive characteristics and deficits in CFS

This thesis also measured two proposed mechanisms of cognitive biases: attentional control and attentional malleability. The findings provide novel contributions to the neuropsychology literature in CFS and add to the theoretical understanding of cognitive biases more broadly.

9.3.3 Attentional control

Two studies within this thesis identified that people with CFS (from the UK and Netherlands) had significantly poorer general attentional control capacity compared to a healthy population. These findings are consistent with other CFS studies using the same objective task (Hou, et al., 2014; Togo, et al., 2015). However, it should be noted that both the UK and Dutch CFS groups were compared to the same healthy population that were recruited from London and were slightly younger than the CFS groups. Perhaps these healthy controls represent a sample with particularly good attentional control. However, this is unlikely as the median and range attentional control scores within this healthy population was similar to that reported by others (Fan, McCandliss, Fossella,
Furthermore, attentional control scores obtained from both CFS populations were comparable (Chapters 5 and 6); and in line with previous CFS research using this task (Hou, et al., 2012; Togo, et al., 2015). Nor did age have any bearing on the effects (Chapters 4 and Chapter 5).

Thus, it seems poor attentional control, as measured by the ANT (Fan, et al., 2005; Fan, et al., 2002) is a robust finding in CFS. This is in contrast to a plethora of other neuropsychological tests, which find generally slowed information processing speed but no consistent neurological deficits on any particular test (Cockshell & Mathias, 2010; Cockshell & Mathias, 2013, 2014; Michiels & Cluydts, 2001). It may be the attentional control segment of the ANT (the flanker task) accurately reflects patients’ difficulty processing information and relatedly the subjective experience of cognitive difficulties. Notably, however poor attentional control was not related to subjective reports of functioning or fatigue in our studies; despite the fact that our measure of fatigue (Chalder Fatigue Scale, Chalder, et al., 1993) includes an assessment of mental fatigue. Nevertheless, while attentional control deficits do not seem directly related to core symptoms in these CFS samples, they are still important to address. Attentional control is closely related to other executive functions, which are helpful and sometimes integral to multitasking (Diamond, 2013). Thus, improving attentional control may be an important treatment outcome for people with CFS.

Chapter 8 identified that, not only is attentional control in CFS amenable to change, but current treatment protocols for CFS (CBT and GET) seem effective at improving this cognitive ability (Chapter 8). This finding corresponds with brain imaging data, which indicate that after a course of CBT patients with CFS have increased grey matter volume.
in brain regions associated with attentional control (De Lange, et al., 2008). However, the mechanisms through which these treatments are able to achieve these improvements are unclear. Reducing anxiety and illness-related worry have been proposed as once such mechanism (Derakshan & Eysenck, 2009). The rational is that anxiety occupies a proportion of the available cognitive resources, leaving fewer resources available for effortful tasks. This theory is supported by findings in the anxiety literature which demonstrate increased anxiety and worry are associated with reduced attentional control (Hayes, et al., 2008; Stefanopoulou, et al., 2014), and by reducing worry and worry related intrusive thoughts, this deficit can be reversed (Bomyea & Amir, 2011; Fox, et al., 2015). Interestingly, the improvement in attentional control in the current CFS data was associated with reduced symptom focusing and anxiety (Chapter 8) which may represent illness-related worry. Perhaps CBT and GET treat the anxiety and symptom focusing in CFS, thus freeing up working memory and improving attentional control as a bi-product. Further studies need to explore the direction of these relationships.

9.3.4 Attentional Malleability

Several studies in the anxiety literature recently explored the concept of attentional malleability- a person’s ability to adopt an attentional bias. These studies indicated the utility of attentional malleability at predicting both vulnerability to developing anxiety in healthy populations (Clarke, et al., 2008), and better response to treatment in anxious populations (Clarke, et al., 2012). As such, attentional malleability was identified as a potentially useful concept to investigate in terms of treatment response in CFS. Chapter 7 found that, as hypothesised, attentional malleability predicted better response to CBT and GET for CFS. This novel finding provides further support for the ‘bias plasticity account’ of attention (Clarke, et al., 2008; Clarke, et al., 2012) which proposes that the more malleable an individual’s attention, the more likely they will benefit from treatments.

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that engage attentional processes. Attentional malleability in CFS warrants further investigation. These findings need to be replicated with larger samples in order to identify whether they are consistent and importantly whether attentional malleability can help explain some of the variance in treatment response. If those with less malleable attention are less likely to benefit from treatment, it would be important to consider how to optimize treatments for individuals with low attentional malleability.

9.3.5 Contribution to experimental research in health psychology

Experimental research within health psychology is small but growing. There is increasing interest in applying experimental methods to assess potential cognitive biases underlying illness beliefs and influencing health behaviours. The potential for experimental research to contribute to health psychology is substantial; however, in order for it to be fruitful, methods must be tailored and adapted appropriately. A failure to do so limits the conclusions drawn from the data and misses the opportunity to expand upon existing self-report data and health psychology models.

Having reviewed the experimental literature in CFS (Chapter 3), and briefly outlined similar experimental work in other areas of health psychology (Chapter 4) it became clear that, no one methodological approach to developing appropriate experimental materials had been used; nor did there seem to be any guidance on how to adapt tasks appropriately for different populations. Given that materials are at the heart of these experimental tasks, it is essential they are subject to the same rigorous development and validation as self-report questionnaires. With this in mind, I published guidance on how to develop population-specific materials in a systematic way; and provided tools to aid researchers in this processes. Employing a standardized and systematic approach to material development can help establish a body of high quality and replicable experimental
research within health psychology. This is particularly pertinent if health psychology research is to capitalize on the developments and rapid expansion of experimental research (e.g. CBM).

Furthermore, the findings from this research, whilst specific to CFS may also be relevant to other chronic conditions. For example, the psychopathology literature has identified that attentional biases are transdiagnostic processes that maintain symptoms across a range of disorders, including generalised anxiety disorder, unipolar depression, specific phobia and panic disorder, amongst others (Mansell, Harvey, Watkins, & Shafran, 2008). While the content of the attentional bias varies according the specific disorder, the process remains the same. Similarly, cognitive biases identified in CFS may also be occurring in other chronic conditions. For example, CFS shares similar cognitive and behavioural features to irritable bowel syndrome and fibromyalgia (Deary, et al., 2007). If research in CFS establishes that cognitive biases are maintaining some of these shared cognitions and behaviours, it may be worthwhile exploring whether cognitive biases also maintain similar cognitions and behaviours in these other conditions.

9.4 Limitations

The limitations of individual studies are discussed within the relevant chapters. Here I will discuss the limitations of the research programme as a whole.

9.4.1 Reliability and validity of the experimental tasks

Both the strengths and limitations of this research largely hinge on the validity and reliability of the experimental paradigms employed. In the following section, I will discuss each of the experimental tasks in turn and consider whether these paradigms were appropriate for use within CFS populations and capable of detecting change over time (as
per the study design); or whether alternative paradigms would have offered a more reliable measure.

The Attention Network Task (Fan, et al., 2005; Fan, et al., 2002) was chosen to measure attentional control as it had been used previously in CFS populations and consistently identified deficits in attentional control, when compared to healthy individuals (Hou, et al., 2014; Togo, et al., 2015). The studies in this thesis corroborate these findings (Chapter 5 and 6). Furthermore, a test of repeated measurement of the ANT found that scores remain robust even after 10 sessions (Ishigami & Klein, 2010). Thus, the pre post design of this research should not be problematic for the ANT. This adds validity to finding of improved attentional control over the course of treatment (Chapter 8).

The ambiguous recognition task developed by Mathews and Mackintosh (2000) was chosen as the measure of interpretation biases. This task measures ‘off-line’ interpretations of ambiguity which are made at more elaborate stages of processing, rather than spontaneous ‘automatic’ interpretations that are assessed by ‘online-tasks’ (see Chapters 3 and 4 for a discussion of off-line and online IB tasks). An off-line task was chosen as the systematic review (Chapter 3) had indicated that interpretation biases were more likely to occur in CFS at these more elaborative stages of processing. The ambiguous scenarios task was the clear choice of off-line interpretation bias tasks as it has been the most widely used (Hirsch, et al., 2016b). However, it is difficult to compare studies that have used this task given that the integral content of the task is adapted according to the population of interest. Within this thesis, the careful structuring of the interpretation bias materials to tap into illness-relevant concerns yet remain ambiguous, led to the detection of interpretation biases across two CFS populations (UK and Dutch) (Chapter 4). However, there was no change in interpretation biases when measured over
two time points, pre- and post-treatment (Chapter 7). This may indicate that treatments did not change interpretation biases, or this may indicate a methodological issue of repeated measurement. Whilst different sets of data were presented to each participant, at each time point, they may have surmised from their first testing session what the task was about, which may have influenced how they responded to the task the second time around. Furthermore, there may be an issue with creating simple change scores on this task. There were large standard deviations in both pre and post treatment interpretation bias scores, indicating that there was large heterogeneity in how people responded to the interpretation bias task at both time points. Creating simple change scores results in a summation of measurement errors and may have obscured any change over time. Test-retest designs and larger studies that assess reliability over time are needed to resolve these issues.

A modified version of the Visual Probe Task (MacLeod, et al., 2002) measured attentional biases and attentional malleability in this thesis. The VPT was chosen as it has been used extensively to assess attentional biases in a variety of populations, including CFS (Hadwin & Richards, 2016; Hou, et al., 2012; Hou, et al., 2014); and more recently has been used to measure attentional malleability (Clarke, et al., 2008; Clarke, et al., 2012). Using this paradigm allows direct comparisons with these studies. However, questions have been looming regarding the reliability and validity of the VPT (e.g. Mogg & Bradley, 1999). Indeed the VPT has been described as unreliable to detect attentional biases in non-clinical samples (Schmukle, 2005) and exhibiting only modest reliability in test-retest designs (Britton, et al., 2013; Price, et al., 2015). Nevertheless, the VPT remains the most widely used measure of attentional bias to date. Alternative paradigms have been proposed, such as visual search task (e.g., Rinck, Becker, Kellermann, & Roth, 2003; Weierich, Treat, & Hollingworth, 2008), eye gaze bias (Armstrong & Olatunji,
2012; Fashler & Katz, 2016; Price, Greven, Siegle, Koster, & De Raedt, 2016a; Wieser, Pauli, Weyers, Alpers, & Mühlberger, 2009; Yang, et al., 2013), and EEG measures such as steady-state evoked potentials (Wieser & Keil, 2014; Wieser, McTeague, & Keil, 2011; Wieser, Miskovic, Rausch, & Keil, 2014). However, few validation studies of these paradigms have been conducted, and as yet, they have not been definitively established as superior to the VPT (Cisler, Bacon, & Williams, 2009). Thus, it seems that whilst the VPT may not be ideal, it offered the most straightforward and comparable assessment of attentional biases at the time.

However, the use of the VPT task inherently limits the conclusions from the data. The VPT does not assess attention as the continuous and dynamic process that it is. Rather it assesses attention at a ‘snap-shot’ in time; assuming that the quicker this ‘snap’ is taken the more ‘automatic’ the process it reflects; i.e. stimuli presented <500ms representing more automatic processing, and >500ms representing later stages of processing. It is unclear whether the 500ms snap of attentional bias in this research is indicative of biases at early or later stages of processing. Furthermore, the VPT cannot tell us about the deployment of attention during this window of time. It might be that attention is deployed, maintained or re-arranged in different ways during this 500ms period; and certain phases may be important in distinct ways in the development and maintenance of attentional biases. For instance, an eye tracking study in chronic pain not only confirmed the overall attentional bias towards pain related information, but also contributed novel data pointing to a pattern of late-phase attentional hypervigilance to injury-related pictures (Fashler & Katz, 2016). Additionally, employing eye-tracking technology to measure these variables could provide a more comprehensive and nuanced picture of attentional biases in CFS.


9.4.2 Study design issues

The study design limits the conclusions of the data. The lack of clinical control group across the studies means it is not certain that these cognitive biases are unique to CFS. Perhaps they are an effect of having a chronic illness more generally. From the cross-sectional data in Chapter 5, it seems cognitive biases in this CFS sample were not influenced by chronicity (measured as duration of illness); however there may be some methodological issues with its measurement, which will be discussed shortly. Furthermore, the lack of comparison group in the follow-up studies (Chapter 7 and Chapter 8) means that we do not know how cognitive biases and attentional control change over the natural course of time. Perhaps improvements would have also occurred in an untreated sample; thus revealing that effects are not attributable to treatment. Future studies should include a clinical wait-list control group and further explore the comparable fluctuations and rigidity of cognitive biases in clinical and healthy populations.

There are also a number of unmeasured, potentially confounding variables to consider, such as intelligence, cognitive ability and medications, omitted in these studies. For example, the use of certain medications, such as anticholinergic drugs (e.g. benzodiazepine), may have had an impact on an individuals’ cognitive ability and thus influenced their performance on the cognitive tasks. This study did not assess the use of medications, though it is likely that some patients would have been on certain anticholinergic drugs, such as benzodiazepines and doxepin, for the treatment of comorbid anxiety and/or depression (respectively). For these people the short stimuli presentation duration in the VPT (500ms) and the requirement to recall the 10 ambiguous scenarios presented in the recognition task, may have been more difficult; thus, their responses may represent this cognitive difficulty rather than a cognitive bias. However,
appropriate data handling should have negated this potential issue; across all the tasks only correct responses were analysed, participants with less than 90% accuracy rate were excluded, and reaction time data for responses <200ms and >2000ms were excluded.

Intelligence may also be important to consider in future studies employing cognitive tasks in CFS. In particular, the ANT measure of attentional control, has been related to fluid intelligence- the reasoning and problem-solving component of executive functioning (Unsworth, Fukuda, Awh, & Vogel, 2014). The only proxy of intelligence in these studies was ‘years in education’, which was equivalent in the CFS and healthy population reported in the cross-sectional study (Chapter 5). Furthermore, ‘years in education’ did not correlate with scores on the ANT. However, ‘years in education’ is a poor proxy of fluid intelligence. Future studies should consider including measures such as the Wechsler Adult Intelligence Scale (Wechsler, 2014), to assess whether responses to cognitive tasks in CFS is affected by general intelligence.

Another limitation is this research is that the CFS samples consisted mainly of women. Though this is representative of the male to female ratio in CFS (Bakken, et al., 2014; Buchwald, et al., 1994; Cho, et al., 2009; Nacul, et al., 2011; Prins, et al., 2006; Skapinakis, et al., 2003), it may have biased our results. For example, Keogh, Hamid, Hamid, and Ellery (2004) found that women had an increased tendency to negatively interpret sensations, compared to men, which was related to greater negative pain responses. In this thesis, the finding of interpretation biases in CFS samples (Chapter 5 and Chapter 6) may have been due to the CFS samples consisting of mostly women. Men with CFS may have different patterns of interpretation. Studies with larger samples sizes and equal numbers of men and women should assess whether there are gender differences in information processing in CFS.
A key strength of this study was the inclusion of those with a clear diagnosis of CFS. All participants met the CDC 1994 diagnostic criteria (Fukuda, et al., 1994), which was confirmed by a consultant psychiatrist or experienced cognitive behavioural therapist and confirmed by meeting cut offs of fatigue and functioning of the Chalder Fatigue Scale (Chalder, et al., 1993) and SF-36 (McHorney, et al., 1994) (respectively). However, the recruitment of participants from specialist CFS treatment centres may have biased the sample. For instance, those willing to attend treatment centres which offer psychological and behavioural treatment for CFS (i.e. CBT and GET), are less likely to have fixed biological illness attributions, and are at least open to the idea of psychological components (Chew-Graham, Brooks, Wearden, Dowrick, & Peters, 2011). It is likely that people with very fixed beliefs about the biological cause of the illness, would not have attended such a treatment service and therefore will not have been included in this research. Perhaps those with more fixed illness beliefs also have stronger cognitive biases. For instance, studies have shown that the more fixed and somatic beliefs about the cause of the illness the more evasive of physical activity people are (Chalder, Power, & Wessely, 1996; Vercoulen, et al., 1998). In an attempt to avoid further injury and be alert to symptoms people may have also developed habitual cognitive biases for salient, illness-related information. Future studies should assess illness attributions and beliefs (e.g. Illness-Perception Questionnaire-Revised, Moss-Morris, et al., 2002) to assess whether these factors predict or interact with how people with CFS attend to and interpret information.

Another potential bias within the CFS samples was the particularly long mean length of illness duration reported. This may be linked to the fact that participants were recruited from a number of specialist CFS clinics within the NHS, thus accessing patients with a
range of demographic and disease characteristics. Additionally, the wording of this question was somewhat ambiguous (‘How long have you had CFS?’). It may have been that some participants answered this question in relation to how long they have had experienced symptoms of CFS, whereas other answered how long since they had received a diagnosis. Unfortunately, data was not available for the mean length of illness within the Dutch CFS population reported in the cross-cultural study in Chapter 5. Illness duration is important as it might be argued that people who have had CFS for some time have become preoccupied with their illness, and these biases develop or are further embedded over time. Though duration of illness did not influence the results in the cross-sectional study (Chapter 5) it would be worth exploring whether chronicity; measured both in terms of symptom duration and time since diagnosis, has a role to play in the expression of cognitive biases in CFS.

Another consideration is the type of onset of CFS. For instance, DeLuca, Johnson, Ellis, and Natelson (1997) found differences in neuropsychological tests in those with sudden versus gradual onset of CFS. Those with sudden onset had more severe impairment in memory than the gradual onset CFS group. Supporting these findings is a twin study (Claypoole, et al., 2007); which found twins with sudden illness onset demonstrated slowed information processing speed compared with those with gradual onset. These findings suggest the mode of illness onset impacts cognitive processes in CFS. The studies in this thesis did not assess the type of illness onset. It would be interesting to examine whether those with different illness onsets had differing cognitive biases, characteristics or deficits and whether these factors influence the illness trajectory.

Importantly, a major limitation of these studies is the relatively small sample sizes. Whilst the cross-sectional study reported in Chapter 5 is the largest to date in this area (CFS,
(n=52; health controls, n=50) and the sample size of the Dutch cohort in (Chapter 6) (n=36) represent average sample sizes for experimental data, these samples were still too small to explore the effects of heterogeneity within CFS. The samples sizes of the follow-up studies (Chapter 7, n=26; Chapter 8, n=20) are at particular risk of Type II error. Future research, with larger, stratified samples should explore the heterogeneity of cognitive processes in CFS.

9.5 Future avenues for research

This thesis has provided a new and encouraging line of experimental research within CFS. However, several questions posed in this thesis need further clarification. Most of these issues have been addressed within limitations section; however, I will provide a brief summary in the next section ‘unanswered questions’. Furthermore, the current research has generated an array of new questions for future research to consider. I will outline these under the heading ‘new questions’, alongside suggestions as to how these might be addressed in future research.

9.5.1 Unanswered questions

Firstly, as previously discussed, we cannot be certain that the cognitive biases in attention and interpretation are unique to CFS. They may represent an effect of having a chronic, disabling condition more generally. Studies should compare cognitive biases in CFS to other chronically ill groups, with comparative levels of disability and illness duration. Secondly, the correlations between cognitive biases and cognitive and behavioural responses to symptoms, while indicative of important relationships between these variables cannot tell us about the direction or causality of these relationships. Further longitudinal, studies with multiple time points, employing mediation and moderation analyses need to assess how these processes may interact with one another.
Computerized cognitive bias modification techniques (CBM) (discussed in Chapter 7 and Chapter 8) offer the methods to assess the causal/maintaining role of cognitive biases in CFS. If cognitive biases have a maintaining role in CFS, the logic goes that modifying the bias would alleviate symptoms. Thus, utilizing CBM techniques could help establish, firstly whether biases in CFS are modifiable and secondly whether they are maintaining some core aspects of CFS.

To address the issues within the longitudinal data (Chapter 7 and Chapter 8) i.e. the small sample size and lack of control group, large randomized control trails (RCT) are required. RCT’s should compare people with CFS in treatment and on a wait list to healthy controls and other chronic illness groups in order to build a comprehensive picture of how these biases operate in different groups and further establish the specificity of these biases in CFS. Longitudinal data with these groups can establish how cognitive biases and attentional control deficits change over the natural course of time and how stable these processes are in healthy populations. Multiple time points would allow mediation analysis to explore whether these biases are important for treatment outcomes.

9.5.2 New questions

This thesis raises a number of interesting lines of inquiry. Firstly, while this research can conclude that people with CFS have biased interpretations at later stages of processing (off-line), we do not know whether people also show biased interpretations at earlier, more spontaneous levels of processing (on-line). To date only one study in CFS has explored this possibility, with null findings (Martin & Alexeeva, 2010). Whilst this study had a high quality rating (15/16) in the systematic review (Chapter 4), the methodology could perhaps have been improved. The study used an online lexical decision task, whereby single ambiguous words (e.g. “tire” =fatigue v’s “tyre” =wheel) were used to
prime target words. The authors did not provide the list of stimuli, so the extent to which these words tapped into core, illness-related concerns is unclear. However, I would argue that there are very few homophones that represent concerns specific to CFS; and of the few that do, one use of the word is typically more common. Perhaps for people to make illness-related inferences in CFS, more contextual information is required. An ‘on-line’ task that is able to achieve this and circumvent the single word issue, is the speeded lexical decision task (Hirsch & Mathews, 2000). In this task, participants read a passage of text, which is ambiguous but has the potential for a threatening interpretation, e.g., being interviewed for a job. At critical points in the text participants are required to make a speeded response to resolve the ambiguity, e.g., ‘As the interviewer asks the first question, you realise that all your presentation will be…’, participants respond to possible targets, ‘useful’ or ‘forgotten’. Quicker responding to threatening resolutions indicates an on-line, spontaneous negative interpretation bias. Such a design could be adapted for use with CFS participants to assess online inferences.

The current research assessed attention and interpretation biases in isolation, using distinct tasks that do not lend themselves to comparison. However, numerous theories suggest that attention and interpretation biases should be correlated (Everaert, et al., 2012; Pincus & Morley, 2001). The paradigms used to assess these biases were not appropriate to test this hypothesis. In order to do so, tasks are needed which use similar materials across cognitive tasks and simultaneously assess these processes, in order to reduce the error variance associated with different experimental tasks (Butler, et al., 2015; Everaert, Tierens, Uzieblo, & Koster, 2013; Hirsch, et al., 2006; Todd, Sharpe, Colagiuri, & Khatibi, 2016; Todd, et al., 2015; White, Suway, Pine, Bar-Haim, & Fox, 2011a). Future studies should employ such techniques to explore whether one bias precedes or predicts the other; or whether they occur simultaneously.
Another methodological consideration for future studies is whether cognitive biases occur for somatosensory information. Theoretical models postulate that an increased attention towards internal somatic cues and misattribution (interpretation bias) of internal sensory information, are key factors in driving CFS (Knoop, et al., 2010; Meeus & Nijs, 2007; Moss-Morris, Deary, & Castell, 2013; Nijs, et al., 2012; Vercoulen, et al., 1998). However, developing experimental methods to assess biases for these types of stimuli is clearly challenging. In pain studies, fear-conditioning paradigms have assessed attentional biases towards anticipatory pain (i.e. electric shock) (Van Damme, et al., 2006; Van Damme, et al., 2004b) and pain-relevant body locations (Bulcke, Van Damme, Durnez, & Crombez, 2013; Van Damme, et al., 2016). In these paradigms, pain stimulus (i.e. an electric shock) is paired with a cue. The degree to which participants subsequently respond to that cue is indicative of their attentional vigilance for the anticipated pain (i.e. electric shock). Employing such designs in CFS is likely to be more difficult. Not only is real-life fatigue difficult to experimentally induce (Caseras, et al., 2008) but furthermore, fatigue itself is heterogeneous in CFS; for example some people experience predominantly post-exertional malaise whereas others may report more mental fatigue and concentration problems (Hickie, et al., 1995). Researchers should consider how best to develop and adapt paradigms in order to assess cognitive biases for internal bodily sensations. Methodologies such as monitoring internal heart rate variability (Beaumont, et al., 2012) and eye-tracking (Fashler & Katz, 2016; Yang, et al., 2013) may provide fruitful avenues for further study.

Turning to the relatively new concept of attentional malleability, the findings of the predictive study in Chapter 7 adds credence to research on attentional malleability to date (Clarke, et al., 2008; Clarke, et al., 2012; Fox, et al., 2011). The current research followed
that of Fox, et al. (2011) in measuring malleability both towards and away from threat and supported the ‘plasticity account’ (Clarke, et al., 2008; Clarke, et al., 2012); which proposes that individual differences in the readiness to adopt an attentional bias (either towards or away from threat), is associated with individual differences in response to treatment. However, it is still unclear, from the previous anxiety literature and the current CFS data, whether clinical populations have poorer attentional malleability compared to healthy individuals. Studies need to establish what constitutes ‘good’ attentional malleability; and secondly the genetic, psychological and behavioural characteristics that define it. Research into attentional malleability is just beginning. Thus far, it seems to be a promising construct, warranting further investigation across disorders. Fox, et al. (2011) associated attentional malleability with a genetic marker, they termed the ‘plasticity gene’. It would be interesting to explore the interaction between this genetic marker of malleability with environmental variables, in prospective and longitudinal studies. Such analyses could shed significant light on how, when and for whom cognitive biases develop and under what circumstances these biases become a problem (e.g. maintaining some form of distress). In CFS, for instance it would be interesting to consider whether this ‘plasticity gene’ might make some people more vulnerable to developing CFS after an adverse experience, such as glandular fever.

9.6 Potential clinical implications

This research has identified that people with CFS have illness-specific attention and interpretation biases, which have some relationships with unhelpful responses to symptoms. The next step is to assess whether these biases play a role in maintaining core aspects of CFS. Cognitive bias modification techniques (CBM; introduced in Chapter 2, section 2.3.3; and further discussed in Chapter 5, Chapter 7 and Chapter 8) offer an experimental paradigm in which to test these hypotheses. However, to date, there is no
single protocol for CBM and CBM studies are not always successful in modifying cognitive biases (Cristea, et al., 2015; Hakamata, et al., 2010; Hallion & Ruscio, 2011; Menne-Lothmann, et al., 2014; Mogg & Bradley, 2016; Mogoaşe, et al., 2014; Pool, et al., 2016). At this point, work is needed to establish (i) whether cognitive biases in CFS are modifiable via CBM (ii) the optimal conditions that elicit change in cognitive biases. Having conducted this basic research, CBM procedures could be adapted for CFS populations, following similar material development procedures outlined in Chapter 3. CBM could then be utilized to test the potentially maintaining role of cognitive biases in CFS.

Should CBM establish a maintaining role of these biases in CFS, there may be clinical utility in further developing CBM for CFS, as an additional therapeutic tool. Though CBM techniques are in their relative infancy, they have shown promise at reducing symptoms in clinical populations (e.g. anxiety) (Hakamata, et al., 2010) and can be an effective adjunct to conventional forms of psychological interventions (Williams, et al., 2013). In CFS, CBM techniques may provide a useful ‘add-on’ for those individuals for whom cognitive biases are a problem (i.e., maintaining some cores aspects of the condition). However, work is needed before CBM can be considered a treatment. In its current form CBM training is time consuming and relatively unengaging (Beard, et al., 2012) and we do not yet know the feasibility or acceptability of delivering CBM in the ‘real world’ (Beard, 2011).

9.7 Conclusions

This research programme illustrates the promising application of experimental research in CFS. The studies identified that people with CFS have illness-specific processing biases and cognitive characteristics that are important for responding to symptoms and
treatment. Importantly, this research identified that these processes are amenable to change, and furthermore, the degree of change in these processes, was associated with the adoption of more adaptive response to symptoms. Studies in other illness groups have shown that altering these processes through more direct techniques (e.g. CBM) can have positive impacts on other biological, emotional and behavioural factors. Similarly, enhancing adaptive cognitive processing, such as positive interpretation biases and more flexible attention allocation, may provide beneficial intervention targets in CFS.

Cognitive processing forms only one component of the CB model of CFS and, alongside cognitive and behavioural factors, other biological and psychosocial factors play key roles. Research should begin to explore how these diverse components interact with one another and how these interactions vary for each individual. Continued research efforts to understand a range of factors preceding, precipitating and perpetuating CFS, that employ a range of methodologies, can help identify the most effective and appropriate targets for intervention and should lead to better understanding of CFS and its effective treatment.
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**Appendix A. Detailed Comparison of CFS Case Definitions**

Table 6 Comparison of case definitions for CFS/ME

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<tr>
<td>Terminology</td>
<td>CFS</td>
<td>CFS</td>
<td>CFS</td>
<td>CFS</td>
<td>ME/CFS</td>
<td>CFS/ME</td>
<td>ME</td>
<td>CFS/ME/ 'systemic exertion intolerance disease' (SEID)</td>
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<tr>
<td>Fatigue requirement</td>
<td>Persistent or relapsing, debilitating fatigue or easy fatigability, that does not resolve with bedrest</td>
<td>Fatigue present more than 50% of the time</td>
<td>Post exertional fatigue</td>
<td>Fatigue not alleviated by rest</td>
<td>Post-exertional malaise and/or fatigue</td>
<td>Post-exertional malaise and/or fatigue</td>
<td>Postexertional neuroimmune exhaustion*</td>
<td>Fatigue, not alleviated by rest and post-exertional malaise.</td>
</tr>
<tr>
<td>Minimum duration of fatigue</td>
<td>6 months</td>
<td>6 months</td>
<td>6 months</td>
<td>6 months</td>
<td>6 months</td>
<td>4 months</td>
<td>Not required</td>
<td>6 months</td>
</tr>
<tr>
<td>Functional impairment</td>
<td>50% decrease in activity</td>
<td>disabling</td>
<td>substantial</td>
<td>substantial</td>
<td>50% decrease in activity</td>
<td>substantial</td>
<td>50% decrease in activity</td>
<td>substantial</td>
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<tr>
<td>New onset</td>
<td>Required</td>
<td>Required</td>
<td>Not required</td>
<td>Required</td>
<td>Not required</td>
<td>Required</td>
<td>Not required</td>
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<tr>
<td>May be present</td>
<td>Impaired mental functioning required</td>
<td>Required</td>
<td>Mental fatigue required</td>
<td>2 or more neurological/cognitive manifestations required</td>
<td>May be present</td>
<td>1 or more symptoms from 4 categories required: neurocognitive impairment; pain; sleep dysfunction; neurosensory perceptual; motor disturbance</td>
<td>Cognitive impairment or orthostatic intolerance required</td>
<td></td>
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<tr>
<td>Other required symptom(s)</td>
<td>None</td>
<td>None</td>
<td>Any 4 of 8: memory or concentration problems, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, new headaches, unrefreshing sleep, post-Chronic pain and sleep dysfunction. Plus at least 1 symptom from 3 categories: autonomic, neuroendocrine, immune</td>
<td>Any 1 of 10: difficulty sleeping muscle and/or joint pain headaches painful lymph nodes without pathological enlargement sore throat cognitive dysfunction physical or mental</td>
<td>Any 1 from immune gastrointestinal or genitourinary impairment categories. Plus any 1 from energy metabolism or transport impairments categories</td>
<td>Unrefreshing sleep</td>
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<tr>
<td>Medical exclusion</td>
<td>Extensive list of known physical causes</td>
<td>Known physical causes</td>
<td>Known physical causes</td>
<td>Clinically important medical conditions, medication side-effects, or ongoing exertion.</td>
<td>Active disease processes that explain most of the major symptoms, treatable sleep disorders, rheumatologic known physical causes</td>
<td>Known physical causes</td>
<td>Known physical causes or ongoing excessive exertion</td>
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<tr>
<td>Psychiatric exclusion</td>
<td>psychosis, bipolar disorder, substance abuse</td>
<td>psychosis, bipolar disorder, eating disorder, organic brain disease, substance abuse,</td>
<td>psychosis, bipolar disorder, substance abuse, eating disorders</td>
<td>past or current psychotic or melancholic depression, bipolar disorder, schizophrenia, delusional disorders, dementia, anorexia nervosa, bulimia nervosa, alcohol or other substance abuse within 2 years before the onset of the chronic fatigue</td>
<td>al disorders and polymyalgia rheumatica, immune disorders.</td>
<td>primary psychiatric disorders and substance abuse</td>
<td>No list provided</td>
<td>primary psychiatric disorders, somatoform disorder, and substance abuse</td>
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**Continued**
|-------------------|--------------------------|---------------------------|---------------------------|------------------------------------------|------------------------|---------------------------------------------|----------------------------------|

and any time afterward.

* Postexertional immune disorder (PENE) as defined by Carruthers, et al., (2011) is a pathological inability to produce sufficient energy on demand with prominent symptoms primarily in the neuroimmune regions. Characteristics are as follows:
1. Marked, rapid physical and/or cognitive fatigability in response to exertion, which may be minimal such as activities of daily living or simple mental tasks, can be debilitating and cause a relapse.
2. Postexertional symptom exacerbation: e.g., acute flu-like symptoms, pain and worsening of other symptoms.
3. Postexertional exhaustion may occur immediately after activity or be delayed by hours or days.
4. Recovery period is prolonged, usually taking 24 h or longer. A relapse can last days, weeks or longer.
5. Low threshold of physical and mental fatigability (lack of stamina) results in a substantial reduction in pre-illness activity level.

Continued
Appendix B. Questionnaire Pack

List of Questionnaire Pack Materials
Participants completed the following self-report measures:
1. Demographics questions (including questions on employment)
2. Chalder Fatigue Scale (Chalder et al., 1993)
3. SF-36 Physical functioning scale (Ware et al., 1994)
4. Work and Social adjustment scale (Mundt et al., 2002)
5. Cognitive Flexibility scale (Martin and Rubin, 1995)
7. Beliefs about emotions scale (Rimes and Chalder, 2007)
8. Hospital Anxiety and Depression scale (Zigmond and Snaith, 1983)
9. Attention Control Scale (ACS) (Derryberry and Reed 2002)
10. The Penn State worry questionnaire (PSWQ) (Meyer, Miller, Metzger, & Borkovec, 1990)

Participants had the option of completing questionnaires in paper form or via a website link:

https://kings.onlinesurveys.ac.uk/t0_questionnaire-pack_information-processing-study
Questionnaire Pack

Information Processing Study

We are very grateful for your help in completing these questions. The information provided helps us to understand more about Chronic Fatigue Syndrome.

There are no right or wrong answers to these questions. We are most interested in your own personal views rather than those of your family or the people who are treating you.

➢ We would like you to answer the questions as honestly and as quickly as possible.

➢ If you find it hard to keep your mind on the statements, take a short break. The questionnaire may be completed over a day or two.

Please either post your completed questionnaire (stamped addressed envelope provided) or bring it with you to your scheduled session with a researcher.

Thank you very much

For office use:

For Research Assistant:

<table>
<thead>
<tr>
<th>Code:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date gathered:</td>
</tr>
<tr>
<td>Date entered:</td>
</tr>
<tr>
<td>Experimenter:</td>
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<tr>
<td>Entered Signature:</td>
</tr>
</tbody>
</table>
1. Are you: Male ☐ Female ☐

2. Do you have a diagnosis of Chronic Fatigue Syndrome (CFS)? Yes ☐ No ☐
   (if ‘no’ please continue to question 3)
   a. If ‘yes’ how long have you had CFS ..........years ............months
   b. Have you previously received any specialist treatment for CFS?
      Yes ☐ No ☐
      i. If ‘yes’ please state which treatment you received. ____________________________
      ii. Approximately how many treatment sessions did you receive? ______________
      iii. Where did you receive this treatment? __________________________
           Any additional information ____________________________

3. Do you have a diagnosis of any of the following:
   a. Irritable Bowel Syndrome ☐
   b. Chronic Pain/ Fibromyalgia ☐
   c. Anxiety disorder ☐
   d. Depression ☐

4. What is your age? ______

5. With which ethnic group do you identify?
   • White ☐
   • Black/African/Caribbean/Black British ☐
   • Mixed/Multiple ethnic groups ☐
   • Asian/Asian British ☐
   • Other ethnic group ☐ (please state)..................................................

6. Are you:
   • Single ☐
   • Married/ Living together ☐
   • Divorced/ separated ☐
   • Widowed ☐

7. What is the highest educational qualification you have received? Please tick one
   • None ☐
   • School (to the end of compulsory education) ☐
   • Tertiary (Secondary school to A-Levels) ☐
   • Vocational Qualification ☐
   • Higher (Undergraduate) ☐
   • Higher (Postgraduate) ☐
   • Other ☐ (please state)..................................................

   2
8. How many years have you been in education? (from beginning of compulsory education)

.............. years

9. Which of these best describes your current work status?

i) Employed

If yes:  
a) Is your employment: Fulltime  Part time  Casual  
b) Are you currently on sick leave? Yes  No  How long for? Months  Days  
c) How many sick days have you had in the last month? Weeks  Days  
d) Are you currently negotiating medical retirement? Yes  No

ii) Unemployed, looking for work

iii) Student, not in paid employment

iv) Homemaker, not working outside home

v) Retired

   Months  Days

vi) Disability/long-term sick leave

   Months  Days

   a) How long have you been on long-term sick leave?

We would like to know more about any problems you have had with feeling tired, weak or lacking in energy in the last month. If you have been feeling tired for a long time please compare yourself to how you felt when last well. Please answer ALL the questions simply by ticking the one answer that you think most nearly applies to you.

<table>
<thead>
<tr>
<th>CFQ</th>
<th>Less than usual</th>
<th>No more than usual</th>
<th>More than usual</th>
<th>Much more than usual</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have problems with tiredness?</td>
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<tr>
<td>2. Do you need to rest more?</td>
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<tr>
<td>3. Do you feel sleepy or drowsy?</td>
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<tr>
<td>4. Do you have problems starting things?</td>
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<td></td>
<td></td>
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<tr>
<td>5. Do you lack energy?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Do you have less strength in your muscles?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Do you feel weak?</td>
<td></td>
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<td></td>
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<tr>
<td>8. Do you have difficulty concentrating?</td>
<td></td>
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</tbody>
</table>
9. Do you make slips of the tongue when speaking?  

10. Do you find it more difficult to find the correct word?  

11. How is your memory?  

<table>
<thead>
<tr>
<th>SF-36</th>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifting or carrying groceries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Climbing several flights of stairs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Climbing one flight of stairs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bending, kneeling or stooping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking more than a mile</td>
<td></td>
<td></td>
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<tr>
<td>Walking half a mile</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Walking 100 yards</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bathing and dressing yourself</td>
<td></td>
<td></td>
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</tbody>
</table>

Using the scale provided please write down a number to represent the extent to which the following are impaired by your illness.  
For example in the first question, if you cannot work due to illness you would write ‘8’.

<table>
<thead>
<tr>
<th>Not at All</th>
<th>Slightly</th>
<th>Definitely</th>
<th>Markedly</th>
<th>Very severely impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

1. Because of my illness my ability to go to work or attend school/college is impaired

2. Because of my illness my home management is impaired (cleaning, shopping, cooking, child care, paying bills, etc)

3. Because of my illness my social & leisure activities are impaired (activities with other people, e.g. outings, visitors, parties, etc)
4. Because of my illness my **private** leisure activities are impaired (activities done alone, e.g. reading, gardening, walking alone, sewing, etc.)

5. Because of my illness my ability to form and maintain **relationships** is impaired

The following statements deal with your beliefs and feelings about your own behaviour. Read each statement and respond by circling the number that best represents your agreement with each statement.

<table>
<thead>
<tr>
<th>CF</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I can communicate an idea in many different ways.</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>I find it difficult to know how to respond in new and unusual situations.</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td>I believe that in many situations there are no totally right or wrong ways of reacting.</td>
<td>0 1 2 3 4</td>
<td></td>
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<tr>
<td>4</td>
<td>When I get stuck, it often seems hard for me to come up with a new way of looking at the problem at hand</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td>I can find workable solutions to seemingly unsolvable problems.</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td>When I am making decisions, I usually have lots of options.</td>
<td>0 1 2 3 4</td>
<td></td>
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<tr>
<td>7</td>
<td>I like to try out new solutions to problems.</td>
<td>0 1 2 3 4</td>
<td></td>
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<tr>
<td>8</td>
<td>I find it easy to predict how different courses of action may lead to different results.</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>9</td>
<td>I have many possible ways of behaving in any given situation.</td>
<td>0 1 2 3 4</td>
<td></td>
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<tr>
<td>10</td>
<td>I find it easy to transfer my knowledge about something to an entirely new situation.</td>
<td>0 1 2 3 4</td>
<td></td>
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<tr>
<td>11</td>
<td>I am willing to listen to other people's opinions.</td>
<td>0 1 2 3 4</td>
<td></td>
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<tr>
<td>12</td>
<td>I welcome new challenges because of the exciting possibilities they may bring.</td>
<td>0 1 2 3 4</td>
<td></td>
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</tbody>
</table>

**Please indicate how much you agree or disagree with the following statements about your current symptoms by ticking the appropriate box.**

Think about a time when you experience symptoms or signs of illness.

<table>
<thead>
<tr>
<th>VIEWS ABOUT YOUR SYMPTOMS</th>
<th>STRONGLY DISAGREE</th>
<th>DISAGREE</th>
<th>NEITHER AGREE NOR DISAGREE</th>
<th>AGREE</th>
<th>STRONGLY AGREE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA1</td>
<td>I am afraid that I will make my symptoms worse if I exercise</td>
<td></td>
<td></td>
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<tr>
<td>FA2</td>
<td>My symptoms would be relieved if I were to exercise</td>
<td></td>
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<tr>
<td>FA3</td>
<td>Avoiding unnecessary activities is the safest thing I can do to prevent my symptoms from worsening.</td>
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<td>-------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
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<tr>
<td>FA4</td>
<td>The severity of my symptoms must mean there is something serious going on in my body</td>
<td></td>
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<tr>
<td>FA9</td>
<td>Even though I experience symptoms, I don't think they are actually harming me.</td>
<td></td>
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<tr>
<td>FA10</td>
<td>When I experience symptoms, my body is telling me that there is something seriously wrong.</td>
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<tr>
<td>FA12</td>
<td>Physical activity makes my symptoms worse.</td>
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<tr>
<td>FA14</td>
<td>Doing less helps symptoms.</td>
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<tr>
<td>FA15</td>
<td>Symptoms are a signal that I am damaging myself.</td>
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<tr>
<td>FA16</td>
<td>I am afraid I will have more symptoms if I am not careful.</td>
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<tr>
<td>FA17</td>
<td>I should avoid exercise when I have symptoms.</td>
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<tr>
<td>C1</td>
<td>I worry that I may become permanently bedridden because of my symptoms</td>
<td></td>
<td></td>
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<tr>
<td>C2</td>
<td>I think that if my symptoms get too severe they may never decrease</td>
<td></td>
<td></td>
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<tr>
<td>C3</td>
<td>If I push myself too hard I will collapse</td>
<td></td>
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<tr>
<td>C4</td>
<td>My illness is awful and I feel that it overwhelms me</td>
<td></td>
<td></td>
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<tr>
<td>C5</td>
<td>If I overdo things it will cause a major relapse</td>
<td></td>
<td></td>
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<tr>
<td>C6</td>
<td>I will never feel right again</td>
<td></td>
<td></td>
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<tr>
<td>SF1</td>
<td>When I experience symptoms, I think about them constantly.</td>
<td></td>
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<tr>
<td>SF2</td>
<td>I worry when I am experiencing symptoms</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SF3</td>
<td>When I am experiencing symptoms it is difficult for me to think of anything else</td>
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<tr>
<td>SF5</td>
<td>I think a great deal about my symptoms</td>
<td></td>
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</tr>
<tr>
<td><strong>VIEWS ABOUT YOUR SYMPTOMS</strong></td>
<td><strong>STRONGLY DISAGREE</strong></td>
<td><strong>DISAGREE</strong></td>
<td><strong>NEITHER AGREE NOR DISAGREE</strong></td>
<td><strong>AGREE</strong></td>
<td><strong>STRONGLY AGREE</strong></td>
</tr>
</tbody>
</table>


We are interested in how you respond to or manage your symptoms when you experience illness or signs of symptoms. Listed below are a number of different responses that people may have to symptoms:

When you experience illness or signs of symptoms Please indicate how often you respond in the following ways by ticking the appropriate box.

<table>
<thead>
<tr>
<th>MANAGING SYMPTOMS</th>
<th>Never</th>
<th>Sometimes</th>
<th>Quite Often</th>
<th>Very Often</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2 I stay in bed to control my symptoms</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>L3 When I experience symptoms, I rest.</td>
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<tr>
<td>L4 I tend to avoid activities that make my symptoms worse</td>
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<tr>
<td>L7 I tend to nap during the day to control my symptoms</td>
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<tr>
<td>AL1 I tend to overdo things when I feel energetic</td>
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<td></td>
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<tr>
<td>AL2 I find myself rushing to get things done before I crash</td>
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<tr>
<td>AL3 I tend to overdo things and then rest up for a while</td>
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<tr>
<td>AL4 I tend to do a lot on a good day and rest on a bad day</td>
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<tr>
<td>L9 I sleep when I'm tired in order to control my symptoms</td>
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<tr>
<td>L10 I avoid making social arrangements in case I'm not up to it.</td>
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</tbody>
</table>
401

ACS
Enter the number that describes how typical or characteristic each item is of you, by circling the appropriate number next to each item.

1. It’s very hard for me to concentrate when there are noises around.
   1 2 3 4

2. When I need to concentrate and solve a problem, I have trouble focusing my attention.
   1 2 3 4

3. When I am working hard on something, I still get distracted by events around me.
   1 2 3 4

4. My concentration is good even if there is music in the room around me.
   1 2 3 4

5. When concentrating, I can focus my attention so that I become unaware of what’s going on in the room around me.
   1 2 3 4

6. When I am reading or studying, I am easily distracted if there are people talking in the same room.
   1 2 3 4

7. When trying to focus my attention on something, I have difficulty blocking out distracting thoughts.
   1 2 3 4

8. I have a hard time concentrating when I’m excited about something.
   1 2 3 4

9. When concentrating I ignore feelings of hunger or thirst.
   1 2 3 4

10. I can quickly switch from one task to another.
    1 2 3 4

11. It takes me a while to get really involved in a new task.
    1 2 3 4

12. It is difficult for me to coordinate my attention between the listening and writing required when taking down information.
    1 2 3 4

13. I can become interested in a new topic very quickly when I need to.
    1 2 3 4

14. It is easy for me to read or write while I’m also talking on the phone.
    1 2 3 4

15. I have trouble carrying on two conversations at once.
    1 2 3 4

16. I have a hard time coming up with new ideas quickly.
    1 2 3 4

17. After being interrupted or distracted, I can easily shift my attention back to what I was doing before.
    1 2 3 4
18. When a distracting thought comes to mind, it is easy for me to shift my attention away from it.  
1. Definitely  
2. Usually  
3. Not often  
4. Not at all

19. It is easy for me to alternate between two different tasks.  
1. Definitely  
2. Usually  
3. Not often  
4. Not at all

20. It is hard for me to break from one way of thinking about something and look at it from another point of view.  
1. Definitely  
2. Usually  
3. Not often  
4. Not at all

HADS
Emotions play an important part in most illnesses. This questionnaire is designed to help us know how you feel. Read each item and circle one of the replies below each item which comes closest to how you have been feeling during the past week. Don’t take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

1. I feel tense or ‘wound-up’:
   1. Most of the time  
   2. A lot of the time  
   3. From time to time, occasionally  
   4. Not at all

2. I still enjoy the things I used to enjoy:
   1. Definitely as much  
   2. Not quite as much  
   3. Only a little  
   4. Hardly at all

3. I get a sort of frightening feeling as if something awful is about to happen:
   1. Very definitely and quite badly  
   2. Yes, but not too badly  
   3. A little, but it doesn’t worry me  
   4. Not at all

4. I can laugh and see the funny side of things:
   1. As much as I always could  
   2. Not quite as much now  
   3. Definitely not so much now  
   4. Not at all

5. Worrying thoughts go through my mind:
   1. A great deal of the time  
   2. A lot of the time  
   3. From time to time but not too often  
   4. Only occasionally

6. I feel cheerful
   1. Not at all  
   2. Not often  
   3. Sometimes  
   4. Most of the time

7. I can sit at ease and feel relaxed
   1. As much as I ever did  
   2. Rather less than I used to  
   3. Definitely less than I used to

8. I feel as if I am slowed down:
   1. Nearly all the time  
   2. Very often  
   3. Sometimes  
   4. Not at all

9. I get a sort of frightened feeling like ‘butterflies’ in the stomach:
   1. Not at all  
   2. Occasionally  
   3. Quite often  
   4. Very often

10. I have lost interest in my appearance:
    1. Definitely  
    2. I don’t take as much care as I should  
    3. I may not take quite as much care as ever  
    4. I take just as much care as ever

11. I feel restless as if I have to be on the move:
    1. Very much indeed  
    2. Quite a lot  
    3. Not very much  
    4. Not at all

12. I look forward with enjoyment to things:
    1. As much as I ever did  
    2. Rather less than I used to  
    3. Definitely less than I used to
4. Hardly at all

13. I get sudden feelings of panic
   1. Very often indeed
   2. Quite often
   3. Not very often
   4. Not at all

14. I can enjoy a good book or radio or TV programme
   1. Often
   2. Sometimes
   3. Not often
   4. Very seldom
Please indicate the extent to which you agree with the following statements by **ticking** the associated box.

<table>
<thead>
<tr>
<th>BAE</th>
<th>Totally agree</th>
<th>Agree very much</th>
<th>Agree slightly</th>
<th>Neutral</th>
<th>Disagree slightly</th>
<th>Disagree very much</th>
<th>Totally disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It is a sign of weakness if I have miserable thoughts.</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2. If I have difficulties I should not admit them to others.</td>
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<tr>
<td>3. If I lose control of my emotions in front of others, they will think less of me.</td>
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<td>4. I should be able to control my emotions.</td>
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<tr>
<td>5. If I am having difficulties it is important to put on a brave face.</td>
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<td>6. If I show signs of weakness then others will reject me.</td>
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<td>7. I should not let myself give in to negative feelings.</td>
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<td>8. I should be able to cope with difficulties on my own without turning to others for support.</td>
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<tr>
<td>9. To be acceptable to others, I must keep any difficulties or negative feelings to myself.</td>
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<tr>
<td>10. It is stupid to have miserable thoughts.</td>
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<tr>
<td>11. It would be a sign of weakness to show my emotions in public.</td>
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<tr>
<td>12. Others expect me to always be in control of my emotions.</td>
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</tbody>
</table>
Instructions: Rate each of the following statements on a scale of 1 ("not at all typical of me") to 5 ("very typical of me"). Please do not leave any items blank.

<table>
<thead>
<tr>
<th></th>
<th>Not at all typical of me</th>
<th>Very typical of me</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. If I do not have enough time to do everything, I do not worry about it.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>2. My worries overwhelm me.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>3. I do not tend to worry about things.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>4. Many situations make me worry.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>5. I know I should not worry about things, but I just cannot help it.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>6. When I am under pressure I worry a lot.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>7. I am always worrying about something.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>8. I find it easy to dismiss worrisome thoughts.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>9. As soon as I finish one task, I start to worry about everything else I have to do.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>10. I never worry about anything.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>11. When there is nothing more I can do about a concern, I do not worry about it any more.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>12. I have been a worrier all my life.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>13. I notice that I have been worrying about things.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>14. Once I start worrying, I cannot stop.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>15. I worry all the time.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>16. I worry about projects until they are all done.</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
</tbody>
</table>

Thank you very much for your help.
Appendix C. Visual Probe Task Materials

Two sets of materials were developed for the Visual Probe Task (MacLeod, et al., 1986). Stimuli appeared on screen as per Figure 6 below.

![Figure 6 Trial on the Visual Probe Task](image)

**Practice Stimuli** (16 trials)

<table>
<thead>
<tr>
<th>apex</th>
<th>duet</th>
</tr>
</thead>
<tbody>
<tr>
<td>whirl</td>
<td>zooms</td>
</tr>
<tr>
<td>cheese</td>
<td>planes</td>
</tr>
<tr>
<td>watches</td>
<td>storing</td>
</tr>
<tr>
<td>accurate</td>
<td>variable</td>
</tr>
<tr>
<td>extrinsic</td>
<td>countable</td>
</tr>
<tr>
<td>matchstick</td>
<td>shortbread</td>
</tr>
<tr>
<td>teal</td>
<td>gilt</td>
</tr>
<tr>
<td>elect</td>
<td>debut</td>
</tr>
<tr>
<td>binary</td>
<td>animal</td>
</tr>
<tr>
<td>strands</td>
<td>sprayed</td>
</tr>
<tr>
<td>cellular</td>
<td>tropical</td>
</tr>
<tr>
<td>scrapbook</td>
<td>fountain</td>
</tr>
<tr>
<td>typewriter</td>
<td>sandwiches</td>
</tr>
<tr>
<td>quiz</td>
<td>lace</td>
</tr>
<tr>
<td>delta</td>
<td>urban</td>
</tr>
</tbody>
</table>
**Stimuli for the main task**

(two sets of 12 matched word pairs)

<table>
<thead>
<tr>
<th>Illness related words</th>
<th>Neutral Words</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Set 1.</strong></td>
<td></td>
</tr>
<tr>
<td>bedridden</td>
<td>buttercup</td>
</tr>
<tr>
<td>collapse</td>
<td>transmit</td>
</tr>
<tr>
<td>immobilised</td>
<td>calligraphy</td>
</tr>
<tr>
<td>fatigue</td>
<td>pockets</td>
</tr>
<tr>
<td>exhausted</td>
<td>messenger</td>
</tr>
<tr>
<td>disabled</td>
<td>calendar</td>
</tr>
<tr>
<td>drained</td>
<td>pitched</td>
</tr>
<tr>
<td>limited</td>
<td>created</td>
</tr>
<tr>
<td>aches</td>
<td>domes</td>
</tr>
<tr>
<td>anxious</td>
<td>whistle</td>
</tr>
<tr>
<td>Incapacitated</td>
<td>infinitesimal</td>
</tr>
<tr>
<td>painful</td>
<td>trumpet</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Illness Related Words</th>
<th>Neutral Words</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Set 2</strong></td>
<td></td>
</tr>
<tr>
<td>impaired</td>
<td>polished</td>
</tr>
<tr>
<td>restricted</td>
<td>newspapers</td>
</tr>
<tr>
<td>debilitating</td>
<td>articulation</td>
</tr>
<tr>
<td>housebound</td>
<td>grapevines</td>
</tr>
<tr>
<td>weak</td>
<td>zone</td>
</tr>
<tr>
<td>powerless</td>
<td>triangles</td>
</tr>
<tr>
<td>unwell</td>
<td>russet</td>
</tr>
<tr>
<td>frustrated</td>
<td>settlement</td>
</tr>
<tr>
<td>tired</td>
<td>brief</td>
</tr>
<tr>
<td>disheartened</td>
<td>stewardesses</td>
</tr>
<tr>
<td>feeble</td>
<td>inland</td>
</tr>
<tr>
<td>shattered</td>
<td>brochures</td>
</tr>
</tbody>
</table>
Appendix D. Ambiguous Scenarios Recognition Task Materials

The task
This interpretative bias task is based on the assessment phase of Mackintosh & Mathews (2000) interpretative bias (IB) re-training task. A title is present on screen followed by a short scenario (4 lines of text) describing an ambiguous scenario. This is followed by a comprehension question. Participants are then asked to rate how pleasant or unpleasant the imagined scenarios was; 1 = extremely unpleasant, to 9 = extremely pleasant.

Later, after the participant has read all 10 scenarios they are presented with a ‘recognition test’. The titles of the scenarios are present in sequential order and the participant is asked to rate four statements in terms of how similar they are to the original text. Instructions were ‘how similar is this sentence to the original description you read?’ Ratings were from 1=very different in meaning, to 4 =very similar in meaning. The statements contain a positive interpretation, a negative interpretation as well as positive and negative foils. The order of the four statements are randomized for each ‘recognition test’.

In the following examples:
1. Positive interpretation
2. Negative interpretation
3. Positive foil (this is positive false information and is not a true interpretation of the text; if it is consistently endorsed it shows a general bias for any positive information)
4. Negative foil (again this is false information and is not a true interpretation of the text; if it is consistently endorsed it shows a general bias for any negative information)

For this project 3 material sets were developed as it was anticipated that CFS participants would be tested on 3 occasions; pre-treatment, mid-treatment and post-treatment. However, due to practicality issues the mid-treatment assessment was dropped. Participants received two different sets of IB materials on two occasions; pre-treatment and post-treatment. Set of materials were randomized to avoid any potential order effects should one set of materials produce. Materials were developed to tap into key themes identified during the stimuli development phase detailed in Chapter 4.

Q.1
Set 1
Theme: Effort
Title: Gardening
On a beautiful sunny day, you decided to do some gardening. You spent most of the day weeding. A week later you’re looking at the garden and think about how you felt after your last gardening session.
Did you plant rose bushes?
1. You remember how satisfying if felt to have the garden looking good.
2. You remember how stiff and sore you felt for a number of days afterwards.
3. You completed the gardening much quicker than you expected.
4. You had to stop gardening, as you were feeling unwell.
Set 2
Title: Phone Conversation with a Friend
You are chatting to a friend on the phone who you haven’t spoken to in quite some time. You have a lot to catch up on and the conversation lasts almost an hour. A few weeks later you have a missed call from your friend and you think about how you felt after the last phone call with them.
Did a miss a call from a friend?
1. You had a nice conversation and your friend had a lot to say.
2. You had problems following the conversation, as your concentration is poor.
3. You had a lovely lunch with your friend and chatted for hours.
4. Your friend rudely interrupted you in order to end the phone call.

Set 3
Title: Babysitting for your niece and nephew
Last week you babysat your niece and nephew and played games with them for hours. The following week your sibling calls and asks for a favour. They ask if you would be able to babysit for the afternoon. You think about how you felt after babysitting last week.
Did you play games with the children?
1. You remember how much you enjoyed playing with the children.
2. You remember how exhausted you were by the end of the day.
3. You remember how excited the children were to go out for dinner.
4. You remember how poorly you were after catching a cold from your niece.

Q.2
Theme: Effort
Set 1
Title: Weekend Break
You and your partner booked to go on a weekend break. You stayed for 2 nights and fitted a lot in. You ended up doing a lot of sightseeing around the city. As you travel home you think about how you found the weekend.
Did you go on a break with a friend?
1. You had an enjoyable and interesting weekend.
2. You found the weekend exhausting.
3. Your partner booked the holiday as a surprise.
4. You had to come home from the holiday early.

Set 2:
Title: Cleaning the House
Last week you spent a day cleaning the house. You hoovered all the carpets in the house and mopped the kitchen floor. A week later you notice the carpets are dirty and need hoovered again. You think about how you felt after the last time you cleaned.
Q. Did you clean the windows?
1. You felt pleased with how nice the house looked after cleaning.
2. You felt stiff and painful for days as you pushed your body too far.
3. You completed the cleaning quicker than you had expected.
4. You were unable to clean last week as you hurt your back.
Set 3.
Title: Team Away Day
You have a new boss at work and they have arranged a team away day. The day involved a lot of team building activities, which required your attention and concentration. As you travel home you think about how you found the activities.
Did you go away for a weekend?
1. You found the team building activities engaging.
2. You found it difficult keeping up with all the activities.
3. You led your team to victory in most of the activities.
4. You lost most of the tasks for your team.

Q.3
Theme: Effort
Set 1
Title: Cleaning the Windows
You decide to clean inside the windows today. You finish cleaning the windows downstairs quicker than you expected and move on to clean the upstairs windows. While climbing the stairs your notice how your shoulders and arms feel.
Did you clean the inside windows?
1. Your shoulders and arms feel like they have had a good workout.
2. Your shoulders and arms feel stiff and painful after over doing things.
3. You cleaned both the inside and outside windows quicker than expected.
4. You fell off a ladder after cleaning the outside windows.

Set 2.
Title: Moving House
You are moving house and have been packing up boxes all day. By the end of the day you have all your items boxed and ready for the move tomorrow. You go to bed that night and know how you will feel in the morning.
Are you moving house tomorrow?
1. You feel excited to move into the new house.
2. You feel stiff and painful after overdoing things.
3. Your friend helped you with your packing.
4. You had to delay the move, as you were ill.

Set 3.
Title: The morning of the holiday
Tomorrow you are going on holiday for a week. You have had a very busy day packing and getting things organized. You set your alarm for the next morning for your flight. You go to bed that night knowing how you will feel when the alarm goes off in the morning.
Did you set your alarm for the morning?
1. When the alarm goes off you will feel excited about the holiday.
2. When the alarm goes off you will feel exhausted and unrefreshed.
3. You don't need to set an alarm because you will wake up early anyway.

4. You forgot to set the alarm the night before and miss your flight.

Q.4
Set 1
Theme: Catastrophizing
Title: Walking the neighbour’s dog
Your neighbour has asked you to walk their dog while they are away on holiday. The dog needs to be walked in the morning and you have been enjoying this activity the last few days. This morning you wake up feeling exhausted. You think about how you will feel if you walk the dog.
Have you been asked to look after the neighbour’s plants?
1. You will feel refreshed after the walk.
2. Your health will suffer if you walk the dog.
3. You jump out of bed to walk the dog.
4. You haven’t been able to walk the dog for the last few days.

Set 2:
Title: Walking to Work
For the last few weeks, you have been walking to work rather than getting the bus. You have been enjoying this short walk and find it refreshing. This morning you wake up feeling physically worn-out. You think about how you will feel if you walk to work.
Did you previously get the train to work?
1. You think you will feel refreshed after the walk.
2. You know you will feel worse after pushing yourself too much.
3. You decide to jog to work instead of walk.
4. You decide to call in sick to work as you are too ill to go in.

Set 3
Title: Grocery Shopping
You have spent the afternoon shopping and bought some groceries. You carry the bags of shopping home which are quite heavy. By the time you get home you feel drained. You manage to go to bed early and know how you will feel in the morning.
Did you carry the shopping home?
1. In the morning you will feel refreshed after getting an early night.
2. In the morning your muscles will hurt and you will be exhausted.
3. When you get home you make dinner and watch television.
4. When you get home you fall asleep on the sofa.

Q.5
Theme: Catastrophizing
Set 1
Title: Falling asleep on the sofa
You were extremely tired last night and fell asleep on the sofa. You wake in the morning feeling uncomfortable. Your body and neck ache. You know how your body will feel when you get up.
Did you fall asleep on the sofa?
1. Your body will feel better once you have walked around and stretched.
2. Your body will be in pain and you will be hardly able to walk.
3. Your body will feel energized as you had a comfortable sleep in bed.
4. Your body will be bruised as you fell off the sofa in your sleep.

Set 2.
Title: The Car Journey
You are going to visit family who live a long drive away. As you sit in the passenger seat you fall asleep and when you wake up you have arrived at your destination. Your legs feel cramped and uncomfortable. You know how your legs will feel when you are out of the car.
Did you fall asleep in the car?
1. Your legs will feel better once you have walked around and stretched.
2. Your legs will be painful and you will need to rest.
3. Your legs will feel fine as you took plenty of breaks during the drive.
4. Your legs will be bruised as you fell getting out of the car.

Set 3
Title Working on the computer
You have spent the day doing some work on the computer. By the end of the day your eyes feel strained from staring at the computer screen. When you have finished your work you decide to close your eyes for half an hour. You know how your eyes will feel after your rest.
Did you play games on the computer?
1. Your eyes will feel better after a short rest.
2. Your eyes will continue to feel heavy and tired.
3. Your eyes do not need a rest as you took plenty of breaks.
4. Your eyes feel strained as you did not wear your glasses.

Q.6
Theme: Catastrophizing
Set 1
Title: Public Transport
You are running late for an appointment and have taken public transport to get there. When you arrive at the station you find the lifts and escalators are out of order. Passengers are advised to take the stairs or get off at the next stop for disabled access. You think about what will happen if you take the stairs.
Are you running late for your appointment?
1. You think the stairs will be effortful but quicker.
2. You think if you take the stairs you could collapse.
3. You walk briskly to your appointment.
4. You fainted on the train on the way to your appointment.

Set 2
Title: Stuck in Traffic
You are running late for a meeting because you are stuck in traffic. You realize if you park the car here it would be a 30 minute walk to the building where your meeting is. You think about what would happen if you walked at a quick pace the whole way there. Have you taken a taxi to the meeting?
1. You will make the meeting on time if you walk quickly.
2. You would be too exhausted to attend the meeting if you walked.
3. You will be on time for the meeting as the taxi driver knows a shortcut.
4. You cancel the meeting as the car has broken down.

Set 3
Title: Rushing to get the train
You are running late for your train. You arrive at the station with a few minutes to spare. The ticket inspector tells you that if you quickly climb the two flights of stairs to the platform you should be able to make the train on time. You know what will happen if you rush up the stairs. Are you in a hurry to get the train?
1. If I run up the stairs you will be out of breath but will make the train.
2. If I run up the stairs I will pay for it later.
3. I have time to sit down and get a coffee in the train station.
4. The ticket inspector tells you that you have just missed the last train.

Q.7
Theme: Catastrophizing
Set 1
Title: The deadline
You are working towards an important deadline for tomorrow and have quite a bit to get done today. By the middle of the day you have got a lot of your work done however you have developed a headache so you take a pain killer tablet. You carry on working and you know how you will feel by the end of the day. Is the deadline today?
1. By the end of the day you will feel pleased to have your work done.
2. By the end of the day you will feel physically awful.
3. You meet the deadline early and help a colleague with their work.
4. Your colleague comments that you look awful and insists you go home immediately.

Set 2
Title: A Busy Morning at Work
You have had a very productive morning at work and have got a lot of jobs done. You take an hour lunch break and realize you have been rushing around all morning. You get ready to go back to work and think about how you will feel by the end of the day.

Did you skip lunch?
1. By the end of the day you will feel pleased to have achieved many of your jobs.
2. By the end of the day you will feel physically drained from rushing around.
3. By the end of the day you have met all your deadlines and are congratulated by your boss.
4. By the end of the day you have developed a headache and decide to take tomorrow off.

Set 3
Title: Family in Town
Some family are in town and you have arranged to spend the day with them. You have an enjoyable morning showing them the local attractions. You go for lunch together and realize you are quite tired from this morning’s activities. As you leave the café you think about how you will feel by the end of the day.

Did you go to a café for lunch?
1. You feel pleased to have shown them around.
2. You feel physically exhausted from the day.
3. You feel pleased that they stayed the night.
4. You feel anxious that you have offended them.

Q.8
Theme: Misattribution of emotions and sensations
Set 1
Title: Walk with a friend
You have arranged to go for a walk with a friend. You meet at the park and your friend suggests taking the longer and more scenic route around the lake. Some of the walk is uphill and as you climb up a particularly steep hill you notice your heart rate increase. It’s easy to know what that means.

Did you walk around the lake?
1. Your increased heart rate is a normal sign of exercise.
2. Your increased heart rate is a sign you are over doing things.
3. Your friend comments on how fit you are.
4. As you climb the hill you slip and hurt your knee.

Set 2
Title: New Neighbour
A neighbour has recently moved in next door and they come over to introduce themselves. A few days later you bump into them in the local shop. You say hello but you have trouble remembering their name. You know why you can’t recall their name.

Did you meet your neighbor in a shop?
1. You can’t recall their name because you have only recently met them.
2. You can’t recall their name due to your on-going memory problems.
3. They reintroduce themselves and you have a long chat in the shop.
4. They ignore you in the shop even though you said hello.
Set 3
Title: Market research interview
You have agreed to do a telephone interview with a market research company. The telephone interview lasts an hour. You have to think hard about some of your answers. When you get off the phone you reflect on how the interview went.
Did the research company send out a survey?
1. The interview was interesting and you had a lot to say.
2. The interview was draining and you had problems with your memory.
3. The interviewer thanks you for the best interview they have done.
4. The interviewer abruptly tells you the interview took too long.

Q.9
Theme: Misattribution of emotions and sensations
Set 1
Title: Catching the Bus
This morning you rush to get a bus on time and you don’t manage to have any breakfast. You just catch the bus, but suddenly notice you feel light headed and weak. You know why you are feeling like this.
Did you have toast for breakfast?
1. You feel light headed because you haven’t eaten.
2. You feel weak and light headed because you over exerted yourself.
3. You feel delighted to have bumped into a friend on the bus.
4. You feel awful and end up missing the bus.

Set 2
Title: Going to bed after a busy day
You have had a very busy day and have been on your feet a lot. You don’t get to bed until later than usual and when you lie down in bed you notice your body feels heavy and you sink into the mattress. You know why your body feels like this.
Have you stayed up later than usual?
1. Your body feels heavy because your muscles are relaxing.
2. Your body feels heavy because you have over exerted yourself.
3. You go to bed early and fall asleep immediately.
4. You can’t sleep for hours and have to take a sleeping tablet.

Set 3
Title: The exercise class
You have started going to a beginners exercise class once a week at your local leisure centre. After a month you feel fitter and decide to enroll in the intermediate class. After attending the first intermediate class you notice your arms and legs are sore. You think about what this means.
Do you have a personal trainer?
1. Your limbs will be sore until you get used to your new exercise regime.
2. You will be bed ridden for days as you have pushed your body too far.
3. Your arms and legs feel stronger after a week of your new exercise regime.
4. You decrease your exercise regimen as you are not fit enough to exercise twice a week.

Q.10
Theme: Misattribution of emotions and sensations

Set 1
Title: The exercise regime
You decide that you must start to exercise more. For the next week you take a little more exercise each day. After several weeks, you are walking faster and further and decide to see how far you can push yourself, when you notice your breathing is laboured.

Have you been exercising for several weeks?
1. Walking faster and further than usual, you have to breathe harder and deeper.
2. Pushing yourself too hard you cannot get enough air and can hardly breathe.
3. Pushing yourself more than usual, you feel your walking is much easier.
4. You push yourself so hard you strain a muscle and hurt yourself.

Set 2.
Title: At the Cinema
You have gone to the cinema with a friend. Your friend picked the film and you do not find it particularly interesting. Half way through the film you notice you are finding it difficult to keep your attention on the story line. You know what this means.

Did your friend pick the film?
1. You find the film boring and it does not hold your attention.
2. Your problems with concentration mean you cannot follow the film.
3. You enjoy the film immensely and are glad you chose it.
4. You leave the film half way through as you find it offensive.

Set 3:
Title: Late night out
Yesterday you attended your friend’s birthday party. You were having such a good time you ended up staying out later than you had planned. When you wake up in the morning you reflect on your decision to stay out late.

Did you attend a family party?
1. You are glad you stayed out as you had a good time.
2. You regret staying late as you will now be in bed all day.
3. You are delighted to have met so many new people at the party.
4. You are very ill from the food at the dinner party.