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

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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) to review the evidence for information processing biases in CFS, (b) determine the nature of these biases; i.e. the stages cognitive biases occur 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.

Key Words: information processing, illness representations, symptom interpretation, attentional bias, interpretive bias, chronic fatigue syndrome, Cognitive behavioural model

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 Commonsense 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 commonsense 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, Krahe & 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 presented 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.

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 symptomology 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.

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 ($p = .059$). 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 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 and 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 & 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 ($p = .055$) 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 ($p = .680$) 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 ($p=.064$). 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 ($p=.054$); 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 scores particularly low in 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 (Cresswell & 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, preattentive 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 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, & Bleijenbergh, 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 Ryckeghem, 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 behavioral 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.

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Table 1. Cognitive processing paradigms

Paradigm	Cognitive mechanism	Proposed type of processing
Modified Emotional Stroop task	Interference effect (lack of inhibitory control) of emotive words on attention	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.
Visual Probe task	Attentional bias towards threatening over neutral stimuli	Stimuli presented for <500ms taps into early automatic orientation of attention. Stimuli presented for >500ms taps into later strategic processing.
Exogenous Cueing task	Orientation of attention	500ms is viewed as having potential for automatic and strategic processing.
On-line interpretative bias task	Interpretation of ambiguous stimuli when first encountered	More automatic, spontaneous processing
Off-line interpretative bias task	Interpretation of ambiguous stimuli when there is opportunity for reflection	Allows for more elaborative processing

Table 2. Sample Characteristics

Author, Year	Diagnostic criteria	Participants, N (male)	HADS Depression Mean (SD)	HADS Anxiety, Mean (SD)	Illness Duration, Years (SD)	Symptom measure	Symptomology, Mean (SD)
Creswell, 2002	Oxford Diagnostic Criteria	CFS, 24 (4)	6.29 (3.37)	9.42 (3.94)	3.62 (2.2)	NR	-----
		Diabetes, 20 (10)	3.65 (3.18)	6.35 (3.18)	10.96 (6.88)		
		HC, 24 (4)	1.96 (1.92)	5.71 (2.49)	$p < 0.001$		
Moss-Morris, 2003	Diagnosis with the CDC criteria in the past year	CFS, 25 (3)	7.21 (2.38)	7.63 (3.89)	11.25 (8.75)	PFRS	118.09 (30.09)
		HC, 24(3)	2.38 (2.59)	5.21 (3.16)			19.29 (15.26)
			$p < 0.01$	$p = 0.05$			$p < 0.001$
Papitsch, 2005 (unpublished)	CDC criteria	CFS, 27 (7)	4.96 (1.93)	9.19(4.39)	4.11 (4.00)	FSS	6.22 (0.53)
		CFS/D, 21 (5)	11.0(1.67)	12.0(3.26)	2.68 (2.99)		6.46 (0.43)
		HC, 21 (5)	1.33(1.8)	3.910(2.84)			2.73 (0.81)
			$p < 0.001$	$p < 0.001$			$p < 0.001$
Gillings, 2007 (unpublished)	Oxford criteria	CFS, 26 (8)	6.57 (4.14)	7.35 (4.06)	NR	NR	-----
		Arthritis, 36 (4)	5.29 (3.60)	7.65 (4.12)			

Author, Year	Diagnostic criteria	Participants, N (male)	HADS Depression Mean (SD)	HADS Anxiety, Mean (SD)	Illness Duration, Years (SD)	Symptom measure	Symptomology, Mean (SD)
		HC, 27 (5)	1.73 (2.32)	5.33 (3.32)			
			$p < 0.001$	$p < 0.01$			
Hou, 2008	CDC criteria	CFS, 11 (3)	7.00 (5.33)	7.70 (4.72)	NR	PFRS	121.9 (58.68)
		HC, 17 (6)	2.71 (2.73)	5.76 (3.85)			38.83 (32.52)
			$p < 0.001$				$p < 0.01$
Arroll, 2009 (unpublished)	CDC criteria	CFS, 21 (5)	-----	-----	-----	NR	-----
		Low Symptoms, 14	6.00 (2.08)	7.14 (3.46)	15.82 (10.63)		
		High Symptoms, 7	8.29 (4.75)	9.71 (5.28)	15.79 (14.72)		
		HC, 10 (2)	-----	-----	-----		
Martin, 2010	CDC criteria	CFS, 33 (16)	5.97 (3.71)	8.25 (3.48)	7.6 (6.7)	NR	-----
		HC, 33 (11)	3.72 (2.30)	8.44 (3.41)			
			$p < 0.01^\dagger$	†			
Hou, 2014	CDC diagnosis within 6 months	CFS, 27(8)	9.6 (3.7)	10.0 (4.0)	5.6 (5.2)	CFQ	28.9 (3.3)
		HC, 35 (15)	1.9 (2.8)	4.5 (2.8)	-----		-----

Author, Year	Diagnostic criteria	Participants, N (male)	HADS Depression Mean (SD)	HADS Anxiety, Mean (SD)	Illness Duration, Years (SD)	Symptom measure	Symptomology, Mean (SD)
			$p < 0.001$ †	$p < 0.001$ †			

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 (Trudie 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 3. Summary of Attentional Bias Results

Author, Year	Task	Stimuli			Main between group findings	Quality Score
		Stimuli Type	Stimuli	Masked		
		Duration				
Creswell, 2002	Modified Stroop (card)	Positive and negative personally descriptive words v. neutral words	Until response	No	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 ($p=.059$)	12
Moss-Morris, 2003	Modified stoop (card)	CFS related words v. depression words v. neutral words	Until response	No	No attentional bias ($p=.42$)	14
Gillings, 2007 (unpublished)	Modified Stroop (computer)	CFS/ME related words v. negative emotional words v. neutral words	Until response	No	No attentional bias ($p>.05$)	11
Papitsch, 2005 (unpublished)	Dot-probe (computer)	Fatigue, illness and depression relevant words v. neutral words v. positive words	500ms	No	An attentional bias in the CFS/D group for illness words compared to HC ($p=.05$). No other group differences.	10

Author, Year	Task	Stimuli			Main between group findings	Quality Score
		Stimuli Type	Stimuli	Masked		
Hou, 2008	Dot- Probe (computer)	Health threat words and pictures v. neutral words and pictures	500ms	Yes	CFS group had an attentional bias towards threat words compared to HC ($p < .01$).	14
Arroll, 2009 (unpublished)	Modified Stroop (computer)	Symptom words v. neutral words	Until response	No	CFS group did not differ from HC in Stroop interference effect ($p > .05$).	11
Martin, 2010	Exogenous cueing task (computer)	Illness words v. social threat words v. neutral words	100ms	Yes	No attentional bias ($p = .412$)	15
Hou, 2014	Dot- Probe (computer)	Health threat words and pictures v. neutral words and pictures	500ms and 1250ms	Yes	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 ($p < .001$).	15

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

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

Author, Year	Task	Stimuli		Main findings	Quality Score
		Priming Stimuli	Target Stimuli		
		and a dot-probe task using the same stimuli.	or depression related. Analysed for generating the same words as in the first word stem task.		
Papitsch, 2005 Study 2, Analysis 2 (unpublished)			Analysed for proportion and type of words generated which were not presented in the previous dot-probe task.	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.	9
Martin, 2010	Lexical decision task	60 homophones with illness, social threat or neutral interpretations.	4 types of target stimuli; non-word, unrelated word, related non-threat word and related threat word.	No interpretative bias in CFS group compared to controls ($p=.680$)	15

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.