**The presence of attentional and interpretation biases in patients with severe MS-related fatigue**

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## Abstract

*Objective:* Severe fatigue is a prevalent and disabling symptom in Multiple Sclerosis (MS). This study tested if a fatigue and physical activity-related attentional bias (AB), and a somatic interpretation bias (IB) is present in severely fatigued patients with MS, compared to healthy controls and patients with chronic fatigue syndrome (CFS/ME).

*Method*: Severely fatigued patients with MS or CFS/ME and healthy controls completed a Visual Probe Task (VPT) assessing fatigue and physical activity-related AB, and an IB task that assesses the tendency to interpret ambiguous information in either a somatically threatening way or in a more neutral manner. The VPT was completed by 38 MS patients, 44 CFS/ME patients, and 46 healthy controls, the IB task by respectively 156, 40 and 46 participants.

*Results:* ANOVA showed no statistical significant group differences in a fatigue-related AB or physical activity-related AB (omnibus test of interaction between topic*condition: $F_{2,125}$ = 1.87; $p$ = .159). Both patient groups showed a tendency to interpret ambiguous information in a somatically threatening way compared to healthy controls ($F_{1,2}$ = 27.61, $p$ < .001). This IB was significantly stronger in MS patients compared to ME/CFS patients. IB was significantly correlated with cognitive responses to symptoms in MS patients.

*Conclusion*: MS patients tend to interpret ambiguous information in a somatically threatening way. This may feed into unhelpful ways of dealing with symptoms, possibly contributing to perpetuation of severe fatigue in MS.

*Keywords*: attentional bias, interpretation bias, fatigue, multiple sclerosis

**Data availability statement**

Requests for data will be reviewed by the principal investigators of the study. Data transfer is possible with permission of the Medical Ethical Board and after signing a data sharing agreement.

**Ethical standards**

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. The study has been approved by the medical ethics committee of the Amsterdam University Medical Centers, VU University Medical Center.

**Introduction**

Multiple Sclerosis (MS) is a neurodegenerative disease characterized by demyelination, axonal loss and inflammation of the central nervous system, causing a variety of symptoms such as motor weakness, sensory deficits, impaired balance and fatigue. The disease course shows great variability and is largely unpredictable. Chronic, severe fatigue is a highly prevalent (75-90%) and burdensome symptom in MS (Goërtz et al., 2021; Kister et al., 2013; Lerdal et al., 2007; Minden et al., 2006; Weiland et al., 2015). Although there are many definitions of fatigue, The Multiple Sclerosis Council for Clinical Practice Guidelines defines MS-related fatigue as "a subjective lack of physical and/or mental energy that is perceived by the individual (or caregiver) to interfere with usual and desired activities"(Multiple Sclerosis Council for Clinical Practice Guidelines, 1998) Research suggests that the aetiology of fatigue in MS is likely to be multifactorial (Braley & Chervin, 2010). In a cognitive behavioural model of MS-related fatigue, Van Kessel and Moss-Morris proposed that whereas disease-specific factors, such as neurodegeneration and inflammation, may initially trigger fatigue, cognitive and behavioural factors, e.g. viewing fatigue as uncontrollable or a sign of bodily damage, symptom-focussing or all-or-nothing behaviour, play a role in maintaining fatigue (van Kessel & Moss-Morris, 2006). Cognitive behavioural therapy (CBT) addressing these factors has been found effective in decreasing fatigue severity in MS patients (de Gier, Beckerman, et al., 2023; Moss-Morris et al., 2019; van den Akker et al., 2017).

In the cognitive model of persistent physical symptoms, automatic attentional and cognitive processes, such as selectively attending to somatic information and habitually interpreting physical sensations as health-threatening, have been proposed to play a role in perpetuating

fatigue (Deary, Chalder, & Sharpe, 2007; Van den Bergh et al., 2017). A salient and often threatening stimulus (i.e. pain) may automatically capture attention (attentional bias). The salience of stimuli can also be influenced by underlying cognitive representations. A study of chronic pain found that patients who had more fearful cognitions about pain attended more to pain (Crombez et al., 2013). Whilst pain is intrinsically salient, it is likely that for someone with a chronic condition who experiences ongoing and debilitating fatigue, fatigue itself becomes salient and threatening. Furthermore, negative cognitive illness-representations may influence the way patients interpret ambiguous situations, leading to a somatic interpretation bias (IB). IB refers to the tendency to interpret ambiguous information in a negative or threatening way as opposed to in a benign or positive way.

In individuals with MS, the relapsing-remitting and often progressive but unpredictable nature of the illness and the accompanying feelings of insecurity may promote information processing biases, such as scanning for signals of potential disease exacerbation (attentional bias) and interpreting somatic sensations in a threatening way (IB). According to Van den Bergh et al.'s model of symptom experience (2017), interpretations of bodily sensations are based on expectations based on past experiences. MS patients are likely to have had negative or threatening somatic experiences such as disease exacerbations, somatosensory deficits, pain, impaired balance or motor weakness, and the chances of experiencing this again are realistic in the context of MS. In a recent study, MS patients reported more damage beliefs compared to other patients with long-term conditions, such as myalgic encephalomyelitis /chronic fatigue syndrome (ME/CFS) and Type 1 Diabetes Mellitus (de Gier, Picariello, et al., 2023). When this prediction generalizes to more commonly occurring bodily sensations, such as fatigue, this may lead to an overestimation of threat, which may negatively affect someone's ability to cope with these symptoms.

Experimental methods have been developed to tap into these more implicit processes and have been used to study attentional and interpretation biases in patients with emotional disorders (Mathews & MacLeod, 2005; Van Bockstaele et al., 2014), functional neurological disorder (FND) (Keynejad et al., 2020), chronic pain and fatigue (Hughes et al., 2016; Van Ryckeghem et al., 2019).

Several studies in ME/CFS, which is defined by severe and debilitating fatigue with no known underlying pathology, found people with ME/CFS to have a tendency to direct attention towards fatigue-related stimuli, when compared to healthy individuals (Hughes et al., 2016; Hughes et al., 2017; Hughes et al., 2018). This AB in CFS patients is thought to reflect a strategy to continually monitor threats in the environment, in this case bodily signals, as opposed to an initial orientation or hypervigilance to threat which is found in patients with anxiety disorders (Hughes et al., 2016; Hughes et al., 2017). These CFS studies focused on biased attention *towards* illness-related stimuli, however, an AB may also serve as an *avoidance* of threatening stimuli, in which case the attention is involuntarily directed *away* from the stimulus. Some evidence has been found for an AB away from physical activity-related stimuli in ME/CFS patients (van Heck, 2019). Fear-avoidance (avoiding activity out of fear for fatigue) is considered a perpetuating factor in chronic fatigue, and its reduction was found to be a mediator in the effect of CBT on fatigue severity in ME/CFS (Chalder et al., 2015) and across chronic medical conditions (de Gier, Picariello, et al., 2023).

In ME/CFS studies patients show a negative IB for ambiguous somatic/illness-related information (Hughes et al., 2016; Hughes et al., 2017). These negative, illness-related interpretations were found to be associated with unhelpful responses to fatigue such as

catastrophic thinking styles, fear-avoidance and all-or-nothing behaviour (Hughes et al., 2017).

To date, however, it is unknown if similar information processing biases play a role in chronic fatigue in medical conditions such as MS. The goal of the present study was therefore to investigate if similar attentional and interpretation biases are present in severely fatigued patients with MS, as in patients with ME/CFS, compared to healthy controls. In addition, to gain some preliminary insight in the clinical relevance of a potential information processing bias in MS, it is interesting to study if these unintentional, automatic responses are associated with more conscious, self-reported cognitions and behaviours in response to symptoms that have been found clinically relevant in previous studies (de Gier, Picariello, et al., 2023). The following research questions were addressed: (1) Do severely fatigued patients with MS or ME/CFS and healthy controls differ in the tendency to direct attention toward fatigue-related stimuli? (2) Do severely fatigued patients with MS or ME/CFS and healthy controls differ in the tendency to direct attention away from physical-activity related stimuli? (3) Do severely fatigued patients with MS or ME/CFS and healthy controls differ in their tendency to interpret ambiguous somatic information in a threatening way? If a significant attentional or interpretation bias is found, is the extent of these biases similar across MS and ME/CFS? Finally, if an attentional or interpretation bias is found, to what extent are these biases correlated with self-reported cognitive and behavioural responses to symptoms known to perpetuate fatigue?

**Materials and methods**

**Study design and study population**

A cross-sectional study comparing information processing biases between two severely fatigued patient groups (MS and CFS/ME) and a healthy control group.

**Participants and procedures**

*MS patients:*

MS patients were participants in a multi-centre Randomized Clinical Trial (RCT) comparing the efficacy of face-to-face CBT and web-based CBT for MS-related fatigue (de Gier, Beckerman, et al., 2023). They were recruited from April 2018 until November 2021. Inclusion criteria were (a) diagnosis of MS, (b) severely fatigued, i.e. a score ≥ 35 on the subscale fatigue of the Checklist Individual Strength (CIS) (Worm-Smeitink et al., 2017), (c) aged between 18 and 70, (d) ambulatory. Participants were excluded when meeting criteria of a depressive disorder, assessed with the Beck Depression Inventory-Primary Care version (BDI-PC) (Beck et al., 1997) and Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 2010); or having other severe psychiatric or somatic comorbidity (Cumulative Illness Rating Scale (Linn, Linn, & Gurel, 1968) item ≥ 3) . For a full description of the enrolment procedure we refer to the study protocol of the RCT (Houniet-de Gier et al., 2020). The IB questionnaire was part of the baseline online assessment of all participants. Only participants treated in the Amsterdam UMC site of the trial completed the VPT prior to the first therapy session.

*ME/CFS patients:*

ME/CFS patients were recruited from December 2018 until June 2019 from a tertiary treatment centre for chronic fatigue at the Amsterdam UMC. Patients were eligible when

the 2003 CDC consensus criteria for CFS were met (i.e., severe, disabling fatigue was present, lasting for at least 6 months, accompanied by at least 4 out of 8 additional symptoms), were aged between 18 and 70, and scored 35 or higher on the CIS fatigue subscale (Worm-Smeitink et al., 2017). Patients were excluded in case of somatic or psychiatric comorbidities that could explain the presence of fatigue. During the first consultation in the treatment centre, patients were informed about the study by the therapist and asked if they were willing to participate. After written informed consent was given, and when patients met the inclusion criteria as confirmed during the standard clinical assessment, the VPT was administered by the research assistant prior to the second intake session. Afterwards participants received an email with a link to the IB questionnaire, which they completed at home. Other questionnaires (see below) were part of the standard clinical assessment. Patients gave written consent for using these data for the present study.

*Healthy controls:*

Healthy controls were recruited from April 2019 until January 2021 by two research assistants and two psychology students in Amsterdam and Nijmegen in their private networks. Healthy controls were eligible when scoring lower than 35 on the CIS fatigue subscale, aged between 18 and 70, without a current psychiatric or somatic condition and never diagnosed with ME/CFS or MS. After written informed consent was obtained, the student/assistant visited the participants at their home to assess the AB task. The AB task was completed in a quiet room without disturbance. Afterwards they received an email with the link to the IB questionnaires and other questionnaires (see below).

**Measures**

*Visual Probe Task*

A Visual Probe Task (VPT) (MacLeod, Mathews, & Tata, 1986) was used to assess patients' vigilance to fatigue-related stimuli and tendency to direct attention away from physical activity-related stimuli. The parameters and stimuli of the VPT were based on the VPT developed by Hughes et al. (2017) consisting of 24 pairs of fatigue-related (e.g. exhausted, headache, weak) and neutral words. These word pairs were translated and used in a replication study in a Dutch CFS sample (Hughes et al., 2018). In the present study, these were combined with 24 pairs of physical activity-related (e.g. running, cycling, lifting) and neutral words as used in the study of Van Heck et al. (2019). A stimuli duration of 500ms was chosen as the previous research shows AB to be evident in CFS populations with this duration (Hughes et al., 2016; Hughes et al., 2017). Stimuli presented for <500ms are thought to tap into early automatic orientation of attention. Stimuli presented for >500ms are thought to tap into later strategic processing. 500ms is viewed as having potential for automatic and strategic processing (Hughes et al., 2016). A more detailed description of the VPT task can be found in Supplement 1.

The VPT task was run on a Dell laptop (the same as used in the study of Hughes et al. (2018)), using ePrime 2.0. The task started with 16 practice trials consisting of only neutral word-pairs. Each trial started with a fixation cross in the centre of the screen (500 ms), followed by 2 words (one fatigue-related or physical activity-related and the other word was neutral), one word was presented above and the other below the fixation point. After 500 ms the words disappeared, and an arrow appeared at the central location of one of the words. Participants were instructed to press "c" on the laptop keyboard when the arrow pointed to the left, and "m" when the arrow pointed to the right, as quickly and accurately as possible. In total, the task consisted of 384 trials of 48 unique word-pairs. The duration of the total task was 15 to 20 minutes.

Individual AB scores were obtained by calculating the difference between the mean reaction times (in ms) to probes replacing the fatigue- or physical activity-related words and the probes replacing the neutral stimuli. AB scores were calculated separately for both word categories (fatigue-related versus physical activity-related). Positive values reflect an AB towards the threatening stimulus, indicating potential hypervigilance, and negative values reflect a tendency to direct attention away from threatening stimuli (avoidance).

*Implicit Interpretation bias task*

An implicit IB task developed by Mathews and Macintosh (2000) and adapted by Hughes et al. (2016) was used to assess the tendency of patients to interpret ambiguous sensations in a negative, somatically threatening way. The online IB task was based on the IB task developed by Hughes at al. (2017), which was already translated in Dutch (Hughes et al., 2018) and extended by 2 scenarios related to fear of disease progression[1] (an example of a scenario can be found in supplement 2). The task was administered online and could be completed at home. During the first part of the task 12 day-to-day ambiguous situations that could be interpreted in either a neutral or a negative somatic manner were presented with a title for each. Participants had to imagine themselves in these situations, rate the "pleasantness" of the situation and answer a question about each scenario. After reading the 12 scenarios, the second part of the task presented the title of a scenario again followed by 4 different sentences to be rated in terms of how similar in meaning they were to the original scenario. Two were potential targets that represented interpretations of the original scenario, one positive and the other a somatically threatening interpretation. The other two sentences

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[1] Hereto, six extra scenarios were developed and piloted in healthy individuals, to test if the interpretations were equally likely. Based on this, two scenarios were selected and added to the final task.

were foils (positive and negative) which were not plausible interpretations of the scenario. Participants were asked to rate all 4 sentences on similarity to the original scenario from 1 (very different in meaning) to 4 (very similar in meaning). The four sentences were presented in random order varying between scenarios. Mean similarity ratings of the positive and somatic interpretations were calculated separately for the analyses. An IB index was obtained by subtracting the mean similarity rating of the positive (target) interpretations from the mean similarity rating of the somatic (target) interpretations. Higher index scores indicate a stronger tendency to interpret ambiguous somatic information in a threatening way.

*Checklist Individual Strength subscale fatigue severity (CIS fatigue):*

The CIS fatigue subscale was used to assess fatigue severity. The CIS is a 20-item self-reported questionnaire consisting of 4 subscales: fatigue severity, reduction in motivation due to fatigue, reduction in physical activity, and concentration problems (Worm-Smeitink et al., 2017). The subscale fatigue severity consists of 8 items scored on a 7-point Likert scale, adding up to a total score varying between 8 to 56. A score of 35 or higher indicates the presence of severe fatigue (Worm-Smeitink et al., 2017). The CIS is a reliable and valid instrument, with Cronbach's α 0.84 to 0.95  (Worm-Smeitink et al., 2017).

*Cognitive and Behavioural Responses to Symptoms Questionnaire (CBRQ)*

The CBRQ was used to assess cognitive and behavioural responses to symptoms assumed to play a perpetuating role in chronic fatigue. The CBRQ contains 5 subscales measuring cognitive responses to symptoms: fear-avoidance, catastrophizing, damage beliefs, embarrassment avoidance, and symptom focusing. Two subscales measure behavioural responses to symptoms: all-or-nothing behaviour and resting-avoidance behaviour. The 40

items are rated on a 5-point Likert scale, with higher scores indicating the tendency towards more maladaptive coping with symptoms. The CBRQ is a reliable and valid questionnaire across long term conditions, with Cronbach's α 0.76 to 0.89 (Picariello et al., 2023; Ryan et al., 2018)

*Sample size*

The sample size estimation was based on the study reporting data on attentional and interpretation biases in patients with ME/CFS compared to healthy controls (Hughes et al., 2017). At least comparable biases were expected to occur in MS patients. Gpower 3.1 software (Faul et al., 2007) was used to calculate the required sample size assuming a significance level of .05, a power of .80 and an $\eta_p^2$ of .09 on the VPT. The required sample size was 34 participants per group, but anticipating a drop-out rate of 15%, we aimed for 40 participants per group.

**Statistical analyses**

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS version 26). Baseline characteristics of the study groups were summarised using descriptive statistics. Differences in age, sex and level of education between the three groups were tested by Analysis of Variance (ANOVA) and chi-square tests. Difference in CIS fatigue between MS and ME/CFS patients was tested using t-tests. When groups differed significantly in baseline characteristics, correlations between that variable and the outcome variables were calculated to determine if the characteristic should be added as a confounder in the analyses.

*Visual Probe Task*

Participants with more than 3 SD missed trial responses compared to the group mean, were excluded from the analysis. Missing responses and reaction times of trials with incorrect responses or extreme outliers (<200 or > 2000 ms) were excluded from the analyses (Hughes et al., 2017). A 2-way mixed ANOVA with condition (MS, ME/CFS, healthy controls) as between-subjects variable and topic (fatigue-related vs physical activity-related) as within-subjects variable was conducted, to test for differences in ABs between groups. In case of a significant omnibus test, post-hoc comparisons between groups were conducted to further explore differences between groups.

*Interpretation bias task[2]*

In line with previous studies, a 2-way mixed MANOVA with diagnosis as between-subjects variable and interpretation (positive vs somatic) as within-subject variable was used (in target items only) to test differences in IB between MS- and ME/CFS-patients and healthy controls (Hughes et al., 2017). Interactions were investigated using other ANOVAs to explore differences between groups on positive and somatic interpretations separately.

*Correlations between biases and self-reported questionnaires*

If significant differences in attentional or interpretation biases were found between MS or ME/CFS patients and healthy controls, then Pearson correlations were calculated between

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[2] First, a 2-way ANOVA was used with target type (target sentence vs foil sentence) and interpretation (positive vs negative/somatic) as within-subjects factors, to examine if a found IB is related to somatic interpretations, and not a tendency to interpret ambiguous information in a generally negative way. Results of this analysis are presented in supplement 4.

CBRQ cognitive subscales and the given bias index in MS and ME/CFS patients separately.

Testing of the correlations was exploratory and no correction for multiple testing was

applied.

**Results**

Of 166 MS patients participating in the RCT, 156 were included in the analyses of the IB task, since 8 participants had a CIS fatigue score < 35 at the time the AB and IB tasks were administered, and 2 MS patients did not complete the IB task. Thirty-nine MS patients completed the VPT, of whom 1 was excluded from the analyses because of excessive missing data (>3 SD above the group mean).

A total of 77 ME/CFS patients were informed about the study of whom 71 were willing to participate. After screening for eligibility, 44 ME/CFS patients participated in the study and completed the VPT. Nine patients were excluded because of age or comorbidity and 18 patients were not able to attend to the VPT-appointment for logistical reasons. Of the 44 participating ME/CFS patients, 40 completed the IB questionnaire.

A total of 62 healthy controls were informed about the study, of whom 46 fulfilled the inclusion criteria. Seven people had excessive missing data on the VPT (> 3 SD above the group mean), which was unexpected, unusual and gave reason to question the reliability of the assessments of these controls. For this reason these participants' data were excluded and replaced by seven new controls. Flow charts can be found in Supplement 3.

The achieved sample size was larger than de sample size needed according to the power analysis .

*Group characteristics*

Table 1 shows the sociodemographic characteristics of each group. The MS group consisted of 121 (78%) females and had a mean age of 45.3. The ME/CFS group consisted of 30 (75%) females and had a mean age of 33.9. The control group consisted of 31 (67%) females and had a mean age of 34.6. The three groups differed significantly in age ($F_{2,245}$ = 24.7, p < .001). Post-hoc t-tests showed that fatigued MS patients were significantly older compared to both

ME/CFS patients and healthy controls, whereas the latter two groups did not differ from one another.

ME/CFS patients reported higher levels of fatigue severity (t = 5.4, p < .001) compared to MS patients.

*Attentional bias*

Table 2 shows mean reaction times (in ms) on the congruent and incongruent trials of both fatigue-related and physical activity-related items and figure 1 shows the ABs per condition. Age was significantly correlated RTs (r = 0.52) but not with the AB scores (r= 0.05 and 0.06 respectively). The mean RT was not significantly correlated with fatigue-related AB (r = 0.12) or physical activity-related AB (r = -0.05). Two-way ANOVA showed no significant difference in AB scores for topic (omnibus test topic: $F_{1,125}$ = 0.10; $p$ = .753), or significant group differences in a fatigue-related AB or physical activity-related AB (interaction between topic*condition $F_{2,125}$ = 1.87; $p$ = .159 ).

*Interpretation bias*

Table 3 shows the mean similarity ratings of the interpretations. Age showed a weak, non-significant, correlation with the somatic interpretation (r = .119), and was not added as a confounder to the analyses. Sample sizes of the groups differed, however groups showed equal variances, and the assumptions for ANOVA were met.

A MANOVA fore targets only, with diagnosis as between subjects factor and interpretation as within subjects factor, showed a significant interpretation by diagnosis interaction ($F_{1,239}$ = 30.78 , $p$ < .001). This was further explored using one-way ANOVAs showing significant

differences between diagnostic groups on somatic interpretations ($F_{1,2}$ = 27.61 , $p$ < .001),

but not on positive interpretations ($F_{1,2}$ = 1.68 , $p$ = .188).

Post-hoc comparisons between groups showed that both MS and ME/CFS patients endorsed

somatic interpretations significantly more than healthy controls (mean difference = 0.66,

95% CI 0.48 to 0.84, Cohen's $d$ = 1.12 and 0.43, 95% CI 0.20 to 0.66, Cohen's $d$ = 0.46

respectively), but for MS patients this was an even stronger effect than for ME/CFS patients

(mean difference = 0.24, 95% CI 0.05 to 0.42, Cohen's $d$ = 0.48). Figure 2 displays the positive

and somatic interpretations per group.


*Relation between biases and cognitive responses to symptoms*

Table 4 shows Pearson correlations between CBRQ subscales and interpretation bias index.

In MS patients, small but significant correlations were found between a bias to make somatic

interpretations and the self-reported fear-avoidance (r=.23), catastrophizing (r=.19), damage

beliefs (r=.31) and symptom focusing (r = .20) CBRQ subscales, indicating that stronger

negative interpretations are associated with a tendency towards more maladaptive coping

with symptoms. In ME/CFS patients, no significant correlations were found.

**Discussion**

This study investigated attentional and interpretation biases in severely fatigued patients with MS. No evidence was found for a fatigue-related or physical activity-related attention bias in patients with MS.

MS patients showed a bias to interpret ambiguous somatic information in a somatically threatening way, compared to healthy controls. Furthermore, there was a significantly greater somatic interpretation bias in MS patients compared to ME/CFS patients; that said, ME/CFS patients also showed a greater somatic interpretation bias than healthy controls, which is in line with previous findings (Hughes et al., 2017; Hughes et al., 2018). As expected, MS patients appear more susceptible to somatic interpretations compared to the other groups. This may influence the interpretation of commonly occurring bodily sensations and lead to an overestimation of threat, and heightened symptom perception.

In fatigued MS patients, somatic interpretations of ambiguous information showed small but significant correlations with self-reported fear-avoidance and catastrophizing about symptoms, beliefs that symptoms are signs of damage, and the tendency to focus on symptoms. Previous research has identified these as fatigue-perpetuating factors in the cognitive-behavioural model of chronic fatigue in MS (van Kessel & Moss-Morris, 2006). Considering the exploratory nature of the correlation analyses the results should be interpreted with caution. These relationships were not found in CFS patients in this study. We found no evidence to support the previously found AB in ME/CFS patients (Hughes et al., 2017; Hughes et al., 2018). This was despite the ME/CFS patients being recruited from the same treatment centre, and having met the same inclusion criteria as the ME/CFS patients in the study of Hughes et al (2018). The large variance in reaction times, however, possibly reflects the heterogeneity of the attention bias in the ME/CFS group, which may be a factor

in explaining the lack of effects. The inconsistency of AB findings between studies may also reflect the low test-re-test reliability of the dot-probe paradigm (Dear et al., 2011) indicating that the bias can vary over time, though research clearly shows that at a group level the bias exists. Further investigation and replication is warranted and may lead to more insight in the role and clinical relevance of AB in chronic fatigue.

The present study used the same VPT paradigm as the study by Hughes et al. (2018), however adjusting the task by adding physical activity-related stimuli extended the task to 384 trials instead of 96 trials. Combining these two conditions with opposed hypothesized effects on attention may have interacted in an unexpected way. However, the Van Heck et al. (2019) study also used 3 types of trial conditions (pain-related, physical activity-related and positive words), consisting of even 600 trials. They did find different responses to the different type of target conditions. The finding of a physical activity-related AB in ME/CFS patients in the study of Van Heck et al. (2019) was not replicated in this study. No indication of an attentional avoidance of physical activity-related stimuli was found in MS or ME/CFS patients. This could imply that physical activity-related stimuli are less intrinsically threatening in the context of severe fatigue. Fatigue is less likely to occur as immediate as pain during physical activity, and is less intrinsically threatening compared to pain. Although fear-avoidance has been found to play an important role in the perpetuation of fatigue, this may be more likely the result of a top-down cognitive process, based on illness representations, than an unintentional bottom-up AB, explaining why no AB for physical activity-related information was found in the current study.

*Clinical implications and future research*

To get a better understanding of the potential mechanistic role of information processing biases, longitudinal studies are needed that change these biases and assess any corresponding change in symptom experience. Recently, promising steps have been made to develop Cognitive Bias Modification training to reduce fatigue in kidney patients (Geerts et al., 2023). It would be interesting to study if the implicit IB is moderated via existing treatments such as cognitive behavioural therapy for MS-related fatigue, in which cognitions and attentional processes are explicitly addressed. Further studies are needed to explore the role of IB in MS-related fatigue specifically.

*Strengths and limitations*

This is the first study to test if implicit information processing biases are implicated in MS-related fatigue. Strengths of this study include the large sample size of MS patients, and the comparison to both ME/CFS patients and healthy controls.

However, there are also some methodological limitations that may have influenced the current study findings. Although the three groups completed the same tasks and questionnaires, the context in which they were recruited and tested differed. The MS patients had completed several questionnaires regarding fatigue in the 2 weeks prior to the assessment of the VPT, which may have had a priming effect regarding fatigue perception. This does not apply to the IB task, which was administered prior to the other study questionnaires. Finally, the healthy controls performed the VPT in their home environment, with the research assistant or student present, whereas the ME/CFS and MS patients were assessed in a quiet room in the university hospital, where the research assistant left the room. It is uncertain to what extent these variations in testing conditions may have influenced performance on the experimental tasks.

It is uncertain to which extent possible response latencies in the laptop may have affected the accuracy of the measured RTs. However, we used within-subjects' ABs (based on a large number of trials) as outcomes instead of raw RTs, and we expect the possible error to have affected the outcomes equally over the groups .

Both the MS and ME/CFS group consisted of patients seeking treatment for severe and chronic fatigue, and although they do not represent all MS and ME/CFS patients, it makes the samples clinically relevant and comparable in that respect. The aim of including the ME/CFS sample was to be able to compare the findings in MS patients to earlier findings in ME/CFS. This sample was comparable to the samples used in previous studies (Hughes et al., 2017; Hughes et al., 2018). The mean CIS fatigue score of the healthy controls was comparable to the mean CIS fatigue score in a large sample of population controls (Worm-Smeitink et al., 2017).

Although the calculated sample size was reached, the sample may have been underpowered to show a significant AB in MS patients compared to healthy controls. However, since the ME/CFS group did not show any trend towards an AB, despite earlier findings, the clinical relevance of a statistically significant finding in a larger sample, is disputable.


*Conclusion*

Patients with MS show a stronger tendency to interpret ambiguous somatic information in a somatically threatening ways compared to healthy controls, with MS patients showing an even stronger IB compared to ME/CFS patients. Although this IB is understandable considering the nature of MS, it may affect patients' ability in dealing with daily fluctuation of symptoms such as fatigue, and contribute to the perpetuation of fatigue.

Future research may gain more insight in the way the IB relates to the fatigue severity in MS and if addressing this more explicitly during interventions for fatigue could potentially optimize treatment outcome.

**Abbreviations:**

AB: attentional bias; IB: interpretation bias; ME/CFS: chronic fatigue syndrome/myalgic encephalomyelitis; MS: Multiple Sclerosis; FND: Functional Neurological Disorder; CBT: cognitive behavioural therapy; RCT: Randomized Clinical Trial; CIS: Checklist Individual Strength; VPT: Visual Probe Task; CI: Confidence Interval

**Informed consent:**

Informed consent was obtained from all individual participants included in the study.

**Welfare of animals**

This article does not contain any studies with animals performed by any of the authors.

**Conflict of Interests**

The authors declare that they have no conflict of interest.

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**Table 1.**

*Group characteristics*

| Variable | Healthy Controls (N= 46) | ME/CFS (N=44) | MS (N=156) | MS† (N=38) | Comparison statistic‡ |
|---|---|---|---|---|---|
| *Age (mean, SD)* | 34.6 (15) | 33.9 (14) | 45.3 (10) | 45.7 (10) | *F = 24.8, p < .001* |
| *Gender (% female)* | 67 | 75 | 78 | 68 | $\chi^2$*= 1.8, p = .400* |
| *Education*§ | | | | | $\chi^2$*= 8.9, p = .065* |
| *Low* | 3 (6.5%) | 2 (4.5%) | 13 (8.3%) | 1 (2.6%) | |
| *Middle* | 9 (19.6%) | 18 (40.9%) | 66 (42.3%) | 11 (28.9%) | |
| *High* | 33 (71.7%) | 24 (54.5%) | 77 (49.4%) | 26 (68.4%) | |
| *else* | | 1 (2.2%) | | | |
| *CIS fatigue*¶ | 22.5 (7.9) | 51.0 (4.8) | 46.1 (5.4) | 47.1 (5.0) | *t = 5.4, p < .001* |
| *CBRQ fear-avoidance* | | 12.4 (4.6) | 10.5 (4.5) | 9.1 (4.7) | |
| *CBRQ catastrophizing* | | 6.7 (3.5) | 6.1 (3.0) | 5.9 (3.5) | |
| *CBRQ damage* | | 8.7 (5.3) | 9.9 (3.4) | 9.1 (4.0) | |
| *CBRQ embarrassment* | | 8.1 (5.3) | 7.4 (5.5) | 7.7 (5.5) | |
| *CBRQ symptom focusing* | | 13.3 (4.4) | 10.3 (4.5) | 9.2 (4.7) | |

† subgroup of MS patients completing the VPT

‡ these analyses are based on the full MS group of N=156

§ Education level classified as low (less than 4 years of secondary education), medium (4 or 5 years of secondary education), or high (6 or more years of secondary education).

¶ comparison between ME/CFS and MS patients

*Abbreviations: ME/CFS: myalgic encephalomyelitis /chronic fatigue syndrome; MS = multiple sclerosis; CIS = checklist individual strength; CBRQ = cognitive and behavioural responses to symptoms questionnaire*
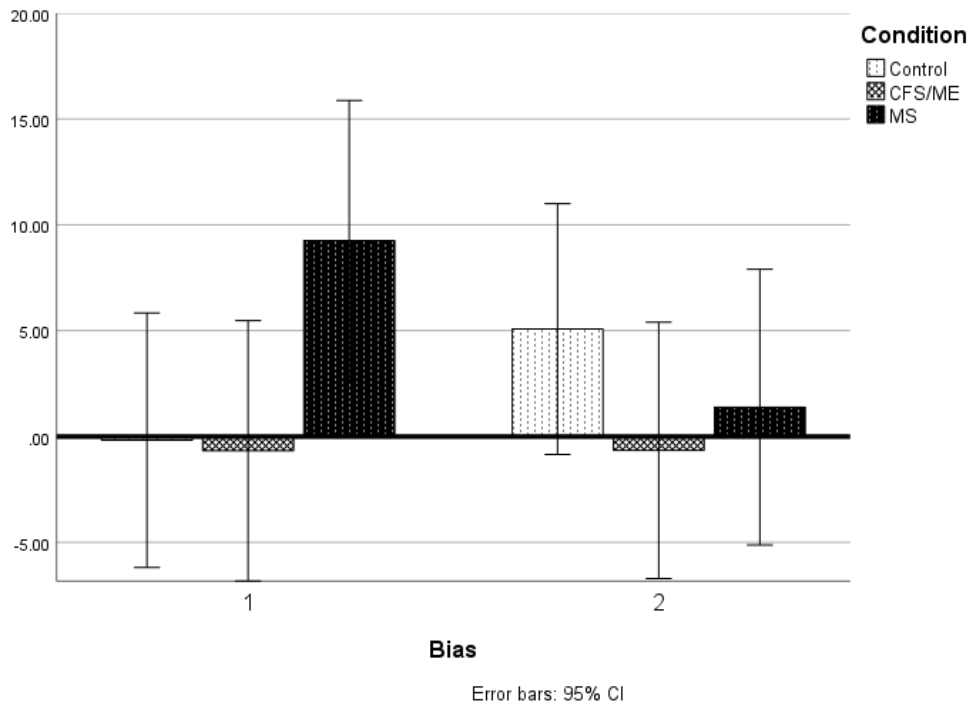
**Table 2.**

*Mean reaction times on congruent and incongruent trials per topic, per diagnostic group*

| Group | Mean number of correct responses (SD) | Topic | Congruence | Reaction time in ms mean (SD) |
|---|---|---|---|---|
| *ME/CFS (n=44)* | 371.8 (9.0) | Fatigue | Congruent | 628.33 (166.25) |
| | | | Incongruent | 627.66 (171.32) |
| | | Physical activity | Congruent | 628.66 (169.27) |
| | | | incongruent | 628.01 (170.50) |
| *Healthy Controls (n=46)* | 368.1 (8.8) | Fatigue | Congruent | 527.18 (78.89) |
| | | | Incongruent | 527.01 (73.13) |
| | | Physical activity | Congruent | 527.16 (72.24) |
| | | | incongruent | 532.24 (74.18) |
| *MS (n=38)* | 372.9 (7.4) | Fatigue | Congruent | 665.10 (104.91) |
| | | | Incongruent | 674.36 (105.90) |
| | | Physical activity | Congruent | 670.90 (108.27) |
| | | | incongruent | 672.29 (104.13) |

*Abbreviations: ME/CFS: myalgic encephalomyelitis /chronic fatigue syndrome; MS = multiple sclerosis*

**Figure 1.**

*Fatigue-related and physical activity-related attentional bias by group*



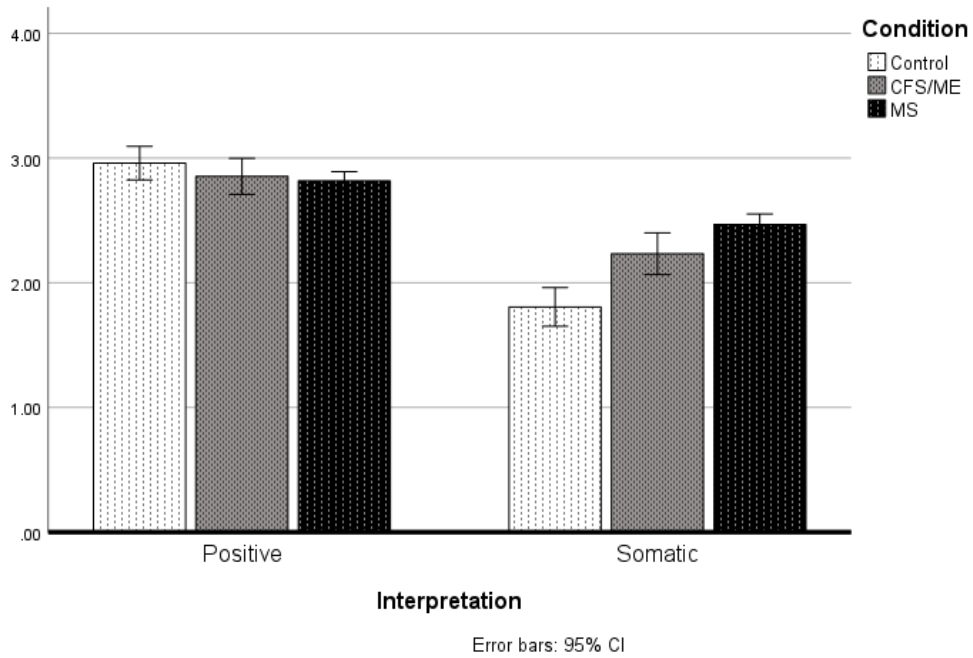*Abbreviations: ME/CFS = myalgic encephalomyelitis /chronic fatigue syndrome; MS = multiple sclerosis*

**Table 3.**

*Mean and SD of interpretations of all groups*

| Similarity rating | ME/CFS (N=40) | MS (N=156) | Healthy controls (N=46) |
|---|---|---|---|
| Similarity rating of positive interpretation | 2.85 (0.42) | 2.82 (046) | 2.96 (0.50) |
| Similarity rating of somatic interpretation | 2.23 (0.52) | 2.47 (0.57) | 1.81 (0.38) |
| Similarity rating of positive foil | 1.35 (0.32) | 1.39 (0.40) | 1.42 (0.36) |
| Similarity rating of negative foil | 1.18 (0.18) | 1.26 (0.25) | 1.22 (0.24) |

*Abbreviations: ME/CFS: myalgic encephalomyelitis /chronic fatigue syndrome; MS = multiple sclerosis*

**Figure 2.**

*Positive and somatic interpretations on Interpretation Bias task for each group*



*Abbreviations: ME/CFS = myalgic encephalomyelitis /chronic fatigue syndrome; MS = multiple sclerosis*

**Table 4**.

*Correlations between interpretation bias, and response to fatigue symptoms (CBRQ subscales)*

| | Interpretation bias index | |
|---|---|---|
| *CBRQ subscales* | MS (n= 156) | ME/CFS (n=40) |
| *Fear-avoidance* | .279** | .088 |
| *Catastrophizing* | .261** | .060 |
| *Damage beliefs* | .276** | .137 |
| *Embarrassment* | .145 | .005 |
| *Symptom focusing* | .207** | -.175 |

** *p* < .001; * *p* < .05

*Abbreviations: ME/CFS: myalgic encephalomyelitis /chronic fatigue syndrome; CBRQ = cognitive and behavioural responses to symptoms questionnaire; MS = multiple sclerosis*

**Statement of contribution**

*What is already known on this subject?*

Several studies  found people with Chronic Fatigue Syndrome (ME/CFS) to have a health-related attentional bias when compared to healthy individuals. One study found that ME/CFS patients also show a tendency to direct attention away from movement-related stimuli. In addition, ME/CFS patient have a tendency to interpret ambiguous somatic information in a threatening way. These negative, illness-related interpretations were associated with unhelpful responses to fatigue such as catastrophic thinking styles, fear-avoidance and all-or-nothing behaviour (Hughes et al., 2017)(Hughes et al., 2017)(Hughes et al., 2017)(Hughes et al., 2017)(Hughes et al., 2017)(Hughes et al., 2017)(Hughes et al., 2017)(Hughes et al., 2017).

*What does this study add?*

- No evidence was found for an attentional bias in fatigued patients with Multiple Sclerosis (MS)

- Patients with MS have a tendency to  interpret ambiguous somatic information in a threatening way.