FATIGUE IN MULTIPLE SCLEROSIS

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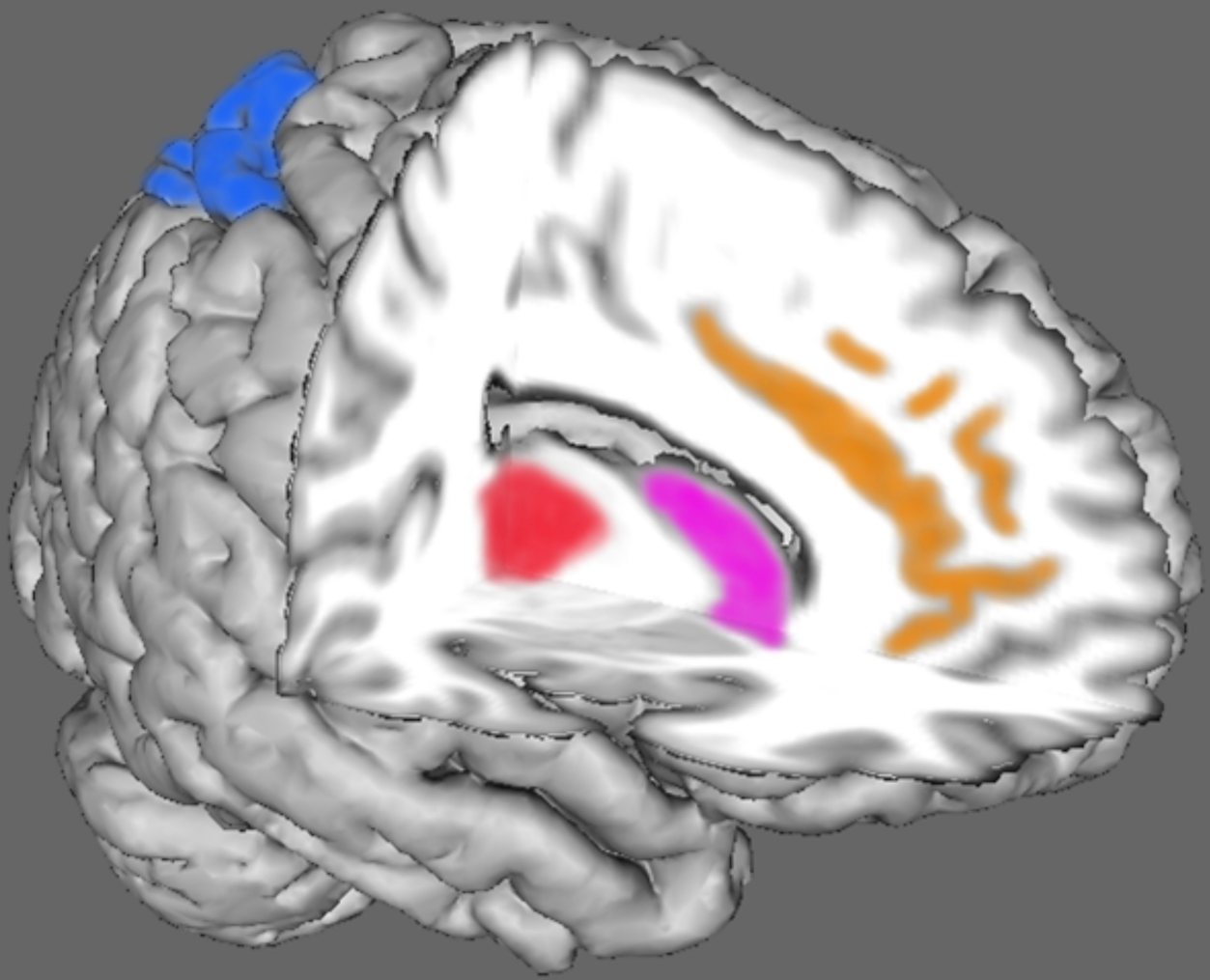

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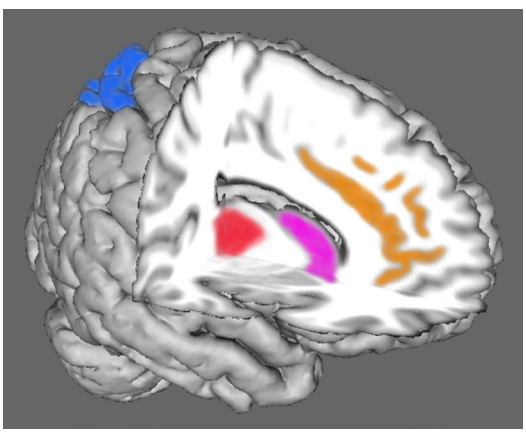
FATIGUE IN MULTIPLE SCLEROSIS

Topic Editors:
Christian Dettmers, Kliniken Schmieder Konstanz, Germany
John DeLuca, Kessler Foundation, USA



Proposed Network for Central Fatigue
© From the Rocco Ortenzio Neuroimaging Laboratory at Kessler Foundation

Dear Readers,

If you are engaged in the treatment of patients with MS (pwMS), this e-book's aim is to offer novel insights to improve on an understanding of one of the major problems of pwMS: fatigue. Although there is increasing research into fatigue and its impact on MS, this collection of ten articles supports a better understanding of fatigue in MS patients. It explores pathophysiological concepts, provoking mechanisms, objective measurements, personality interactions, pharmacological and non-pharmacological interventions and summarizes clinical management. It is written by neurologists, psychologists, scientists and therapists and addresses this group of people, who deal with pwMS in private, clinical, rehabilitation or scientific settings. Its aim is to communicate high-quality information, knowledge and experience on MS to healthcare professionals, while providing global support for the international MS community.

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EDITORIAL
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Editorial: Fatigue in Multiple Sclerosis

Christian Dettmers[1] and John DeLuca[2]*

[1] *Kliniken Schmieder Konstanz, Konstanz, Germany,* [2] *Neuropsychology and Neuroscience Laboratory, Kessler Foundation, West Orange, NJ, USA*

Keywords: fatigue, fatigability, multiple sclerosis, cognition, functional imaging, pathophysiology, treatment, sleep disorders

The Editorial on the Research Topic

Fatigue in Multiple Sclerosis

Fatigue in Multiple Sclerosis (MS) is one of the most debilitating symptoms in patients with Multiple Sclerosis (pwMS). It interferes significantly with career as well as participation in everyday life activities. It is an enormous burden to the pwMS, his/her family and friends. Direct and indirect costs are extraordinary, both financial and psychosocial. Ongoing scientific studies struggle to understand the pathophysiology of fatigue in the hope of improving options for treatment. The past decade has seen much progress with important developments emerging to understand different phenomena related to fatigue. Most helpful and essential when discussing fatigue is the distinction between subjective sensations and objective changes in performance (1) and between trait and state fatigue (2). This Research Topic brings together ten novel and exciting perspectives written by leading authorities in this area from around the world from both clinical and scientific perspectives to understand the multidimensional nature of fatigue.

The first two chapters propose some new and unique concepts in trying to explain fatigue. *Dobryakova, Genova, DeLuca, and Wylie* summarize various lines of evidence suggesting that dopamine imbalance plays a major role in developing fatigue (Dobryakova et al.). The model builds upon an earlier framework for studying fatigue suggested by Chaudhuri and Behan (3, 4), who suspected that central fatigue was a "failure of the non-motor functions of the basal ganglia." The current manuscript reviews the structural and functional neuroimaging evidence as well as pharmacological studies that suggest the critical role that dopamine plays in fatigue.

Hanken, Eling, and Hildebrandt focus on different aspects in their model (Hanken et al.). They suggest that the subjective feeling of fatigue is related to inflammation and increased levels of cytokines such as interleukin-1 (IL-1), IL-6, TNF-alpha. These inflammatory substances cause a sickness behavior – described as a highly organized strategy of an organism to cope with the infection. These authors refer to the original description of the sickness behavior by Maes et al. (5). From their structural imaging study, the authors concluded that structural alterations of the brain related to fatigue may be found in the insula, anterior cingulate cortex, and the hypothalamus. These structures are related to homeostasis and representation of internal bodily states.

Intuitively one might expect that the cognitive load has a significant impact on fatigue. Interestingly, *Sandry, Genova, Dobryakova, DeLuca, and Wylie* describe that it is not the cognitive load, but rather the length of the task (i.e., time on task) that is the major driving force in developing fatigue (Sandry et al.). This is intriguing and has practical implications for organizing daily routine and workloads in pwMS. They also raise the question, whether a decrease in information processing efficiency is the major obstacle or whether working memory is of equal importance, and also discuss whether fatigue is domain specific.

Edited by:
Hans-Peter Hartung, Heinrich-Heine University Düsseldorf, Germany

Reviewed by:
Jörg Kraus, Public Hospital Zell am See, Austria
Iris-Katharina Penner, COGITO Center Düsseldorf, Germany

****Correspondence:***
Christian Dettmers
c.dettmers@kliniken-schmieder.de

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Lukoschek, Sterr, Claros-Salinas, Gütler, and Dettmers compare fatigue in a large population of pwMS and stroke patients using the vitality index of the SF-36. Normalized vitality scores in pwMS and stroke were clearly lower than in healthy controls (Lukoschek et al.). Fatigue was higher in pwMS than in stroke patients. Both patient groups showed no positive correlation between physical functioning and fatigue. Fatigue correlated with the working capacity in pwMS, but not in stroke patients. This work shows the dramatic impact of fatigue on pwMS.

Sehle, Vieten, Mündermann, and Dettmers elaborated on the objective assessment of motor fatigue (Sehle et al.). In a previous paper, they demonstrated that the attractor is a sensitive tool to describe variation and variability in gait patterns (6). This allowed for sensitive discrimination between pwMS with and without fatigue (7). Beside its relevance for assessment of motor fatigue this tool may serve as a model for the organic component of cognitive fatigue as "activity dependent loss of function" [analog to "activity dependent conduction block" (8)].

While motor fatigue represents a well-characterized concept of organic fatigue, fatigue is clearly multidimensional. *Schreiber, Lang, Kiltz, and Lang* elaborate on personality traits, disease coping, anxiety and depression, and their interaction (Schreiber et al.). It is not a question of either organic or psychogenic factors in describing fatigue, but in most instances, both factors contribute to the expression of fatigue. The authors suggest that fatigue in initial stages of MS might be largely driven by factors associated with disease coping, while in later stages inflammatory processes and lesions might dominate.

Although sleep disturbances are recognized as a cause of secondary fatigue, and although one might intuitively consider sleep disturbance as a contributing factor to fatigue, its prevalence, nature, and importance in patients suffering from fatigue are widely under-represented. *Strober* summarizes her own data and the literature regarding the contribution of sleep disturbance to the expression of fatigue (Strober).

The following chapters address pharmacological and non-pharmacological interventions in pwMS. Disease modifying drugs are generally used to reduce relapses and progression. *Kunkel, Fischer, Faiss, Daehne, Köhler, and Faiss* describe the effect of Natalizumab on cognition, fatigue. and depression in a longitudinal, observational study that spanned a 2-year period (Kunkel et al.). They found significant improvements in attention and depression after this period.

Penner, Sivertsdotter, Celius, Fuchs, Schreiber, Berkö, and Svenningsson raised a similar issue (Penner et al.). In a previous study, they described the improvement of total, motor, and cognitive fatigue during treatment with Natalizumab and 1-year follow-up. In the present chapter, they analyze the relationship between fatigue depression and daytime sleepiness. They found a close relationship between all three variables without being able to establish a causal relationship.

Khan, Amatya, and Galea completed the collection with a clinical summary on the management of fatigue in pwMS (Khan et al.). Treatment options include non-pharmacological interventions such as multi-disciplinary rehabilitation, specific rehabilitation interventions, and physical modalities such as exercise, aquatic therapy, Tai chi, cooling devices among others. Behavioral and educational interventions are also assessed, including fatigue management programs, energy conservation programs, mindfulness-based interventions, and cognitive and psychological interventions. Pharmacological interventions are reviewed as well and the evidence levels are summarized.

This Research Topic represents the first attempt to provide novel and the most up-to-date clinical, psychological, and physiological data related to fatigue. It is a "must" for every clinician, neurologist, and psychologist dealing with pwMS and/or fatigue.

REFERENCES

1. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology* (2013) **80**(4):409–16. doi:10.1212/WNL.0b013e31827f07be
2. Genova HM, Rajagopalan V, Deluca J, Das A, Binder A, Arjunan A, et al. Examination of cognitive fatigue in multiple sclerosis using functional magnetic resonance imaging and diffusion tensor imaging. *PLoS One* (2013) **8**(11):e78811. doi:10.1371/journal.pone.0078811
3. Chaudhuri A, Behan PO. Fatigue and basal ganglia. *J Neurol Sci* (2000) **179**(S 1–2):34–42. doi:10.1016/S0022-510X(00)00411-1
4. Chaudhuri A, Behan PO. In vivo magnetic resonance spectroscopy in chronic fatigue syndrome. *Prostaglandins Leukot Essent Fatty Acids* (2004) **71**(3):181–3. doi:10.1016/j.plefa.2004.03.009
5. Maes M, Berk M, Goehler L, Song C, Anderson G, Galecki P, et al. Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. *BMC Med* (2012) **10**:66. doi:10.1186/1741-7015-10-66
6. Vieten MM, Sehle A, Jensen RL. A novel approach to quantify time series differences of gait data using attractor attributes. *PLoS One* (2013) **8**(8):e71824. doi:10.1371/journal.pone.0071824
7. Sehle A, Vieten M, Sailer S, Mundermann A, Dettmers C. Objective assessment of motor fatigue in multiple sclerosis: the Fatigue index Kliniken Schmieder (FKS). *J Neurol* (2014) **261**(9):1752–62. doi:10.1007/s00415-014-7415-7
8. Vucic S, Burke D, Kiernan MC. Fatigue in multiple sclerosis: mechanisms and management. *Clin Neurophysiol* (2010) **121**(6):809–17. doi:10.1016/j.clinph.2009.12.013

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REVIEW ARTICLE
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The dopamine imbalance hypothesis of fatigue in multiple sclerosis and other neurological disorders

Ekaterina Dobryakova[1,2]*, Helen M. Genova[2,3], John DeLuca[2,3,4] and Glenn R. Wylie[2,3,5]

[1] *Traumatic Brain Injury Laboratory, Kessler Foundation, West Orange, NJ, USA*
[2] *Department of Physical Medicine and Rehabilitation, Rutgers – New Jersey Medical School, Newark, NJ, USA*
[3] *Neuropsychology and Neuroscience Laboratory, Kessler Foundation, West Orange, NJ, USA*
[4] *Department of Neurology and Neurosciences, Rutgers – New Jersey Medical School, Newark, NJ, USA*
[5] *War Related Illness and Injury Study Center, Department of Veterans Affairs, East Orange, NJ, USA*

Edited by:
Christian Dettmers, Kliniken Schmieder Konstanz, Germany

Reviewed by:
Maria Engström, Linköping University, Sweden
Olivia Marie Reinhold Svolgaard, Copenhagen University Hospital Hvidovre, Denmark

****Correspondence:***
Ekaterina Dobryakova, Traumatic Brain Injury Laboratory, Kessler Foundation, 1199 Pleasant Valley Way, West Orange, NJ 07052, USA
e-mail: edobryakokva@kesslerfoudnation.org

Fatigue is one of the most pervasive symptoms of multiple sclerosis (MS), and has engendered hundreds of investigations on the topic. While there is a growing literature using various methods to study fatigue, a unified theory of fatigue in MS is yet to emerge. In the current review, we synthesize findings from neuroimaging, pharmacological, neuropsychological, and immunological studies of fatigue in MS, which point to a specific hypothesis of fatigue in MS: the dopamine imbalance hypothesis. The communication between the striatum and prefrontal cortex is reliant on dopamine, a modulatory neurotransmitter. Neuroimaging findings suggest that fatigue results from the disruption of communication between these regions. Supporting the dopamine imbalance hypothesis, structural and functional neuroimaging studies show abnormalities in the frontal and striatal regions that are heavily innervated by dopamine neurons. Further, dopaminergic psychostimulant medication has been shown to alleviate fatigue in individuals with traumatic brain injury, chronic fatigue syndrome, and in cancer patients, also indicating that dopamine might play an important role in fatigue perception. This paper reviews the structural and functional neuroimaging evidence as well as pharmacological studies that suggest that dopamine plays a critical role in the phenomenon of fatigue. We conclude with how specific aspects of the dopamine imbalance hypothesis can be tested in future research.

Keywords: dopamine, fatigue, mesocorticolimbic system, methylphenidate, MRI

INTRODUCTION

Fatigue is a common symptom in multiple sclerosis (MS), with up to 90% of individuals with MS reporting fatigue (1). Moreover, more than half of individuals with MS report fatigue to be their worst symptom (2). For this reason, the topic of fatigue in MS has generated a great deal of research in the domains of neuropsychology, neuroscience, and pharmacology. Other clinical populations also report fatigue including: 80% of individuals with traumatic brain injury (TBI) (3), 56% of individuals with Parkinson's Disease (PD) (4), 99% of cancer patients (5), 88% of individuals with human immunodeficiency virus (88%) (6), as well as individuals with chronic fatigue syndrome (CFS) who experience fatigue for more than 6 months for no known psychiatric or neurological reasons (7).

Fatigue is characterized by a lack of energy, feelings of exhaustion that are unaided by sleep, and the perception that one is unable to perform mental and physical activities (8). Although fatigue has been studied extensively, in part because it affects such a wide range of clinical populations, there has been no unifying framework within which to understand fatigue. In this review, we propose such a framework, with the aim of providing structure for this developing field of study.

We propose that fatigue arises due to a dopamine imbalance within the central nervous system (CNS). One of the ultimate goals of this review is to investigate the evidence that supports the dopamine imbalance hypothesis by examining studies showing structural and functional abnormalities in areas enervated by dopamine and clinical trials showing alleviation of fatigue after dopamine medication.

The current review examines the evidence in support of the dopamine imbalance hypothesis by focusing on central fatigue, which can be experienced as both physical and mental in nature. Further, the current review builds upon a previous framework of fatigue proposed by Chaudhuri and Behan (9), which suggests that central fatigue might arise due to the "failure of the *non-motor* functions of the basal ganglia" [(9), p. 40]. This hypothesis was developed based on evidence from both animal and clinical studies, which showed the effects of basal ganglia damage to be similar to the symptoms of central fatigue. The authors emphasized subcortical pallido–thalamo-cortical interactions and urged to clarify the influence of dopamine and serotonin on fatigue, since these neurotransmitters effect the activation of the pallido–thalamocortical loop. In the current review, we suggest a more precise mechanism based on recent studies that fatigue might develop as a result of a dopamine imbalance.

DOPAMINE: A BRIEF REVIEW

Dopamine is a modulatory neurotransmitter that is termed a catecholamine due to its chemical composition. Dopamine is the most common catecholamine in the CNS (10, 11) and is a precursor

to the two other catecholamines, norepinephrine and epinephrine. In the CNS, dopamine is synthesized in two subcortical brain regions, specifically, the substantia nigra pars compact (SNc) and the ventral tegmental area (VTA) (10, 12–14). Dopaminergic neurons project from the SNc and VTA to various cortical areas and thus can be segregated onto several dopaminergic pathways: (1) the nigrostriatal pathway, which links the SNc with the striatum, and (2) the mesocorticolimbic pathway, which starts at the VTA and projects to the striatum, limbic areas, and the prefrontal cortex (PFC) (10, 13, 15, 16). Finally, dopamine from a third pathway is synthesized in the hypothalamus and projects to the pituitary gland, where it is involved in the inhibition of prolactin release, a hormone that is important in immune system regulation[1] (10) (**Figure 1**). Catecholamines also play an important role in the modulation of the immune system, with dopamine being synthesized and released by immune cells (17, 18).

Dopamine receptors (DRs) can be found in both the CNS and in the immune system. There are five types of DRs (D1, D2, D3, D4, and D5), subdivided into two groups: D1-like and D2-like. The D1 and D5 receptors belong to the D1-like group, while the rest of the DRs belong to the D2-like group of receptors (10, 13). These receptors have different distribution densities in the CNS, depending on the brain region. For example, more D1-like receptors are located in the PFC, while more D2-like receptors are found in the striatum. Therefore, different medications have a somewhat specific affinity for DRs and that way can have a greater effect on a specific brain region (e.g., a medication targeting D1 may have more influence on the PFC and its function than on the striatum) (19).

[1]Note that there are actually four pathways: (1) nigrostriatal, (2) mesolimbic, (3) mesocortical, and (4) hypothalamic (tuberoinfundibular). However, in human research, whether it is pharmacological or neuroimaging, it is not possible to specifically delineate the pathways, hence, here, we collapse the second and the third pathways, referring to them as the mesocorticolimbic pathway.

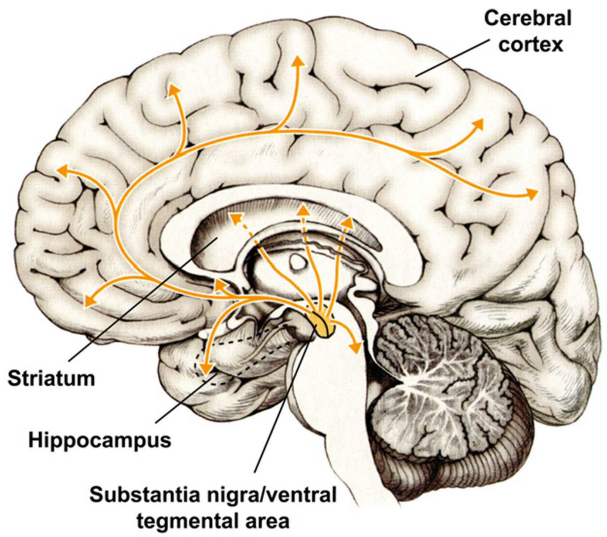

FIGURE 1 | A representation of dopaminergic projections throughout the brain. Adapted from Dalley and Roiser (14).

Dopamine has been known to play an important role in motor function. However, evidence from several past decades show that dopamine also plays a significant role in motivation and cognition. Specifically, dopamine has been shown to be involved in learning of action–outcome associations (20–22). In addition, dopamine has been shown to be involved in effortful behavior: the depletion of dopamine from the striatum or the administration of dopamine antagonists has been shown to result in the cessation of effortful reward-seeking behavior. That is, animals that learned to exert effort (e.g., climb a barrier or press a lever several times) for a larger food reward, start to prefer a smaller reward that can be obtained without effort exertion (23, 24). PFC dopamine has been shown to play an important role in working memory (25, 26). Further, increased amount of dopamine release in the striatum and the PFC has been shown to be associated with cognitive flexibility [see Ref. (27) for review].

THE EFFECTS OF DOPAMINE ON FATIGUE IN THE CENTRAL NERVOUS SYSTEM

SUPPORT FROM STRUCTURAL NEUROIMAGING

Dopamine imbalance can be caused by changes in brain structure, particularly when structures critical for dopaminergic projections are damaged. Recent structural neuroimaging studies implicate regions of the mesocorticolimbic pathway with the fatigue experienced by several clinical populations, including those with MS. Structural impairments in the VMPFC and the striatum have been observed in fatigued individuals, suggesting a role for dopamine in fatigue (28). Pardini et al. (29) found that reduced white matter integrity in the VMPFC, a region that receives dopaminergic projections, was associated with increased fatigue in MS. In another investigation, Pardini et al. (30) assessed fatigue in individuals with TBI, finding that persons with damage localized to the VMPFC had higher levels of fatigue relative to persons with damage localized to the dorsolateral PFC or other areas of the cortex. Genova et al. (31) also showed that individuals with MS who have high fatigue have increased white matter pathology in the internal capsule, which links the striatum with the PFC (32).

Further evidence for the involvement of the mesocorticolimbic regions comes from stroke research: Tang et al. (33, 34) reported that striatal infarcts are associated with post-stroke fatigue. Additionally, magnetic resonance spectroscopy findings showed lower levels of choline concentration and *N*-acetylcholine/creatine ratio (indicative of decreased neuronal integrity) in the striatum in patients with CFS and MS, respectively (9, 35).

SUPPORT FROM FUNCTIONAL NEUROIMAGING

Several functional neuroimaging studies also point to the involvement of mesocorticolimbic pathway in individuals with neurological damage who report fatigue. One of the earliest functional neuroimaging studies that implicated dopaminergic regions in fatigue used positron emission tomography (PET) to assess differences in brain activity at rest (i.e., without task) in individuals with MS (36). MS individuals, who scored high on the Fatigue Severity Scale (FSS) (37) exhibited reduced regional synaptic activity. That is, they exhibited lower levels of glucose metabolism in the PFC and in the striatum compared to individuals with MS who did not report fatigue (36).

Functional magnetic resonance imaging (fMRI) studies further support the dopamine imbalance hypothesis. Esposito and colleagues (38) examined the influence of fatigue in healthy individuals on resting-state network activity, i.e., task-independent activation of brain networks. Healthy individuals were scanned both at rest and while performing the *n*-back task at the beginning and at the end of: (1) a fatigue-free day and (2) a fatigue-inducing day. Participants reported increased mental fatigue and effort after performing the *n*-back task, but only at the end of the fatigue-inducing day. Moreover, reduced connectivity after the fatigue-inducing day was observed in the frontal control network that receives dopaminergic projections and is associated with executive abilities such as working memory. Other recent studies have also found altered connectivity in the mesocorticolimbic pathway in association with fatigue. Engström et al. (39) showed that MS individuals who have high fatigue show reduced mesocorticolimbic connectivity compared to healthy adults during a complex working memory task. Finke et al. (40) showed that high fatigue scores in individuals with MS were negatively correlated with resting-state mesocorticolimbic connectivity. At the same time, pharmacological studies show a reduction in fatigue following a dopamine agonist medication regimen [e.g., Ref. (41, 42)]. Connectivity between the regions of the mesocorticolimbic pathway has been shown to increase after dopamine agonist administration (bromocriptine and methylphenidate) (43–45). Taken together, these findings suggest that fatigue is associated with reduced connectivity between the regions innervated with dopamine, possibly due to reduced dopamine levels.

A potential difficulty in examining neural correlates of fatigue during task-related functional neuroimaging studies is the assessment of fatigue itself. In most of the clinical studies, fatigue is assessed with a self-report questionnaire, such as the FSS (37) or the Modified Fatigue Impact Scale (MFIS). These questionnaires provide non-specific, "global" data about the effect of "trait" fatigue on physical, social, and other activities performed during the previous weeks. However, functional neuroimaging studies are performed during well-controlled cognitive tasks that are tied to a specific time period and specific cognitive processes. A logical solution for this potential problem is to assess fatigue during task performance. Genova et al. (31) did precisely that: they asked participants with MS to rate their fatigue on a scale from 0 (not at all fatigued) to 100 (most fatigued), before and after a task-switching paradigm, a task that heavily relies on executive processing, during fMRI (46–48). These authors showed that activity in the striatum, a primary input nucleus of the mesocorticolimbic pathway, is greater in MS individuals who had higher on-task, or "state," fatigue compared to healthy individuals (31). Similarly, a recent study reported impaired striatal functioning in individuals with CFS (49). Collectively, these functional neuroimaging findings suggest that individuals with fatigue have impaired functioning of the mesocorticolimbic pathway, likely due to a dopamine imbalance within the regions of this network.

SUPPORT FROM BEHAVIORAL PHARMACOLOGY

A large body of evidence in support of the dopamine imbalance hypothesis is available from pharmacological studies. Several clinical trials investigated the efficacy of psychostimulant medications on fatigue in MS (50–53). Modafinil is a drug approved for treatment of narcolepsy and has been shown effective in reducing sleepiness (54). This medication might be the drug of choice for fatigue treatment in MS, since fatigue often co-occurs with (or is conflated with) sleepiness (55). However, studies that examined modafinil efficacy for fatigue have been inconclusive due to small sample sizes and methodological issues (open-label) (2, 56, 57). Amantadine has also been used to treat fatigue in MS. Amantadine is a dopamine agonists that leads to an increase in extracellular dopamine levels through promoting dopamine synthesis and blocking reuptake. A recent randomized blinded trial with four treatment groups (modafinil, amantadine, acetyl-L-carnitine, and placebo) showed amantadine to be successful in reducing fatigue (53). Of note is that Ledinek et al. (53) only included in their study MS individuals who were undergoing interferon-beta treatment (IFNβ). IFNβ is an immunomodulator that recently has been shown to aid in catecholamine synthesis (58), with dopamine being the most common catecholamine, as has been mentioned above. While this evidence is promising, the majority of clinical trials with amantadine are still underpowered and hence cannot provide conclusive evidence (51).

Several recent clinical trials have examined the efficacy of methylphenidate in treating fatigue. Methylphenidate, which has been approved for treatment of attention deficit hyperactivity disorder and narcolepsy, is a dopamine agonist that acts by inhibiting presynaptic dopamine transporters leading to suppression of dopamine reuptake (59, 60). That is, due to reuptake suppression, more dopamine remains in the synapse. Recently, a double-blind randomized placebo-controlled (DBRC) study utilizing methylphenidate showed a decrease in fatigue in 36 Parkinson's patients (61). A DBRC trial with 60 CFS patients also showed that 20 mg of methylphenidate over 4 weeks is effective in reducing fatigue (41). Roth et al. (62) evaluated the effectiveness of a 30 mg methylphenidate dose on fatigue in 36 cancer patients in a DBRC trial, resulting in decreased fatigue after 6 weeks of treatment (62). While clinical trials with methylphenidate on MS fatigue are ongoing, the above findings support the dopamine imbalance hypothesis and suggest that restoring dopamine levels by means of dopaminergic medication results in fatigue reduction.

MODULATORY EFFECTS OF DOPAMINE

Unlike the two major neurotransmitters, glutamate and gamma aminobutyric acid, which have excitatory and inhibitory properties, respectively, dopamine is a neuromodulator. Studies in animals and humans show that the influence of dopamine on cognition follows an inverted "U" shape function (13, 25), with too much or too little dopamine administration leading to impaired cognitive performance. Fatigue might be subject to a similar mechanism. In the case of working memory, Gibbs and D'Esposito (63) found that healthy participants who were given a dopamine agonist (i.e., bromocriptine) showed an increase in working memory capacity (63). Harel et al. (64) showed a similar effect in individuals with MS. The authors conducted a DBRC study with 26 MS patients. Patients were classified as working memory impaired according to baseline performance on a complex task that involves working memory, processing speed, and attention. Compared to

the placebo control group, follow-up task performance in the treatment group significantly improved after a single dose of methylphenidate (10 mg) taken 1 h before task follow-up (64). According to the dopamine imbalance hypothesis, administration of a dopamine agonist, such as the methylphenidate, should have lead to an increase in dopamine levels in the brain and a negative correlation between fatigue and performance; unfortunately, Harel et al. (64) did not report fatigue measures such as the FSS and the MFIS, or on-task fatigue.

Neuroimaging studies on working memory show that performance improvement in individuals with low working memory capacity is accompanied by increased connectivity between mesocorticolimbic structures increases after dopamine agonist administration (43). Vytlacil et al. (65) also showed a correlation between increased connectivity of the striatum and the midbrain nuclei (VTA and SN) and working memory performance after bromocriptine administration in individuals with low working memory capacity; an opposite pattern of results was observed in individuals with high working memory capacity. Similarly to what has been observed in the working memory literature, fatigue has been shown to be associated with reduced connectivity between mesocorticolimbic structures (39, 40). However, the effect of dopamine on mesocorticolimbic activation and connectivity in individuals with fatigue has not yet been investigated.

According to the gating hypothesis, dopamine might modulate cognition due to its interaction with other neurotransmitters in the PFC. When there is too much dopamine, the "gate" for excitatory inputs from glutamate neurons to post-synaptic PFC cells shuts down, while too little dopamine allows interference between different inputs (13, 19, 25). Similar to the gating hypothesis relating dopamine levels to cognition, the dopamine imbalance hypothesis proposes that fatigue might occur when there is too much or too little dopamine. Several studies show that while fatigue decreases with dopaminergic medication, the effect might be dose-dependent. Johansson et al. (42) observed a decrease in fatigue while participants were on a low dose of methylphenidate (5 mg), with an even greater decrease in fatigue observed when participants were on a higher dose of methylphenidate (20 mg). Similar results were obtained in hospice patients (66). Advanced cancer patients who reported high baseline fatigue, had greater fatigue reduction after 20 mg of methylphenidate (67, 68). Another DBRC trial with 109 human immunodeficiency virus participants showed methylphenidate titration to be effective in reducing fatigue. However, while some patients took the maximum dose of the medication to achieve fatigue reduction (up to 60 mg per day), other patients were able to achieve fatigue reduction with a lower dose (69).

Taken together, these studies highlight the modulatory effect of dopamine on cognition and fatigue. However, there is no evidence showing an increase in fatigue when there is too much dopamine in the CNS. Therefore, it remains to be tested if and at what dose dopamine medication ceases to be helpful in reducing fatigue. Given that dopamine is a neuromodulator that has been shown to have a variable effect on cognition (i.e., too low or too high levels of dopamine do not improve cognitive functioning), it is likely that it has a similar effect on fatigue. That is, fatigue might result from too much or too little dopamine in the brain.

THE ROLE OF DOPAMINE IN THE IMMUNE SYSTEM

Based in large part on the evidence from the MS animal model, experimental autoimmune encephalomyelitis (EAE), MS is considered to be an autoimmune disorder of the CNS. To a large extent, the immune system depends on the functioning of the leukocytes or white blood cells. T cells are a type of white blood cell that produce an immune response, i.e., they are activated when the body needs to fight an infection. In autoimmune diseases, including MS, T cells proliferate and attack healthy cells (18), passing though the blood–brain barrier into the CNS. It has been shown that proliferating $CD4^+$ cells (a type of T cells) express the D3 receptor that contributes to the destruction of dopamine neurons in the SN and generate interferon-γ, a compound that proliferates inflammation and prevents dopamine synthesis (11, 18, 70, 71). This potentially can result in decreased dopamine levels. Indeed, animal studies showed that CNS dopamine depletion by means of administration of the neurotoxin that kills dopamine cells in the SN leads to EAE exacerbation, while daily administration of a dopamine agonist, bromocriptine that has an affinity for D2 DRs (of which the striatum has a high concentration), has been shown to have beneficial effects on EAE. Treatment with bromocriptine has been shown to result in reduced severity and duration of relapses in rats with acute EAE. It also leads to the suppression of prolactin, a pituitary hormone that is inhibited by dopamine synthesized in the hypothalamus (see above) (10, 11, 17, 72). Though highly speculative, this line of reasoning suggests that fatigue might occur due to the dopamine imbalance that starts in the immune system, subsequently affecting the CNS.

IFNβ is an immunomodulatory drug approved for treatment in relapsing remitting MS. It is the first line of treatment and has been shown to prevent relapses. There are two types of IFNβ: IFNβ-1a and IFNβ-1b (73). Even though the precise mechanism of action of the IFNβ is not completely understood, it is thought that IFNβ prevents relapses and slows disability progression through retarding inflammatory processes, such as T-cell proliferation and passing of the $CD4^+$ T cells through the blood–brain barrier. More importantly, recent findings also show that IFNβ treatment leads to increased production of dopamine (58, 73–75).

Given that IFNβ increases dopamine synthesis, while dopaminergic medications help increase levels of dopamine in the brain, it is possible that individuals with MS on the IFNβ treatment might benefit more from the dopaminergic fatigue treatment or even have lower levels of fatigue than individuals with MS on a different treatment. To our knowledge, there is only one study that looked at fatigue in relapsing remitting MS with IFNβ treatment (76). Melanson et al. (76) in a non-randomized open-label study showed that fatigue decreases in patients on IFNβ treatment.

OTHER FATIGUE HYPOTHESES

SEROTONIN

In their seminal paper, Chaudhuri and Behan (9) called on researchers to clarify the roles of dopamine and serotonin in fatigue. Indeed, both neurotransmitters innervate the basal ganglia, with serotonergic neurons projecting to the basal ganglia from the raphe nuclei (77–79). The serotonin hypothesis developed because fatigue is a symptom of depression that is often treated with selective serotonin reuptake inhibitors. Serotonergic

levels in the CNS are particularly relevant in sports medicine, as exercise has been shown to increase serotonin levels in the brain, leading to amotivation (80, 81).

A few studies in clinical populations provide evidence in support of the serotonin hypothesis, suggesting that increased levels of serotonin might lead to fatigue (82–84). For example, Pavese and colleagues used ^{18}F-DOPA and ^{11}C-*N*, *N*-dimethyl-2-(2-amino-4-cyanophenylthio) benzylamine to investigate dopamine storage capacity and serotonin transmission, respectively, in the brain of on-medication PD patients with and without fatigue (85). This PET imaging study specifically focused on the basal ganglia and limbic structures. The region-of-interest analysis revealed significant differences in serotonin transmission between PD patients with and without fatigue. However, significant differences in dopamine storage capacity between PD patients with and without fatigue were revealed only through the voxel-based analysis. Thus, the results of this study support the serotonin hypothesis and suggest that serotonin transmission might play a more important role than striatal dopamine capacity in PD-related fatigue. Unfortunately, the study of Pavese et al. had a rather small sample size (8–10 per group) rendering the results inconclusive.

Clearly, delineating the neurobiological processes underlying such a complex phenomenon as fatigue will not be simple. It is likely that the interaction of several neurotransmitters systems is involved in fatigue. Given the large body of evidence showing the mesocorticolimbic network and, in particular the basal ganglia involvement in fatigue, it is difficult to negate the involvement of serotonin neurons that also innervate the basal ganglia. However, recent studies show that decreased functioning of serotonergic receptors leads to increased functioning of dopaminergic neurons and dopamine release [for review see Ref. (86)]. Therefore, given the preponderance of evidence to date, it appears that the dopamine imbalance hypothesis of fatigue has the most support.

INFLAMMATORY CYTOKINES

Recently, it has been suggested that inflammatory cytokines, compounds released by the cells of the immune system during inflammation, might be the cause of fatigue. The cytokine hypothesis developed based on the observation that fatigue co-occurs in individuals who have inflammatory biomarkers, such as tumor necrosis factor-α, interleukin-1, interleukin-6, and interferon-γ (8, 87–89).

A large body of evidence in support of the cytokine hypothesis comes from animal literature (8, 89). Indeed, animal studies show that after administration of inflammatory cytokines in the CNS, animals are less willing to exert effort in order to obtain a reward. Nunes et al. (90) showed that administration of the inflammatory cytokine interleukin-1β reduced effortful behavior in rats (decreased amount of lever presses). However, it is important to point out that effortful behavior is dopamine-dependent. Lesioning a region of the fronto-striatal network or dopamine depletion from fronto-striatal regions results in a cessation of effortful behavior (23, 91, 92). Thus, it is possible that the effect of cytokines on dopamine levels leads to fatigue, with dopamine levels being the culprit in generating fatigue and not the cytokines *per se*. Indeed, a recent study showed that methamphetamine, a psychostimulant that affects dopamine and, to a lesser extent, serotonin neurons, reduces frontocortical inflammatory cytokine levels (93), while other studies show that inflammatory cytokines have an effect on striatal functioning and dopamine release (87). Thus, such data may support the dopamine imbalance hypothesis, suggesting that the presence of inflammatory cytokines leads to dopamine imbalance.

SUMMARY AND CONCLUSION

In this review, we propose that fatigue arises due to an imbalance of dopamine, a modulatory neurotransmitter, in the CNS and the immune system. Based on the evidence cited above and building upon a previous framework on fatigue (9), we propose that fatigue depends on the base levels of dopamine in the CNS. Neuroimaging studies in clinical populations with fatigue repeatedly show structural and functional impairments in regions heavily innervated by dopaminergic neurons, namely the striatum and the PFC (See Supplementary Table 1 for the list of studies). While these brain structures underlie a wide range of processes, converging evidence suggests that an imbalance in dopamine plays a key role in fatigue. Indeed, dopaminergic medication that increases dopamine levels in the brain has been shown to increase the functioning and connectivity between these regions in healthy individuals and to decrease fatigue in clinical populations (See Supplementary Table 2 for the list of studies). Thus, the dopamine imbalance hypothesis provides a unifying framework for the study of fatigue.

Given this framework, future research should be geared toward testing specific aspects of the hypothesis. While studies in cognition show that dopamine has a modulatory influence on cognitive performance, clinical trials in fatigue so far only show that dopaminergic medication decreases fatigue. Since fatigue and cognitive functions such as working memory and attention rely on a similar neural network, it is likely that dopamine has a modulatory effect on fatigue as well. Future neuroimaging and pharmacological research is needed to directly test whether this is the case. Thus, an important question is, does fatigue increase as dopamine levels increase above optimal levels? Another question that should be investigated is whether dopamine agonist administration decreases on-task or "state" fatigue in conjunction with performance improvement. This will help in linking objective measures of performance, which have been shown to be affected by dopamine, with subjective on-task fatigue ratings. Pharmacological studies should evaluate the effect of a dopaminergic medication not only in comparison to a placebo but also in comparison with non-dopaminergic medications, to show whether fatigue is differentially affected by a dopaminergic medication versus, for example, serotonergic medication.

Neuroimaging studies should focus on manipulating mesocorticolimbic network activity in controlled experimental settings. This would allow researchers to observe network functioning in fatigued individuals and to answer specific questions about the time course of network activation in a controlled environment. Investigating the time course of network activation during task performance would reveal whether it correlates with on-task fatigue. It is also worth looking at whether the increased connectivity observed after dopamine medication, which has been shown to lead to an increase in working memory performance, is associated with fatigue reduction. Answering these questions will

provide valuable evidence about the underlying mechanisms of fatigue, and will ultimately allow us to develop targeted treatments for fatigue.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/Journal/10.3389/fneur.2015.00052/abstract

REFERENCES

1. Walker LAS, Berard JA, Berrigan LI, Rees LM, Freedman MS. Detecting cognitive fatigue in multiple sclerosis: method matters. *J Neurol Sci* (2012) **316**:86–92. doi:10.1016/j.jns.2012.01.021
2. Zifko UA. Management of fatigue in patients with multiple sclerosis. *Drugs* (2004) **64**:1295–304. doi:10.2165/00003495-200464120-00003
3. Cantor JB, Gordon W, Gumber S. What is post TBI fatigue? *NeuroRehabilitation* (2013) **32**:875–83. doi:10.3233/NRE-130912
4. Friedman JH, Abrantes A, Sweet LH. Fatigue in Parkinson's disease. *Expert Opin Pharmacother* (2011) **12**:1999–2007. doi:10.1517/14656566.2011.587120
5. Barsevick A, Frost M, Zwinderman A, Hall P, Halyard M. I'm so tired: biological and genetic mechanisms of cancer-related fatigue. *Qual Life Res* (2010) **19**:1419–27. doi:10.1007/s11136-010-9757-7
6. Jong E, Oudhoff LA, Epskamp C, Wagener MN, van Duijn M, Fischer S, et al. Predictors and treatment strategies of HIV-related fatigue in the combined antiretroviral therapy era. *AIDS* (2010) **24**:1387–405. doi:10.1097/QAD.0b013e328339d004
7. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International chronic fatigue syndrome study group. *Ann Intern Med* (1994) **121**:953–9. doi:10.7326/0003-4819-121-12-199412150-00009
8. Harrington ME. Neurobiological studies of fatigue. *Prog Neurobiol* (2012) **99**:93–105. doi:10.1016/j.pneurobio.2012.07.004
9. Chaudhuri A, Behan PO. Fatigue and basal ganglia. *J Neurol Sci* (2000) **179**:34–42. doi:10.1016/S0022-510X(00)00411-1
10. Vallone D, Picetti R, Borrelli E. Structure and function of dopamine receptors. *Neurosci Biobehav Rev* (2000) **24**:125–32. doi:10.1016/S0149-7634(99)00063-9
11. Cosentino M, Marino F. Adrenergic and dopaminergic modulation of immunity in multiple sclerosis: teaching old drugs new tricks? *J Neuroimmune Pharmacol* (2013) **8**:163–79. doi:10.1007/s11481-012-9410-z
12. Nieoullon A. Dopamine and the regulation of cognition and attention. *Prog Neurobiol* (2002) **67**:53–83. doi:10.1016/S0301-0082(02)00011-4
13. Seamans JK, Yang CR. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Prog Neurobiol* (2004) **74**:1–57. doi:10.1016/j.pneurobio.2004.05.006
14. Dalley JW, Roiser JP. Dopamine, serotonin and impulsivity. *Neuroscience* (2012) **215**:42–58. doi:10.1016/j.neuroscience.2012.03.065
15. Haber SN, Fudge JL, McFarland NR. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J Neurosci* (2000) **20**:2369–82.
16. Haber SN, Kim KS, Mailly P, Calzavara R. Reward-related cortical inputs define a large striatal region in primates that interface with associative cortical connections, providing a substrate for incentive-based learning. *J Neurosci* (2006) **26**:8368–76. doi:10.1523/JNEUROSCI.0271-06.2006
17. Basu S, Dasgupta PS. Dopamine, a neurotransmitter, influences the immune system. *J Neuroimmunol* (2000) **102**:113–24. doi:10.1016/S0165-5728(99)00176-9
18. Pacheco R, Contreras F, Zouali M. The dopaminergic system in autoimmune diseases. *Front Immunol* (2014) **5**:117. doi:10.3389/fimmu.2014.00117
19. Tzschentke TM. Pharmacology and behavioral pharmacology of the mesocortical dopamine system. *Prog Neurobiol* (2001) **63**:241–320. doi:10.1016/S0301-0082(00)00033-2
20. Hollerman JR, Tremblay L, Schultz W. Influence of reward expectation on behavior-related neuronal activity in primate striatum. *J Neurophysiol* (1998) **80**:947–63.
21. Schultz W. Predictive reward signal of dopamine neurons. *J Neurophysiol* (1998) **80**:1–27.
22. Stefani MR, Moghaddam B. Rule learning and reward contingency are associated with dissociable patterns of dopamine activation in the rat prefrontal cortex, nucleus accumbens, and dorsal striatum. *J Neurosci* (2006) **26**:8810–8. doi:10.1523/JNEUROSCI.1656-06.2006
23. Salamone JD, Correa M, Mingote S, Weber SM. Nucleus accumbens dopamine and the regulation of effort in food-seeking behavior: implications for studies of natural motivation, psychiatry, and drug abuse. *J Pharmacol Exp Ther* (2003) **305**:1–8. doi:10.1124/jpet.102.035063
24. Assadi SM, Yucel M, Pantelis C. Dopamine modulates neural networks involved in effort-based decision-making. *Neurosci Biobehav Rev* (2009) **33**:383–93. doi:10.1016/j.neubiorev.2008.10.010
25. Cools R, D'Esposito M. Inverted-U shaped dopamine actions on human working memory and cognitive control. *Biol Psychiatry* (2011) **69**:e113–25. doi:10.1016/j.biopsych.2011.03.028
26. Takahashi H, Yamada M, Suhara T. Functional significance of central D1 receptors in cognition: beyond working memory. *J Cereb Blood Flow Metab* (2012) **32**:1248–58. doi:10.1038/jcbfm.2011.194
27. Klanker M, Feenstra M, Denys D. Dopaminergic control of cognitive flexibility in humans and animals. *Front Neurosci* (2013) **7**:201. doi:10.3389/fnins.2013.00201
28. Dobryakova E, DeLuca J, Genova HM, Wylie GR. Neural correlates of cognitive fatigue: cortico-striatal circuitry and effort–reward imbalance. *J Int Neuropsych Soc* (2013) **19**(8):849–53. doi:10.1017/S1355617713000684
29. Pardini M, Bonzano L, Mancardi GL, Roccatagliata L. Frontal networks play a role in fatigue perception in multiple sclerosis. *Behav Neurosci* (2010) **124**:329–36. doi:10.1037/a0019585
30. Pardini M, Krueger F, Raymont V, Grafman J. Ventromedial prefrontal cortex modulates fatigue after penetrating traumatic brain injury. *Neurology* (2010) **74**:749–54. doi:10.1212/WNL.0b013e3181d25b6b
31. Genova HM, Rajagopalan V, Deluca J, Das A, Binder A, Arjunan A, et al. Examination of cognitive fatigue in multiple sclerosis using functional magnetic resonance imaging and diffusion tensor imaging. *PLoS One* (2013) **8**:e78811. doi:10.1371/journal.pone.0078811
32. Koch K, Wagner G, Schachtzabel C, Schultz CC, Güllmar D, Reichenbach JR, et al. Association between white matter fiber structure and reward-related reactivity of the ventral striatum. *Hum Brain Mapp* (2013) **35**(4):1469–76. doi:10.1002/hbm.22284
33. Tang WK, Chen YK, Mok V, Chu WCW, Ungvari GS, Ahuja AT, et al. Acute basal ganglia infarcts in poststroke fatigue: an MRI study. *J Neurol* (2010) **257**:178–82. doi:10.1007/s00415-009-5284-2
34. Tang WK, Liang HJ, Chen YK, Chu WCW, Abrigo J, Mok VCT, et al. Poststroke fatigue is associated with caudate infarcts. *J Neurol Sci* (2013) **15**:131–5. doi:10.1016/j.jns.2012.10.022
35. Téllez N, Alonso J, Río J, Tintoré M, Nos C, Montalban X, et al. The basal ganglia: a substrate for fatigue in multiple sclerosis. *Neuroradiology* (2008) **50**:17–23. doi:10.1007/s00234-007-0304-3
36. Roelcke U, Kappos L, Lechner-Scott J, Brunnschweiler H, Huber S, Ammann W, et al. Reduced glucose metabolism in the frontal cortex and basal ganglia of multiple sclerosis patients with fatigue: a 18F-fluorodeoxyglucose positron emission tomography study. *Neurology* (1997) **48**:1566–71. doi:10.1212/WNL.48.6.1566
37. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* (1989) **46**:1121–3. doi:10.1001/archneur.1989.00520460115022
38. Esposito F, Otto T, Zijlstra FRH, Goebel R. Spatially distributed effects of mental exhaustion on resting-state FMRI networks. *PloS One* (2014) **9**(4):e94222. doi:10.1371/journal.pone.0094222
39. Engström M, Flensner G, Landtblom A-M, Ek A-C, Karlsson T. Thalamo-striato-cortical determinants to fatigue in multiple sclerosis. *Brain Behav* (2013) **3**:715–28. doi:10.1002/brb3.181
40. Finke C, Schlichting J, Papazoglou S, Scheel M, Freing A, Soemmer C, et al. Altered basal ganglia functional connectivity in multiple sclerosis patients with fatigue. *Mult Scler* (2014). doi:10.1177/1352458514555784
41. Blockmans D, Persoons P, Van Houdenhove B, Bobbaers H. Does methylphenidate reduce the symptoms of chronic fatigue syndrome? *Am J Med* (2006) **119**:e23–30. doi:10.1016/j.amjmed.2005.07.047

42. Johansson B, Wentzel A, Andrell P, Odenstedt J, Mannheimer C, Ronnback L. Evaluation of dosage, safety and effects of methylphenidate on post-traumatic brain injury symptoms with a focus on mental fatigue and pain. *Brain Inj* (2014) **28**:304–10. doi:10.3109/02699052.2013.865267
43. Wallace DL, Vytlacil JJ, Nomura EM, Gibbs SEB, D'Esposito M. The dopamine agonist bromocriptine differentially affects fronto-striatal functional connectivity during working memory. *Front Hum Neurosci* (2011) **5**:32. doi:10.3389/fnhum.2011.00032
44. Konova AB, Moeller SJ, Tomasi D, Volkow ND, Goldstein RZ. Effects of methylphenidate on resting-state functional connectivity of the mesocorticolimbic dopamine pathways in cocaine addiction. *JAMA Psychiatry* (2013) **70**:857–68. doi:10.1001/jamapsychiatry.2013.1129
45. Mueller S, Costa A, Keeser D, Pogarell O, Berman A, Coates U, et al. The effects of methylphenidate on whole brain intrinsic functional connectivity. *Hum Brain Mapp* (2014) **35**(11):5379–88. doi:10.1002/hbm.22557
46. Wylie GR, Javitt DC, Foxe JJ. Jumping the gun: is effective preparation contingent upon anticipatory activation in task-relevant neural circuitry? *Cereb Cortex* (2006) **16**:394–404. doi:10.1093/cercor/bhi118
47. Wylie GR, Sumowski JF, Murray M. Are there control processes, and (if so) can they be studied? *Psychol Res* (2011) **75**(6):535–43. doi:10.1007/s00426-011-0354-3
48. Weaver SM, Foxe JJ, Shpaner M, Wylie GR. You can't always get what you want: the influence of unexpected task constraint on voluntary task switching. *Q J Exp Psychol (Hove)* (2014) **67**(11):2247–59. doi:10.1080/17470218.2014.917115
49. Miller AH, Jones JF, Drake DF, Tian H, Unger ER, Pagnoni G. Decreased basal ganglia activation in subjects with chronic fatigue syndrome: association with symptoms of fatigue. *PLoS One* (2014) **9**:e98156. doi:10.1371/journal.pone.0098156
50. Krupp LB, Coyle PK, Doscher C, Miller A, Cross AH, Jandorf L, et al. Fatigue therapy in multiple sclerosis: results of a double-blind, randomized, parallel trial of amantadine, pemoline, and placebo. *Neurology* (1995) **45**:1956–61. doi:10.1212/WNL.45.11.1956
51. Pucci E, Branãs P, D'Amico R, Giuliani G, Solari A, Taus C. Amantadine for fatigue in multiple sclerosis. *Cochrane Database Syst Rev* (2007) **1**:CD002818. doi:10.1002/14651858.CD002818.pub2
52. Stankoff B, Waubant E, Confavreux C, Edan G, Debouverie M, Rumbach L, et al. Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study. *Neurology* (2005) **64**:1139–43. doi:10.1212/01.WNL.0000158272.27070.6A
53. Ledinek AH, Sajko MC, Rot U. Evaluating the effects of amantadine, modafinil and acetyl-L-carnitine on fatigue in multiple sclerosis – result of a pilot randomized, blind study. *Clin Neurol Neurosurg* (2013) **1155**:S86–9. doi:10.1016/j.clineuro.2013.09.029
54. Kumar R. Approved and investigational uses of modafinil: an evidence-based review. *Drugs* (2008) **68**:1803–39. doi:10.2165/00003495-200868130-00003
55. Kaminska M, Kimoff RJ, Schwartzman K, Trojan DA. Sleep disorders and fatigue in multiple sclerosis: evidence for association and interaction. *J Neurol Sci* (2011) **302**:7–13. doi:10.1016/j.jns.2010.12.008
56. Rammohan KW, Rosenberg JH, Lynn DJ, Blumenfeld AM, Pollak CP, Nagaraja HN. Efficacy and safety of modafinil (provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. *J Neurol Neurosurg Psychiatry* (2002) **72**:179–83. doi:10.1136/jnnp.72.2.179
57. Sheng P, Hou L, Wang X, Wang X, Huang C, Yu M, et al. Efficacy of modafinil on fatigue and excessive daytime sleepiness associated with neurological disorders: a systematic review and meta-analysis. *PLoS One* (2013) **8**:e81802. doi:10.1371/journal.pone.0081802
58. Zaffaroni M, Marino F, Bombelli R, Rasini E, Monti M, Ferrari M, et al. Therapy with interferon-beta modulates endogenous catecholamines in lymphocytes of patients with multiple sclerosis. *Exp Neurol* (2008) **214**:315–21. doi:10.1016/j.expneurol.2008.08.015
59. Volkow ND, Wang G, Fowler JS, Logan J, Gerasimov M, Maynard L, et al. Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. *J Neurosci* (2001) **21**:RC121.
60. Prommer E. Methylphenidate: established and expanding roles in symptom management. *Am J Hosp Palliat Care* (2012) **29**:483–90. doi:10.1177/1049909111427029
61. Mendonça DA, Menezes K, Jog MS. Methylphenidate improves fatigue scores in Parkinson disease: a randomized controlled trial. *Mov Disord* (2007) **22**:2070–6. doi:10.1002/mds.21656
62. Roth AJ, Nelson C, Rosenfeld B, Scher H, Slovin S, Morris M, et al. Methylphenidate for fatigue in ambulatory men with prostate cancer. *Cancer* (2010) **116**:5102–10. doi:10.1002/cncr.25424
63. Gibbs SEB, D'Esposito M. Individual capacity differences predict working memory performance and prefrontal activity following dopamine receptor stimulation. *Cogn Affect Behav Neurosci* (2005) **5**:212–21. doi:10.3758/CABN.5.2.212
64. Harel Y, Appleboim N, Lavie M, Achiron A. Single dose of methylphenidate improves cognitive performance in multiple sclerosis patients with impaired attention process. *J Neurol Sci* (2009) **276**:38–40. doi:10.1016/j.jns.2008.08.025
65. Vytlacil J, Kayser A, Miyakawa A, D'Esposito M. An approach for identifying brainstem dopaminergic pathways using resting state functional MRI. *PLoS One* (2014) **9**:e87109. doi:10.1371/journal.pone.0087109
66. Kerr CW, Drake J, Milch RA, Brazeau DA, Skretny JA, Brazeau GA, et al. Effects of methylphenidate on fatigue and depression: a randomized, double-blind, placebo-controlled trial. *J Pain Symptom Manage* (2012) **43**:68–77. doi:10.1016/j.jpainsymman.2011.03.026
67. Moraska AR, Sood A, Dakhil SR, Sloan JA, Barton D, Atherton PJ, et al. Phase III, randomized, double-blind, placebo-controlled study of long-acting methylphenidate for cancer-related fatigue: north central cancer treatment group NCCTG-N05C7 trial. *J Clin Oncol* (2010) **28**:3673–9. doi:10.1200/JCO.2010.28.1444
68. Yennurajalingam S, Palmer JL, Chacko R, Bruera E. Factors associated with response to methylphenidate in advanced cancer patients. *Oncologist* (2011) **16**:246–53. doi:10.1634/theoncologist.2010-0214
69. Breitbart W, Rosenfeld B, Kaim M, Funesti-Esch J. A randomized, double-blind, placebo-controlled trial of psychostimulants for the treatment of fatigue in ambulatory patients with human immunodeficiency virus disease. *Arch Intern Med* (2001) **161**:411–20. doi:10.1001/archinte.161.3.411
70. Cosentino M, Zaffaroni M, Ferrari M, Marino F, Bombelli R, Rasini E, et al. Interferon-gamma and interferon-beta affect endogenous catecholamines in human peripheral blood mononuclear cells: implications for multiple sclerosis. *J Neuroimmunol* (2005) **162**:112–21. doi:10.1016/j.jneuroim.2005.01.019
71. González H, Contreras F, Prado C, Elgueta D, Franz D, Bernales S, et al. Dopamine receptor D3 expressed on CD4+ T cells favors neurodegeneration of dopaminergic neurons during Parkinson's disease. *J Immunol* (2013) **190**:5048–56. doi:10.4049/jimmunol.1203121
72. Dijkstra CD, van der Voort ER, De Groot CJA, Huitinga I, Uitdehaag BMJ, Polman CH, et al. Therapeutic effect of the D2-dopamine agonist bromocriptine on acute and relapsing experimental allergic encephalomyelitis. *Psychoneuroendocrinology* (1994) **19**:135–42. doi:10.1016/0306-4530(94)90003-5
73. Dhib-Jalbut S, Marks S. Interferon-beta mechanisms of action in multiple sclerosis. *Neurol* (2010) **74**(Suppl 1):S17–24. doi:10.1212/WNL.0b013e3181c97d99
74. Giorelli M, Livrea P, Trojano M. Dopamine fails to regulate activation of peripheral blood lymphocytes from multiple sclerosis patients: effects of IFN-beta. *J Interferon Cytokine Res* (2005) **25**:395–406. doi:10.1089/jir.2005.25.395
75. Cosentino M, Zaffaroni M, Trojano M, Giorelli M, Pica C, Rasini E, et al. Dopaminergic modulation of CD4+CD25(high) regulatory T lymphocytes in multiple sclerosis patients during interferon-β therapy. *Neuroimmunomodulation* (2012) **19**:283–92. doi:10.1159/000336981
76. Melanson M, Grossberndt A, Klowak M, Leong C, Frost EE, Prout M, et al. Fatigue and cognition in patients with relapsing multiple sclerosis treated with interferon β. *Int J Neurosci* (2010) **120**:631–40. doi:10.3109/00207454.2010.511732
77. Parent M, Wallman M-J, Gagnon D, Parent A. Serotonin innervation of basal ganglia in monkeys and humans. *J Chem Neuroanat* (2011) **41**:256–65. doi:10.1016/j.jchemneu.2011.04.005
78. Mathur BN, Lovinger DM. Serotonergic action on dorsal striatal function. *Parkinsonism Relat Disord* (2012) **1**:129–31. doi:10.1016/S1353-8020(11)70040-2
79. De Deurwaerdère P, Lagière M, Bosc M, Navailles S. Multiple controls exerted by 5-HT2C receptors upon basal ganglia function: from physiology to pathophysiology. *Exp Brain Res* (2013) **230**:477–511. doi:10.1007/s00221-013-3508-2
80. Meeusen R, Watson P, Hasegawa H, Roelands B, Piacentini MF. The serotonin hypothesis and beyond. *Sports Med* (2006) **36**:881–909. doi:10.2165/00007256-200636100-00006
81. Meeusen R, Roelands B. Central fatigue and neurotransmitters, can thermoregulation be manipulated? *Scand J Med Sci Sports* (2010) **20**(Suppl 3):19–28. doi:10.1111/j.1600-0838.2010.01205.x

82. Yamamoto S, Ouchi Y, Onoe H, Yoshikawa E, Tsukada H, Takahashi H, et al. Reduction of serotonin transporters of patients with chronic fatigue syndrome. *Neuroreport* (2004) **15**:2571–4. doi:10.1097/00001756-200412030-00002
83. Hesse S, Moeller F, Petroff D, Lobsien D, Luthardt J, Regenthal R, et al. Altered serotonin transporter availability in patients with multiple sclerosis. *Eur J Nucl Med Mol Imaging* (2014) **41**:827–35. doi:10.1007/s00259-013-2636-z
84. The GKH, Verkes RJ, Fekkes D, Bleijenberg G, van der Meer JWM, Buitelaar JK. Tryptophan depletion in chronic fatigue syndrome, a pilot cross-over study. *BMC Res Notes* (2014) **7**:650. doi:10.1186/1756-0500-7-650
85. Pavese N, Metta V, Bose SK, Chaudhuri KR, Brooks DJ. Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction. *Brain* (2010) **133**:3434–43. doi:10.1093/brain/awq268
86. Di Giovanni G, Esposito E, Di Matteo V. Role of serotonin in central dopamine dysfunction. *CNS Neurosci Ther* (2010) **16**:179–94. doi:10.1111/j.1755-5949.2010.00135.x
87. Felger JC, Miller AH. Cytokine effects on the basal ganglia and dopamine function: the subcortical source of inflammatory malaise. *Front Neuroendocrinol* (2012) **33**:315–27. doi:10.1016/j.yfrne.2012.09.003
88. Smith AP. Twenty-five years of research on the behavioural malaise associated with influenza and the common cold. *Psychoneuroendocrinology* (2013) **38**:744–51. doi:10.1016/j.psyneuen.2012.09.002
89. Dantzer R, Heijnen CJ, Kavelaars A, Laye S, Capuron L. The neuroimmune basis of fatigue. *Trends Neurosci* (2014) **37**:39–46. doi:10.1016/j.tins.2013.10.003
90. Nunes EJ, Randall PA, Estrada A, Epling B, Hart EE, Lee CA, et al. Effort-related motivational effects of the pro-inflammatory cytokine interleukin 1-beta: studies with the concurrent fixed ratio 5/ chow feeding choice task. *Psychopharmacology (Berl)* (2014) **231**:727–36. doi:10.1007/s00213-013-3285-4
91. Salamone JD, Correa M, Nunes EJ, Randall PA, Pardo M. The behavioral pharmacology of effort-related choice behavior: dopamine, adenosine and beyond. *J Exp Anal Behav* (2012) **97**:125–46. doi:10.1901/jeab.2012.97-125
92. Ishiwari K, Weber SM, Mingote S, Correa M, Salamone JD. Accumbens dopamine and the regulation of effort in food-seeking behavior: modulation of work output by different ratio or force requirements. *Behav Brain Res* (2004) **151**:83–91. doi:10.1016/j.bbr.2003.08.007
93. Stolyarova A, Thompson AB, Barrientos RM, Izquierdo A. Reductions in frontocortical cytokine levels are associated with long-lasting alterations in reward valuation after methamphetamine. *Neuropsychopharmacology* (2014). doi:10.1038/npp.2014.309

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The representation of inflammatory signals in the brain – a model for subjective fatigue in multiple sclerosis

Katrin Hanken[1], Paul Eling[2] and Helmut Hildebrandt[1]*

[1] *Department of Neurology, Klinikum Bremen-Ost, Bremen, Germany*
[2] *Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Nijmegen, Netherlands*

Edited by:
Christian Dettmers, Kliniken Schmieder Konstanz, Germany

Reviewed by:
Christian Dettmers, Kliniken Schmieder Konstanz, Germany
Yuhong Yang, The Ohio State University Medical Center, USA

***Correspondence:**
Helmut Hildebrandt, e-mail: helmut.hildebrandt@uni-oldenburg.de

In multiple sclerosis (MS) patients, fatigue is rated as one of the most common and disabling symptoms. However, the pathophysiology underlying this fatigue is not yet clear. Several lines of evidence suggest that immunological factors, such as elevated levels of pro-inflammatory cytokines, may contribute to subjective fatigue in MS patients. Pro-inflammatory cytokines represent primary mediators of immune-to-brain-communication, modulating changes in the neurophysiology of the central nervous system. Recently, we proposed a model arguing that fatigue in MS patients is a subjective feeling, which is related to inflammation. Moreover, it implies that fatigue can be measured behaviorally only by applying specific cognitive tasks related to alertness and vigilance. In the present review, we focus on the subjective feeling of MS-related fatigue. We examine the hypothesis that the subjective feeling of MS-related fatigue may be a variant of inflammation-induced sickness behavior, resulting from cytokine-mediated activity changes within brain areas involved in interoception and homeostasis including the insula, the anterior cingulate, and the hypothalamus. We first present studies demonstrating a relationship between pro-inflammatory cytokines and subjective fatigue in healthy individuals, in people with inflammatory disorders, and particularly in MS patients. Subsequently, we discuss studies analyzing the impact of anti-inflammatory treatment on fatigue. In the next part of this review, we present studies on the transmission and neural representation of inflammatory signals, with a special focus on possible neural concomitants of inflammation-induced fatigue. We also present two of our studies on the relationship between local gray and white matter atrophy and fatigue in MS patients. Finally, we discuss some implications of our findings and future perspectives.

Keywords: multiple sclerosis, subjective fatigue, inflammation, pro-inflammatory cytokines, neuroimmunomodulation, insula, anterior cingulate cortex, hypothalamus

INTRODUCTION

In multiple sclerosis (MS) patients, fatigue is rated as one of the most common and disabling symptoms. Its prevalence ranges from 65 to 97%, and it tends to seriously impair approximately one-third of all MS patients (1–4). Fatigue significantly impairs a patient's quality of life, bearing negative effects on performance at work and on the patient's social and private life (2, 5). Despite many investigations, the pathophysiology underlying MS-related fatigue is not yet clear. Proposed mechanisms for fatigue include primary causes such as gray matter atrophy (6–8), demyelination and axonal loss (9), functional cortical reorganization (10, 11), neuroendocrine dysregulation (12) as well as an immune system dysfunction (13, 14). On the other hand, also secondary causes such as sleep problems, medication, and depression have been suggested to be associated with MS-related fatigue (15, 16).

Based on our recently performed review on the relation between fatigue, cognitive performance, and brain atrophy in MS patients (17), we proposed a new model of MS-related fatigue. This model argues that subjective fatigue is a feeling resulting from inflammation-induced neural processing within interoceptive and homeostatic brain areas. Moreover, it argues that fatigue is only associated with specific cognitive states, such as alertness and vigilance, which depend on a high level of endogenous attention and which can be easily distracted by internal events like thoughts, feelings, and emotions (18). Hence, increased focusing on interoceptive aspects due to inflammation may disturb information processing of external stimuli and may interfere with sustained attention to a vigilance task causing a decrease in performance. Additionally, we suggest that this specific performance decrement may be exaggerated by brain atrophy or neurochemical dysfunction affecting the alerting/vigilance system (see **Figure 1**). **Figure 1** (lower part) comprises the two different central phenomena, which we believe a complete theory of fatigue has to explain, i.e., subjective fatigue as a feeling and objective fatigue as the measurable decrement in behavioral performance. It also shows the two different causes (inflammation-induced changes in neural activity and specified focal brain atrophy), which can lead either to the feeling of fatigue and the objective impairment in sustained attention tasks or to the impairment in sustained attention tasks alone.

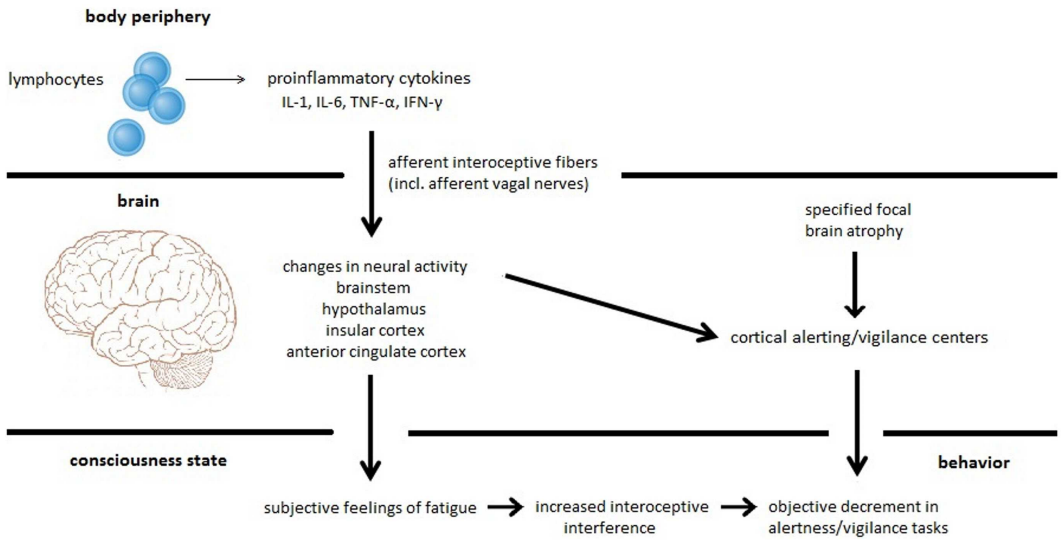

FIGURE 1 | Proposed model for MS-related fatigue. Peripherally released pro-inflammatory cytokines IL-1, IL-6, TNF-α, and INF-γ activate immune-to-brain communication pathways such as afferent interoceptive nerve fibers (particularly afferents of the vagus nerve). These afferent nerve fibers innervate interoceptive and homeostatic brain areas including regions of the brainstem, the hypothalamus, the insula, and the anterior cingulate. Inflammation-induced activity changes within these brain regions cause the subjective feeling of fatigue. Furthermore, interoceptive information processing constitutes interoceptive interference resulting in a distraction of cognitive processes such as alertness and vigilance tasks that heavily rely on intrinsic alertness. This specific fatigue-related alertness and vigilance decrement can be exaggerated by focal brain atrophy affecting the alertness/vigilance network.

In the present review, we focus on the first aspect, namely the explanation of fatigue as a subjective feeling resulting from inflammation. Pro-inflammatory cytokines are elevated during inflammation and appear to represent primary mediators of the immune-to-brain-communication. Peripheral pro-inflammatory cytokines act specifically on brain regions involved in interoception and homeostasis to initiate physiological and behavioral changes such as fatigue (19). Consequently, we hypothesize that the subjective feeling of MS-related fatigue may be a variant of inflammation-induced sickness behavior, resulting from cytokine-mediated activity changes within brain areas involved in interoception and homeostasis including the insula, the anterior cingulate, and the hypothalamus. To evaluate this hypothesis, we will look at studies that investigated neural correlates of peripheral inflammation.

FATIGUE AND PRO-INFLAMMATORY CYTOKINES IN HEALTHY INDIVIDUALS

Assuming that subjective fatigue is a feeling resulting from central actions of increased peripheral pro-inflammatory cytokine concentrations, elevated levels of pro-inflammatory cytokines should also cause fatigue in healthy individuals. Weisdorf et al. (20) have demonstrated the important role of pro-inflammatory cytokines in the generation of fatigue by showing that several pro-inflammatory cytokines such as IL-1, IL-2, IL-6, IFN-γ, and TNF-α cause fatigue and somnolence in healthy individuals when administered exogeneously.

Furthermore, when healthy individuals become sick, they generate sickness behavior. The term sickness behavior has been used to refer to behavior that may be regarded as an adaptive response to acute infections or injuries (21). Everyone who has been suffering from a viral or bacterial infection will know what it means to "feel sick." Major symptoms of sickness behavior may include fatigue, depression, anhedonia, anorexia, and increased pain sensitivity (22, 23). The syndrome may be fully present in some patients but only partly in others, depending on the severity and nature of inflammatory processes (24). The physiological and behavioral components of sickness behavior represent a highly organized strategy of an organism to cope with the infection. Sickness behavior appears to be primarily induced and regulated by pro-inflammatory cytokines such as IL-1α, IL-1β, TNF-α, and IL-6 (25–27). These cytokines are produced at the site of infection by activated immune cells and act centrally to induce physiological and behavioral components of sickness behavior (26, 28). This evidence suggests that the neurophysiology of sickness behavior may be responsible for the generation of inflammation-related fatigue.

Kerr et al. (27) studied healthy individuals, individuals at the time of acute viral infection (human parvovirus B 19) and after a mean follow-up period of 22.5 month. They demonstrated that circulating levels of TNF-α and IFN-γ were raised during acute and convalescent viral infection and that these elevated cytokine levels were strongly associated with subjective feelings of fatigue. Similar findings were reported by Hannestad et al. (29). These authors found that endotoxin-induced systemic inflammation increased serum levels of TNF-α and IL-6 as well as subjective fatigue in healthy individuals.

Kluge et al. (30, 31) analyzed immunomodulatory effects of antipsychotic drugs olanzapine and clozapine, which frequently produce sedation and sleepiness that share many similarities to fatigue (32). These researchers found that both drugs activate the

cytokine system. Clozapine treatment was predominantly associated with an increase in TNF-α, sTNFr-1, sTNFr-2, IL-2r, and IL-6, whereas olanzapine treatment was found to be related to an increase in TNF-α, sIL-2r, and sTNFr-2.

FATIGUE AND PRO-INFLAMMATORY CYTOKINES IN INFLAMMATORY DISORDERS

Assuming that subjective fatigue is a feeling related to elevated pro-inflammatory cytokine levels, fatigue should be a major symptom in disorders with an underlying inflammatory pathophysiology. Actually, fatigue is a frequent complaint of patients suffering from inflammatory disorders such as chronic fatigue syndrome (33, 34), cancer (35), or autoimmune and autoinflammatory diseases such as systemic lupus erythematosus (36, 37), rheumatoid arthritis (38), Sjögren's syndrome (39), and MS (3). Fatigue is also often reported by patients suffering from diseases that show signs of inflammation such as traumatic brain injury (40), stroke (41), Parkinson disease (42), sleep apnea (43), and human immunodeficiency virus infection (44). All these disorders are characterized by increased pro-inflammatory cytokine concentrations, strengthening the assumption that subjective fatigue may be due to elevated pro-inflammatory cytokines and their effect on the central nervous system (CNS).

Maes et al. (23) measured inflammatory markers in 107 patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), 37 patients with chronic fatigue, and 20 healthy individuals. They found higher serum levels of IL-1 and TNF-α in patients with ME/CFS than in chronic fatigue patients and healthy controls. Furthermore, they found a significant correlation between increased serum IL-1, TNF-α, and subjective fatigue in patients suffering from ME/CFS. Meyers et al. (45) studied 54 patients with acute myelogenous leukemia and myelodysplastic syndrome before treatment initiation. They demonstrated significantly increased levels of circulating cytokines IL-1, IL-1ra, IL-6, IL-8, TNF-α, impaired cognitive functions, and elevated levels of subjective fatigue in these patients. Increased concentrations of IL-6, IL-1ra, and TNF-α were significantly correlated to subjective fatigue. Similar results were obtained by Bower et al. (46) who compared serum markers associated with pro-inflammatory cytokine activity in 20 fatigued breast cancer survivors and 20 non-fatigued survivors. Fatigued breast cancer survivors showed significantly higher serum levels of IL-1ra, sTNFr-2, and neopterin than survivors without fatigue. Moreover, cancer-related fatigue is commonly exacerbated by radio- and chemotherapy, which is thought to increase serum levels of pro-inflammatory cytokines (45, 47, 48). Greenberg et al. (49) examined this issue by evaluating the effect of radiotherapy on subjective fatigue and serum IL-1 in 15 men receiving radiation treatment for prostate cancer. They observed an association between the rise in serum IL-1 and the increase in subjective fatigue during radiotherapy. Cameron et al. (50) performed a longitudinal study (from time of treatment to 12 month later) investigating serum cytokine levels in 13 breast cancer patients with fatigue and 15 controls without post-cancer fatigue and did not find significant differences in cytokine levels between these two groups. However, the blood sampling for the analysis was conducted several weeks after the penultimate treatment cycle. Thus, relevant changes in cytokine concentration associated with treatment-related fatigue might have been missed. Moreover, the number of participants was very small and might have led to a Type II statistical error. Ormstad et al. (41) investigated the association between cytokine serum levels 72 h after stroke onset and fatigue scores at 6 and 12 month in 45 ischemic stroke patients. They found that acute serum levels of IL-1β positively correlated with the fatigue score at 6 month after stroke.

Most of these studies point to an association between pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α and fatigue in disorders characterized by elevated cytokine levels. This well-documented association between elevated pro-inflammatory cytokines and increased subjective fatigue may well have implications for the explanation of fatigue. Thus, research on the relation between subjective fatigue and pro-inflammatory cytokines appears to be of great interest for a better understanding of MS-related fatigue.

FATIGUE AND PRO-INFLAMMATORY CYTOKINES IN MULTIPLE SCLEROSIS PATIENTS

Multiple Sclerosis is considered to be an autoimmune inflammatory disorder of the CNS, in which autoreactive T-lymphocytes recognize CNS-specific proteins resulting in inflammation, demyelination, and axon degeneration (51). Pro- and anti-inflammatory cytokines are commonly up-regulated in parallel in most MS patients (52). Compared to healthy individuals, MS patients display increased serum and cerebrospinal fluid levels of pro-inflammatory cytokines such as IFN-γ, TNF-α, lymphotoxin-α, IL-2, IL-1β, and anti-inflammatory cytokines such as IL-10, IL-13, and TGF-β (52, 53). Given that pro-inflammatory cytokines have been linked to fatigue in various conditions with an underlying immunomodulatory pathology, it is not surprising that fatigue is regarded as one of the most common and disabling symptoms in MS (2–4).

Several lines of evidence suggest that immune factors play a major role in MS-related fatigue, supporting our hypothesis that MS-related fatigue might be some sort of inflammation-induced sickness behavior resulting from cytokine-induced changes in CNS neurophysiology. MS patients often complain of a higher fatigue level during relapses, which are characterized by an increased immune activation, representing an up-modulation of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and lymphotoxin-α (52, 54–56). Moreover, the administration of immunomodulatory medication such as interferon-beta frequently causes short-term effects such as reversible fatigue in MS (55, 57, 58). Goebel et al. (59) studied the effect of interferon-beta (IFN-β-1b) on plasma levels of inflammatory cytokines in eight healthy men. They found that interferon-beta injection led to an immediate increase in TNF-α, IL-6, and IL-10 plasma levels. Nicoletti et al. (60) studied the impact of short-term interferon-beta treatment on blood cytokine levels in 14 relapsing-remitting MS patients. They found that MS patients treated with interferon-beta showed increased serum levels of IL-6, IFN-γ, and IL-10.

Studies on the relationship between pro-inflammatory cytokines and MS-related fatigue demonstrated a significant association between subjective fatigue and the stimulated production capacity for IFN-γ and TNF-α (14, 61). Pokryszko-Dragan et al. (61) evaluated the stimulated production of IFN-γ by peripheral

$CD3^+$- and $CD4^+$-T lymphocytes in 20 MS patients with and 20 without fatigue as determined by the Fatigue Severity Scale (FSS). They found an increased stimulated IFN-γ production in severely fatigued MS patients. Heesen et al. (14) compared whole blood stimulatory capacity for pro- (TNF-α, IFN-γ) and anti-inflammatory (IL-10) cytokines in 15 MS patients with and 15 MS patients without fatigue as determined by the FSS. They found that patients with fatigue displayed significantly increased TNF-α and IFN-γ production capacities. Flachenecker et al. (13) reported similar findings by studying 37 MS patients. They demonstrated a significant association between TNF-α mRNA expression in peripheral blood cells and FSS scores, independent from age, disease duration, disease course, disability, interferon treatment, or signs of autonomic dysfunction. Finally, Bertolone et al. (62) measured serum levels of IL-1β, Il-6, β-2-microglobolin, sIL-2r, and soluble CD8 in 30 MS patients with severe fatigue. They found a significant correlation between beneficial effects of amantadine and pemoline on subjective fatigue and reductions in serum levels of IL-1β and IL-6.

On the other hand, Rudick and Barna (63) did not find significant differences in IL-2 levels comparing 8 fatigued MS patients and 50 healthy controls. Other studies that failed to demonstrate an association between inflammatory processes and MS-related subjective fatigue did not measure direct pro-inflammatory cytokine concentrations (64, 65). Instead, they analyzed concentrations of inflammatory markers such as urinary neopterin or they measured indirect effects of pro-inflammatory cytokines.

Summing up, studies on the relationship between pro-inflammatory cytokines and MS-related subjective fatigue highlight an association between elevated pro-inflammatory cytokines IFN-γ, TNF-α, IL-1, IL-6, and increased feelings of fatigue. These findings support our hypothesis that subjective fatigue in MS patients might be a variant of inflammation-induced sickness behavior resulting from cytokine-induced changes in CNS neurophysiology.

ANTI-INFLAMMATORY TREATMENT AND FATIGUE

Providing that pro-inflammatory cytokines and their effect on the CNS induce the feeling of fatigue, anti-inflammatory treatment should reduce subjective fatigue. Actually, anti-TNF-α treatment strategies have shown to ameliorate subjective fatigue in patients suffering from rheumatoid arthritis and sleep apnea (66, 67). Anakinra, an IL-1 receptor antagonist used in rheumatoid arthritis, also showed significant improvements on fatigue scores (68). In patients with Sjögren's syndrome, inhibition of IL-1β caused a 50% reduction in subjective fatigue (39). Finally, bupropion, a psychopharmacological drug with anti-inflammatory properties against TNF-α, has shown to reduce excessive daytime sleepiness (69).

If subjective fatigue in MS patients represents an internal state resulting from increased pro-inflammatory cytokine levels, anti-inflammatory treatment should also have beneficial effects on fatigue in MS patients. However, there are hardly any studies on the effect of anti-inflammatory cytokines on MS-related fatigue. Glatiramer acetate, used in the treatment of MS, has anti-inflammatory properties and seems to reduce fatigue in MS patients (70, 71). Furthermore, natalizumab treatment, which was found to reduce circulating plasma levels of TNF-α, IL-6, and IL-10 as well as cerebrospinal fluid levels of IL-1β, IL-6, and IL-8, seems to have a beneficial effect on subjective fatigue in MS patients (72–75). Interestingly, aerobic exercise leads to a reduction in subjective fatigue in MS patients (76, 77). Regular aerobic exercise in MS patients was found to induce anti-inflammatory actions such as the stimulated production of anti-inflammatory cytokines and the inhibited production of pro-inflammatory cytokines TNF-α and IFN-γ (78). Therefore, the beneficial effect of aerobic exercise on MS-related fatigue may be due to its anti-inflammatory implications. Finally, body cooling, which was found to have a positive impact on MS-related fatigue, also seems to decrease pro-inflammatory cytokine (IL-1) production by peripheral blood cells (79, 80).

All these observations point to a beneficial effect of anti-inflammatory treatment options on subjective fatigue in disorders with elevated levels of pro-inflammatory cytokines, supporting our hypothesis of a relationship between pro-inflammatory cytokines and fatigue.

NEURONAL ASPECTS OF FATIGUE – TRANSMISSION AND REPRESENTATION OF INFLAMMATORY SIGNALS IN THE BRAIN

If subjective fatigue is a feeling such as anxiety or pain, one would expect this feeling to be represented cortically. Consequently, the question arises which brain areas are associated with processing the feeling fatigue. According to our hypothesis, we expect brain areas, related to central effects of peripheral inflammation and immunomodulation, to be associated with fatigue. To understand how peripheral pro-inflammatory cytokines may produce this feeling of fatigue, we will now review studies on the transmission and central representation of peripheral inflammatory signals and its association with fatigue.

It is commonly presumed that peripherally released cytokines act on the brain via two pathways: one fast neural transmission pathway involving primary afferent nerves innervating the body site of inflammation and a slow humoral transmission pathway involving cytokines originating from the choroid plexus and circumventricular organs (22, 28, 81).

Studies have shown that primary afferent nerves, especially afferents of the vagus nerve, play a key role in the neural transmission of peripheral immune signals to the brain (82–86). For example, immunohistochemical studies demonstrated an activation of vagal primary afferent neurons after having treated rats with peripheral endotoxin or IL-1β (87, 88). Other animal studies have shown that sectioning the abdominal vagus nerve abolished most brain-mediated illness responses induced by the peripheral administration of endotoxin or IL-1β (89, 90). Sensory neurons of the vagal nerve appear to possess receptors for pro-inflammatory cytokines and the activation of afferent nerve fibers by peripherally released cytokines presumably represents a fast pathway and direct activation of specified brain targets (26, 81). However, the specific neural substrates that process immunosensory information remain elusive. Animal experiments using immunohistochemistry to detect the expression of c-Fos identified immunoreactive neurons in the primary projection area of the afferent vagus nerves, represented by the nucleus tractus solitaris, and in secondary projection areas such as the parabrachial nucleus, the

hypothalamic paraventricular and supraoptic nuclei, the thalamus, the bed nucleus of the stria terminalis, the central nucleus of the amygdala, the insular cortex, the anterior cingulate cortex (ACC), and the medial prefrontal cortex (91–95). All these brain structures are implicated in homeostasis and in the representation of internal bodily states (interoception). However, only few animal experiments analyzed the association between central and behavioral effects of pro-inflammatory cytokines. Gaykema et al. (90, 91) studied the effect of lipopolysaccharide challenge on behavior and neural activity (Fos expression) in rats. Shortly after systemic peripheral inflammation, rats presented symptoms of sickness behavior, such as fatigue. Furthermore, researchers demonstrated a significant relation between symptoms of sickness behavior and suppressed activity of orexinergic and histaminergic neurons located in the hypothalamus.

In humans, a growing number of neuroimaging studies have investigated central effects of peripheral inflammation and have generally confirmed the important role of the insula and the ACC in immunomodulation (29, 96–99). Rosenkranz et al. (99) used functional magnetic resonance imaging (fMRI) to study the role of the CNS in the regulation of inflammation in allergic asthmatic patients. They found an association between peripheral TNF-α in response to immunological challenge and activity in the ACC as well as between eosinophils and activity in the insula. Similar results were obtained by Eisenberger et al. (97) who analyzed the relationship between neural activity using fMRI and pro-inflammatory cytokine activity in individuals exposed to endotoxin. The authors found an association between endotoxin-induced elevations in IL-6 and increased neural activity in the dorsal ACC and the anterior insula in females but not in males. Ohira et al. (98) recorded immune indices and regional cerebral blood flow in men, using positron emission tomography. They observed a correlation between the increase in natural killer cells and the increase in regional cerebral blood flow in the left insula, the medial and bilateral orbitofrontal cortex, and in the anterior middle prefrontal cortex. Furthermore, they demonstrated a correlation between a decrease in T helper cells and a decrease in regional cerebral blood flow in the right insula and the medial orbitofrontal cortex. Hannestad et al. (29) analyzed this issue by using positron emission tomography to identify brain regions that are involved in the response to endotoxin administration in humans. This research group found that systemic inflammation causes an increase in peripheral TNF-α and IL-6 concentrations. Moreover, they found that endotoxin administration led to a higher normalized glucose metabolism in the insula and to a lower normalized glucose metabolism in the ACC. Summing up, nearly all of these studies demonstrated a relationship between inflammatory markers and activity changes within the insula and the ACC. Only one neuroimaging study, performed by Harrison et al. (96), examined the relationship between inflammation-induced activity changes within the brain and inflammation-induced fatigue. These authors demonstrated that systemic inflammation in healthy individuals causes an increase in neural activity in the insula and the anterior cingulate and that these activity changes predict variations in inflammation-associated fatigue. Moreover, the authors showed that the association between inflammation-associated fatigue and increased activity in the insula and anterior cingulate relies on afferent, rather than on efferent autonomic effects, suggesting that fatigue as a core symptom of sickness behavior emerges from afferent interocepive information processing.

These findings point to an implication of interoceptive and homeostatic brain regions like the insula, the anterior cingulate, and the hypothalamus in immunomodulation and suggest that these areas might represent neural correlates of inflammation-induced fatigue.

THE POSSIBLE ROLE OF THE INSULA, THE ANTERIOR CINGULATE AND THE HYPOTHALAMUS IN THE GENERATION OF INFLAMMATION-RELATED SUBJECTIVE FATIGUE

Assuming that subjective fatigue is a feeling represented in cortical areas that are involved in interoception and homeostasis, we now take a closer look at the brain regions that have been found frequently to be implicated in inflammation: the insula, the ACC, and the hypothalamus.

In human beings, convergent afferent vagal and spinal interoceptive fibers terminate in the anterior insula providing a central representation of well-being. Craig et al. (100) found that activity in the posterior insula correlated with stimulus intensities, whereas activity in the anterior insula correlated with subjective feelings of these stimuli intensities, suggesting that the anterior insula provides a basis for the generation of subjective feelings. The insula and the ACC have both been implicated in sensing and responding to physiological disturbances (101). Some authors suggest that afferent homeostatic signaling is integrated in the anterior insula and that the subsequent efferent response is driven by the ACC (101, 102). According to that hypothesis, inflammation would activate all regions of the insula resulting in the generation of subjective feelings of sickness behavior such as fatigue. On the other hand, the ACC would provide the basis for ongoing adjustments to behavior and physiology to restore and maintain our well-being.

The hypothalamus was found to be related to inflammation-induced fatigue in animal experiments and is an important structure for regulating wakefulness and sleep. Orexinergic neurons in the lateral hypothalamus and histaminergic neurons located in the posterior hypothalamus play a key role in inducing and maintaining wakefulness and vigilance (103). Consequentially, observed inflammation-driven inhibition of orexinergic and histaminergic neurons in the hypothalamus might contribute to subjective fatigue as well as to fatigue-related vigilance impairment.

STUDIES ON THE INVOLVEMENT OF THE INSULA, THE ANTERIOR CINGULATE AND THE HYPOTHALAMUS IN MS-RELATED FATIGUE

Zellini et al. (104) used T1 relaxation time as a sensitive measure to indicate pathological changes in the hypothalamus in 44 relapsing-remitting MS patients. Compared to 13 healthy controls, MS patients had a significantly higher T1 relaxation time in the hypothalamus. Moreover, the authors found a significant positive correlation between T1 relaxation times and patients' fatigue scores, as assessed with the FSS. These findings point to an association between pathological changes in the hypothalamus and MS-related fatigue, supporting our hypothesis that the hypothalamus, especially histaminergic and orexinergic neurons, might play an important role for fatigue in MS patients.

Recently, we investigated the association between the integrity of posterior hypothalamic fibers and the level of cognitive fatigue in 49 relapsing-remitting MS patients using diffusion tensor imaging (105). We found that non-cognitively fatigued patients revealed greater axial and radial diffusivity for fibers between brainstem areas and the posterior hypothalamus, indicating tissue loss. This tissue loss might have resulted from demyelination and/or degeneration of investigated fibers including afferent interoceptive fibers and afferents of the vagal nerve that innervate the posterior hypothalamus, including the histaminergic system and other brain regions such as the insular cortex. Consequently, loss of fiber integrity might reduce inflammation-induced suppression of histaminergic neurons as well as inflammation-induced activity in the insula, resulting in a decreased feeling of fatigue.

In another recent study, we analyzed the association between subjective fatigue and cortical thickness in two independent data sets, encompassing in total 96 relapsing-remitting MS patients (106). In both data sets, regression analysis revealed thickness of the right insular cortex as an independent predictor of the patients' FSS score. Patients without fatigue had a thinner right insular cortex than patients with fatigue, suggesting that the right insular cortex plays an important role in the generation of fatigue and that atrophy in this area apparently results in a decrease of fatigue.

Hesse et al. (107) used positron emission tomography and a serotonin transporter-selective tracer to investigate serotonergic activity in 23 MS patients and 22 healthy controls. Compared to healthy controls, MS patients had lower serotonin transporter availability in the cingulate cortex, the thalamus, and the insula and increased availability in the orbitofrontal cortex. Moreover, the authors found a positive correlation between patients' serotonin transporter availability in the insula and fatigue scores (assessed via the Würzburger Erschöpfungsinventar bei MS), pointing to an involvement of the insular cortex in the generation of MS-related fatigue.

Several lines of evidence suggest that atrophy as well as functional changes in the ACC are related to fatigue in MS patients (6, 8, 10, 108, 109). Multiple structural imaging studies found an association between increased white and gray matter atrophy in the ACC and subjective fatigue in MS patients (6, 8, 108). Furthermore, functional imaging studies found that MS patients with fatigue have a larger and more significant activation of the ACC during the execution of simple motor tasks than patients without fatigue (10, 109). These findings support our assumption that the ACC is an important neural structure related to MS-related fatigue.

IMPLICATIONS OF THESE FINDINGS FOR OUR FATIGUE MODEL

We recently proposed a fatigue model arguing that two independent mechanisms may contribute to subjective and objective fatigue in MS patients: (1) subjective fatigue as a feeling is related to inflammation-induced information processing within interoceptive and homeostatic brain areas and (2) objective fatigue as the measureable decrement in behavioral performance is related to atrophy in the cortico-subcortical vigilance network [(17); see **Figure 1**].

We propose that subjective fatigue in MS patients is a feeling that reflects an internal state depending on interoceptive information processing. Thus, similar to pain, fatigue may contribute to increased interoceptive information processing and it may act as a source of interoceptive interference. Hence, our model proposes that subjective fatigue can be measured behaviorally only by applying specific cognitive tasks that rely on a high degree of *intrinsic alertness* such as vigilance and alertness tasks. Moreover, it argues that a vigilance and alertness decrement may be enhanced by brain atrophy and/or neurochemical dysfunction of the alerting/vigilance system. According to this model, fatigue in MS patients may differ depending on the disease progress. During disease onset inflammatory processes might predominantly cause subjective fatigue, whereas in later disease stages advanced brain atrophy of specified brain regions might predominantly contribute to objective fatigue. This assumption has implications for the treatment of MS-related fatigue: while anti-inflammatory treatment options might show beneficial effects during disease onset, it may not help any more in advanced disease stages.

In this review we focused on the association between inflammation, the subjective feeling of fatigue and its possible neural correlates. The empirical findings discussed above all point to a relationship between elevated levels of peripheral TNF-α, IFN-γ, IL-1β, and IL-6 and subjective fatigue, supporting our hypothesis that subjective fatigue in MS patients is related to inflammation. Furthermore, the findings demonstrate that elevated levels of peripheral pro-inflammatory cytokines activate afferent interoceptive fibers, including afferents of the vagus nerve which innervate brain regions involved in interoception and homeostasis, such as the insula (particularly the anterior insula), the anterior cingulate and the hypothalamus. Hence, we suggest that inflammation-induced activity changes in these brain regions may reflect the neural substrates of the feeling of fatigue.

In general, our fatigue model currently can best be tested by using vigilance and alertness tasks. Furthermore, MRI techniques like diffusion tensor imaging may be helpful in analyzing afferent nerve fibers that transmit inflammatory signals to the brain. Analysis of the relationship between cortical thickness or localized lesions in interoceptive brain regions and fatigue might support our fatigue model. To show that fatigue is a feeling related to inflammation that is represented in interoceptive/homeostatic brain regions like the insula, the ACC and the hypothalamus, functional imaging studies combined with the assessment of subjective fatigue and the evaluation of cytokine levels would be necessary.

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REFERENCES

1. Bakshi R, Shaikh ZA, Miletich RS, Czarnecki D, Dmochowski J, Henschel K, et al. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. *Mult Scler* (2000) **6**:181–5. doi:10.1191/135245800701566052
2. Freal JE, Kraft GH, Coryell JK. Symptomatic fatigue in multiple sclerosis. *Arch Phys Med Rehabil* (1984) **65**:135–8.
3. Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. *Arch Neurol* (1988) **45**:435–7. doi:10.1001/archneur.1988.00520280085020
4. Van der Werf SP, Jongen PJ, Lycklama a' Nijeholt GJ, Barkhof F, Hommes OR, Bleijenberg G. Fatigue in multiple sclerosis: interrelations between fatigue

complaints, cerebral MRI abnormalities and neurological disability. *J Neurol Sci* (1998) **160**:164–70. doi:10.1016/S0022-510X(98)00251-2
5. Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. *Mult Scler* (2003) **9**:219–27. doi:10.1191/1352458503ms904oa
6. Andreasen AK, Jakobsen J, Soerensen L, Andersen H, Petersen T, Bjarkam CR, et al. Regional brain atrophy in primary fatigued patients with multiple sclerosis. *Neuroimage* (2010) **50**:608–15. doi:10.1016/j.neuroimage.2009.12.118
7. Calabrese M, Rinaldi F, Grossi P, Mattisi I, Bernardi V, Favaretto A, et al. Basal ganglia and frontal/parietal cortical atrophy is associated with fatigue in relapsing–remitting multiple sclerosis. *Mult Scler* (2010) **16**:1220–8. doi:10.1177/1352458510376405
8. Sepulcre J, Masdeu JC, Goñi J, Arrondo G, Vélez de Mendizábal N, Bejarano B, et al. Fatigue in multiple sclerosis is associated with the disruption of frontal and parietal pathways. *Mult Scler* (2009) **15**:337–44. doi:10.1177/1352458508098373
9. Tartaglia MC, Narayanan S, Francis SJ, Santos AC, De Stefano N, Lapierre Y, et al. The relationship between diffuse axonal damage and fatigue in multiple sclerosis. *Arch Neurol* (2004) **61**:201–7. doi:10.1001/archneur.61.2.201
10. Filippi M, Rocca MA, Colombo B, Falini A, Codella M, Scotti G, et al. Functional magnetic resonance imaging correlates of fatigue in multiple sclerosis. *Neuroimage* (2002) **15**:559–67. doi:10.1006/nimg.2001.1011
11. Leocani L, Colombo B, Magnani G, Boneschi FM, Cursi M, Paolo R, et al. Fatigue in multiple sclerosis is associated with abnormal cortical activation to voluntary movement-EEG evidence. *Neuroimage* (2001) **13**:1186–92. doi:10.1006/nimg.2001.0759
12. Gottschalk M, Kümpfel T, Flachenecker P, Uhr M, Trenkwalder C, Holsboer F, et al. Fatigue and regulation of the hypothalamo-pituitary-adrenal axis in multiple sclerosis. *Arch Neurol* (2005) **62**:277–80. doi:10.1001/archneur.62.2.277
13. Flachenecker P, Bihler I, Weber F, Gottschalk M, Toyka KV, Rieckmann P. Cytokine mRNA expression in patients with multiple sclerosis and fatigue. *Mult Scler* (2004) **10**:165–9. doi:10.1191/1352458504ms991oa
14. Heesen C, Nawrath L, Reich C, Bauer N, Schulz KH, Gold SM. Fatigue in multiple sclerosis: an example of cytokine mediated sickness behaviour? *J Neurol Neurosurg Psychiatry* (2006) **77**:34–9. doi:10.1136/jnnp.2005.065805
15. Kos D, Kerckhofs E, Nagels G, D'hooghe MB, Ilsbroukx S. Origin of fatigue in multiple sclerosis: review of the literature. *Neurorehabil Neural Repair* (2008) **22**:91–100. doi:10.1177/1545968306298934
16. Schwid SR, Covington M, Segal BM, Goodman AD. Fatigue in multiple sclerosis: current understanding and future directions. *J Rehabil Res Dev* (2002) **39**:211–24.
17. Hanken K, Eling P, Hildebrandt H. Is there a signature for MS related fatigue? *Mult Scler* (2014). doi:10.1177/1352458514549567
18. Helton WS, Warm JS. Signal salience and the mindlessness theory of vigilance. *Acta Psychol* (2008) **129**:18–25. doi:10.1016/j.actpsy.2008.04.002
19. Dantzer R, Heijnen CJ, Kavelaars A, Laye S, Capuron L. The neuroimmune basis of fatigue. *Trends Neurosci* (2014) **37**:39–46. doi:10.1016/j.tins.2013.10.003
20. Weisdorf D, Katsanis E, Verfaillie C, Ramsay NK, Haake R, Garrison L, et al. Interleukin-1 alpha administered after autologous transplantation: a phase I/II clinical trial. *Blood* (1994) **84**:2044–9.
21. Clark IA, Budd AC, Alleva LM. Sickness behaviour pushed too far – the basis of the syndrome seen in severe protozoal, bacterial and viral diseases and post-trauma. *Malar J* (2008) **7**:208–15. doi:10.1186/1475-2875-7-208
22. Dantzer R. Cytokine-induced sickness behavior: mechanisms and implications. *Ann N Y Acad Sci* (2001) **933**:222–34. doi:10.1111/j.1749-6632.2001.tb05827.x
23. Maes M, Twisk FN, Kubera M, Ringel K. Evidence for inflammation and activation of cell-mediated immunity in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): increased interleukin-1, tumor necrosis factor-alpha, PMN-elastase, lysozyme and neopterin. *J Affect Disord* (2012) **3**:933–9. doi:10.1016/j.jad.2011.09.004
24. Vollmer-Conna U, Fazou C, Cameron B, Li H, Brennan C, Luck L, et al. Production of pro-inflammatory cytokines correlates with the symptoms of acute sickness behaviour in humans. *Psychol Med* (2004) **34**:1289–97. doi:10.1017/S0033291704001953
25. Bluthe RM, Walter V, Parnet P, Laye S, Lestage J, Verrier D, et al. Lipopolysaccharide induces sickness behaviour in rats by a vagal mediated mechanism. *Compt Rend l'Acad Sci III* (1994) **317**:499–503.
26. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelly KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* (2008) **9**:46–56. doi:10.1038/nrn2297
27. Kerr JR, Barah F, Mattey DL, Laing I, Hopkins SJ, Hutchinson IV, et al. Circulating tumour necrosis factor-α and interferon-γ are detectable during acute and convalescent parvovirus B_{19} infection and are associated with prolonged and chronic fatigue. *J Gen Virol* (2001) **82**:3011–9.
28. Konsman JP, Panet P, Dantzer R. Cytokine-induced sickness behaviour: mechanism and implications. *Trends Neurosci* (2002) **25**:154–9. doi:10.1016/S0166-2236(00)02088-9
29. Hannestad J, Subramanyam K, DellaGioia N, Planeta-Wilson B, Weinzimmer D, Pittman B, et al. Glucose Metabolism in the insula and cingulate is affected by systemic inflammation in humans. *J Nucl Med* (2012) **53**:601–7. doi:10.2967/jnumed.111.097014
30. Kluge M, Schuld A, Schacht A, Himmerich H, Dalal M, Wehmeier PM, et al. Effects of clozapine and olanzapine on cytokine systems are closely linked to weight gain and drug-induced fever. *Psychoneuroendocrinology* (2009) **34**:118–28. doi:10.1016/j.psyneuen.2008.08.016
31. Kluge M, Himmerich H, Wehmeier PM, Rummel-Kluge C, Dalal M, Hinze-Selch D, et al. Sleep propensity at daytime as assessed by multiple sleep latency tests (MSLT) in patients with schizophrenia increases with clozapine and olanzapine. *Schizophr Res* (2012) **135**:123–7. doi:10.1016/j.schres.2011.12.017
32. Weschenfelder J, Sander C, Kluge M, Kirkby KC, Himmerich H. The influence of cytokines on wakefulness regulation: clinical relevance, mechanisms and methodological problems. *Psychiatr Danub* (2012) **24**:112–26.
33. Buchwald D, Wener MH, Pearlman T, Kith P. Markers of inflammation and immune activation in chronic fatigue and chronic fatigue syndrome. *J Rheumatol* (1997) **24**:372–6.
34. Patarca R. Cytokines and chronic fatigue syndrome. *Ann N Y Acad Sci* (2001) **933**:185–200. doi:10.1111/j.1749-6632.2001.tb05824.x
35. Kurzrock R. The role of cytokines in cancer-related fatigue. *Cancer* (2001) **92**:1684–8. doi:10.1002/1097-0142(20010915)92:6+<1684::AID-CNCR1497>3.0.CO;2-Z
36. Kozora E. Fatigue in systemic lupus erythematosus and related autoimmune disorders. In: DeLuca J, editor. *Fatigue as a Window to the Brain.* Cambridge, MA: MIT Press (2005). p. 243–64.
37. Dufour N, Dubé B, Breitbart W. HIV-related fatigue. In: Deluca J, editor. *Fatigue as a Window to the Brain.* Cambridge, MA: MIT Press (2005). p. 187–207.
38. Dupond JL. Fatigue in patients with rheumatic diseases. *Joint Bone Spine* (2011) **78**:156–60. doi:10.1016/j.jbspin.2010.05.002
39. Norheim KB, Harboe E, Gøransson LG, Omdal R. Interleukin-1 inhibition and fatigue in primary Sjogren's syndrome – a double blind, randomised clinical trial. *PLoS One* (2012) **7**(1):e30123. doi:10.1371/journal.pone.0030123
40. Belmont A, Agar N, Hugeron C, Gallais B, Azouvi P. Fatigue and traumatic brain injury. *Annales de réadaptation et de médecine physique* (2006) **49**:370–4. doi:10.1016/j.annrmp.2006.04.018
41. Ormstad H, Aass HCD, Amthor K-F, Lund-Sørensen N, Sandvik L. Serum cytokine and glucose levels as predictors of poststroke fatigue in acute ischemic stroke patients. *J Neurol* (2011) **258**:670–6. doi:10.1007/s00415-011-5962-8
42. Hagell P, Brundin L. Towards an understanding of fatigue in Parkinson disease. *J Neurol Neurosurg Psychiatry* (2009) **80**:489–92. doi:10.1136/jnnp.2008.159772
43. Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab* (2000) **85**:1151–8. doi:10.1210/jcem.85.3.6484
44. Darko DF, Mitler MM, Henriksen SJ. Lentiviral infection, immune response peptides and sleep. *Adv Neuroimmunol* (1995) **5**:57–77. doi:10.1016/0960-5428(94)00044-O
45. Meyers CA, Albitar M, Estey E. Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. *Cancer* (2005) **104**:788–93. doi:10.1002/cncr.21234
46. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosom Med* (2002) **64**:604–11. doi:10.1097/00006842-200207000-00010
47. Berger AM, Gerber LH, Mayer DK. Cancer-related fatigue-implications for breast cancer survivors. *Cancer* (2012) **15**:2261–9. doi:10.1002/cncr.27475
48. Bower JE, Ganz PA, Tao ML, Hu W, Belin TR, Sepah S, et al. Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. *Clin Cancer Res* (2009) **15**:5534–40. doi:10.1158/1078-0432.CCR-08-2584
49. Greenberg DB, Gray JL, Mannix CM, Eisenthal S, Carey M. Treatment-related fatigue and serum interleukin-1 levels in patients during external beam

irradiation for prostate cancer. *J Pain Symptom Manage* (1993) **8**:196–200. doi:10.1016/0885-3924(93)90127-H
50. Cameron BA, Bennett B, Li H, Boyle F, deSouza P, Wilcken N, et al. Post-cancer fatigue is not associated with immune activation or altered cytokine production. *Ann Oncol* (2012) **23**:2890–5. doi:10.1093/annonc/mds108
51. Conlon P, Oksenberg JR, Zhang J, Steinman L. The immunobiology of multiple sclerosis: an autoimmune disease of the central nervous system. *Neurobiol Dis* (1999) **6**:149–66. doi:10.1006/nbdi.1999.0239
52. Navikas V, Link H. Review: cytokines and the pathogenesis of multiple sclerosis. *J Neurosci Res* (1996) **45**:322–33. doi:10.1002/(SICI)1097-4547(19960815)45:4<322::AID-JNR1>3.0.CO;2-B
53. Martins TB, Rose JW, Jaskowski TD, Wilson AR, Husebye D, Seraj HS, et al. Analysis of proinflammatory and anti-inflammatory cytokine serum concentrations in patients with multiple sclerosis by using a multiplexed immunoassay. *Am J Clin Pathol* (2011) **136**:696–704. doi:10.1309/AJCP7UBK8IBVMVNR
54. Hautecoeur P, Forzy G, Gallois P, Demirbilek V, Feugas O. Variations of IL2, IL6, TNF alpha plasmatic levels in relapsing remitting multiple sclerosis. *Acta Neurol Belg* (1997) **97**:240–3.
55. Krupp LB. Fatigue in multiple sclerosis. *CNS Drugs* (2003) **17**:225–34. doi:10.2165/00023210-200317040-00002
56. Rieckmann P, Albrecht M, Kitze B, Weber T, Tumani H, Broocks A, et al. Tumor necrosis factor-a messenger RNA expression in patients with relapsing-remitting multiple sclerosis is associated with disease activity. *Ann Neurol* (1995) **37**:82–8. doi:10.1002/ana.410370115
57. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. *Neurology* (1996) **46**:907–11. doi:10.1212/WNL.46.4.907
58. Neilley LK, Goodin DS, Goodkin DE, Hauser SL. Side effect profile of interferon beta-1b in MS: results of an open label trial. *Neurology* (1996) **46**:552–4. doi:10.1212/WNL.46.2.552
59. Goebel MU, Baase J, Pithan V, Exton MS, Saller B, Schedlowski M, et al. Acute interferon β-1b administration alters hypothalamic-pituitary-adrenal axis activity, plasma cytokines and leukocyte distribution in healthy subjects. *Psychoneuroendocrinology* (2002) **27**:881–92. doi:10.1016/S0306-4530(01)00099-3
60. Nicoletti F, Di Marco R, Patti F III, Zaccone P, L'Episcopo MR, Reggio E, et al. Short-term treatment of remitting multiple sclerosis patients with interferon (IFN)-β1B transiently increases the blood levels of interleukin (IL)-6, IL-10 and IFN-γ without significantly modifying those of IL-1ß, IL-2, IL-4 and tumor necrosis factor. *Cytokine* (2000) **12**:682–7. doi:10.1006/cyto.1999.0616
61. Pokryszko-Dragan A, Frydecka I, Kosmaczewska A, Ciszak L, Bilinska M, Gruszka E, et al. Stimulated peripheral production of interferon-gamma is related to fatigue and depression in multiple sclerosis. *Clin Neurol Neurosurg* (2012) **114**:1153–8. doi:10.1016/j.clineuro.2012.02.048
62. Bertolone K, Coyle PK, Krupp LB, Doscher CA. Cytokine correlates of fatigue in multiple sclerosis. *Neurology* (1993) **43**:A356.
63. Rudick RA, Barna BP. Serum interleukin 2 and soluble interleukin 2 receptor in patients with multiple sclerosis who are experiencing severe fatigue. *Arch Neurol* (1990) **47**:254–5. doi:10.1001/archneur.1990.00530030018008
64. Giovannoni G, Thompson AJ, Miller DH, Thompson EJ. Fatigue is not associated with raised inflammatory markers in multiple sclerosis. *Neurology* (2001) **28**:676–81. doi:10.1212/WNL.57.4.676
65. Mainero C, Faroni J, Gasperini C, Filippi M, Giugni E, Ciccarelli O, et al. Fatigue and magnetic resonance imaging activity in multiple sclerosis. *J Neurol* (1999) **246**:454–8. doi:10.1007/s004150050382
66. Elliot MJ, Maini RN, Feldmann M, Kalden JR, Antoni C, Smolen JS, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor (cA2) versus placebo in rheumatoid arthritis. *Lancet* (1994) **344**:1105–10. doi:10.1016/S0140-6736(94)90628-9
67. Vgontzas AN, Zoumakis E, Lin HM, Bixler EO, Trakada G, Chrousos GP. Marked decrease in sleepiness in patients with sleep apnea by etanercept, a tumor necrosis factor-α antagonist. *J Clin Endocrinol Metab* (2004) **89**:4409–13. doi:10.1210/jc.2003-031929
68. Omdal R, Gunnarsson R. The effect of interleukin-1 blockade on fatigue in rheumatoid arthritis–a pilot study. *Rheumatol Int* (2005) **25**:481–4. doi:10.1007/s00296-004-0463-z
69. Wilkes S. Bupropion. *Drugs Today* (2006) **42**:671–81. doi:10.1358/dot.2006.42.10.1025701
70. Metz LM, Patten SB, Rose SM, McGuinness SD, Harris CJ, Bakker JI, et al. Multiple sclerosis fatigue is decreased at 6 months by glatiramer acetate (Copaxone). *J Neurol* (2001) **248**:115.
71. Ziemsen T, Hoffman J, Apfel R, Kern S. Effects of glatiramer acetate on fatigue and days of absence from work in first-time treated relapsing-remitting multiple sclerosis. *Health Qual Life Outcomes* (2008) **6**:67. doi:10.1186/1477-7525-6-67
72. Iaffaldano P, Viterbo RG, Paolicelli D, Lucchese G, Portaccio E, Goretti B, et al. Impact of natalizumab on cognitive performances and fatigue in relapsing multiple sclerosis: a prospective, open-label, two years observational study. *PLoS One* (2012) **7**(4):e35843. doi:10.1371/journal.pone.0035843
73. Mellergård J, Edström M, Vrethem M, Ernerudh J, Dahle C. Natalizumab treatment in multiple sclerosis: marked decline of chemokines and cytokines in cerebrospinal fluid. *Mult Scler* (2010) **16**:208–17. doi:10.1177/1352458509355068
74. Svenningsson A, Falk E, Celius EG, Fuchs S, Schreiber K, Berkö S, et al. Natalizumab treatment reduces fatigue in multiple sclerosis. results from the TYNERGY trial; a study in the real life setting. *PLoS One* (2013) **8**(3):e58643. doi:10.1371/journal.pone.0058643
75. Yildiz M, Tettenborn B, Putzki N. Multiple sclerosis-associated fatigue during disease-modifying treatment with natalizumab, interferon-beta and glatiramer acetate. *Eur Neurol* (2011) **65**:231–2. doi:10.1159/000324028
76. Mostert S, Kesselring J. Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. *Mult Scler* (2002) **8**:161–8. doi:10.1191/1352458502ms779oa
77. Petajan JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW. Impact of aerobic training on fitness and quality of life in multiple sclerosis. *Ann Neurol* (1996) **39**:432–41. doi:10.1002/ana.410390405
78. Golzari Z, Shabkhiz F, Soudi S, Kordi MR, Hashemi SM. Combined exercise training reduces IFN-γ and IL-17 levels in the plasma and the supernatant of peripheral blood mononuclear cells in women with multiple sclerosis. *Int Immunopharmacol* (2010) **10**:1415–9. doi:10.1016/j.intimp.2010.08.008
79. Coyle PK, Krupp LB, Doscher C, Deng Z, Milazzo A. Clinical and immunological effects of cooling in multiple sclerosis. *Neurorehabil Neural Repair* (1996) **10**:9–15. doi:10.1177/154596839601000102
80. Flensner G, Lindencrona C. The cooling-suit: case studies of its influence on fatigue among eight individuals with multiple sclerosis. *J Adv Nurs* (2002) **37**:541–50. doi:10.1046/j.1365-2648.2002.02129.x
81. Quan N, Banks WA. Brain-immune communication pathways. *Brain Behav Immun* (2007) **21**:727–35. doi:10.1016/j.bbi.2007.05.005
82. Goehler LE, Lyte M, Gaykema R. Infection-induced viscerosensory signals from the gut enhance anxiety: implications for psychoneuroimmunology. *Brain Behav Immun* (2007) **21**:721–6. doi:10.1016/j.bbi.2007.02.005
83. Hansen MK, O'Connor KA, Goehler LE, Watkins LR, Maier SF. The contribution of the vagus nerve in interleukin-1β-induced fever is dependent on dose. *Am J Physiol Regul Integr Comp Physiol* (2001) **280**:929–34.
84. Hermann GE, Rogers RC. TNFalpha: a trigger of autonomic dysfunction. *Neuroscientist* (2008) **14**:53–67. doi:10.1177/1073858407305725
85. Roth J, de Souza GEP. Fever induction pathways: evidence from responses to systemic or local cytokine formation. *Braz J Med Biol Res* (2001) **34**:301–14. doi:10.1590/S0100-879X2001000300003
86. Watkins LR, Maier SF, Goehler LE. Cytokine-to-brain communication: a review and analysis of alternative mechanisms. *Life Sci* (1995) **57**:1011–26. doi:10.1016/0024-3205(95)02047-M
87. Gaykema RPA, Goehler LE, Tilders FJH, Bol JGJM, McGorry M, Fleshner M, et al. Bacterial endotoxin induces Fos immunoreactivity in primary afferent neurons of the vagus nerve. *Neuroimmunomodulation* (1998) **5**:234–40. doi:10.1159/000026343
88. Goehler LE, Gaykema RPA, Hammack SE, Maier SF, Watkins LR. Interleukin-1 induces c-Fos immunoreactivity in primary afferent neurons of the vagus nerve. *Brain Res* (1998) **804**:306–10. doi:10.1016/S0006-8993(98)00685-4
89. Bluthe RM, Michaud B, Kelley KW, Dantzer R. Vagotomy blocks behavioural effects of interleukin-1 injected via the intraperitoneal route but not via other systemic routes. *Neuroreport* (1996) **7**:15–7. doi:10.1097/00001756-199606170-00008
90. Gaykema RPA, Park S-A, McKibbin CR, Goehler LE. Lipopolysaccharide suppresses activation of the tuberomamillary histaminergic system concomitant with behavior: a novel target of immune sensory pathways. *Neuroscience* (2008) **152**:273–87. doi:10.1016/j.neuroscience.2007.10.042

91. Gaykema RPA, Daniels TE, Shapiro NJ, Thacker GC, Park S-M, Goehler LE. Immune challenge and satiety-related activation of both distinct and overlapping neuronal populations in the brainstem indicate parallel pathways for viscerosensory signaling. *Brain Res* (2009) **1294**:61–79. doi:10.1016/j.brainres.2009.07.076
92. Goehler LE, Gaykema R, Hansen MK, Anderson K, Maier SF, Watkins LR. Vagal immune-to-brain communication: a visceral chemosensory pathway. *Auton Neurosci* (2000) **85**:49–59. doi:10.1016/S1566-0702(00)00219-8
93. Thayer JF, Sternberg EM. Neural aspects of immunomodulation: focus on the vagus nerve. *Brain Behav Immun* (2010) **24**:1223–8. doi:10.1016/j.bbi.2010.07.247
94. Ter Horst GJ, Postema F. Forebrain parasympathetic control of heart activity: retrograde transneuronal viral labeling in rats. *Am J Physiol* (1997) **273**:2926–30.
95. Wan W, Wetmore L, Sorensen CM, Greenberg AH, Nance DM. Neural and biochemical mediators of endotoxin- and stress-induced c-fos expression in the rat brain. *Brain Res Bull* (1994) **34**:7–14. doi:10.1016/0361-9230(94)90179-1
96. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Dolan RJ, et al. Neural origins of human sickness in interoceptive responses to inflammation. *Biol Psychiatry* (2009) **66**:415–22. doi:10.1016/j.biopsych.2009.03.007
97. Eisenberger NI, Inagaki TK, Mashal NM, Irwin MR. Inflammation and social experience: an inflammatory challenge induces feelings of social disconnection in addition to depressed mood. *Brain Behav Immun* (2010) **24**:558–63. doi:10.1016/j.bbi.2009.12.009
98. Ohira H, Isowa T, Nomura M, Ichikawa N, Kimura K, Miyakoshi M, et al. Imaging brain and immune association accompanying cognitive appraisal of an acute stressor. *Neuroimage* (2008) **39**:500–14. doi:10.1016/j.neuroimage.2007.08.017
99. Rosenkranz MA, Busse WW, Johnston T, Swenson CA, Crisafi GM, Jackson MM, et al. Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. *Proc Natl Acad Sci U S A* (2005) **102**:13319–24. doi:10.1073/pnas.0504365102
100. Craig AD, Chen K, Bandy D, Reiman EM. Thermosensory activation of insular cortex. *Nat Neurosci* (2000) **3**:184–90. doi:10.1038/72131
101. Craig AD. How do you feel – now? The anterior insula and human awareness. *Nat Rev Neurosci* (2009) **10**:59–70. doi:10.1038/nrn2555
102. Rosenkranz MA, Davidson RJ. Affective neural circuitry and mind–body influences in asthma. *Neuroimage* (2009) **47**:972–80. doi:10.1016/j.neuroimage.2009.05.042
103. Nishino S. Hypothalamus, hypocretins/orexin, and vigilance control. *Handb Clin Neurol* (2011) **99**:765–82. doi:10.1016/B978-0-444-52007-4.00006-0
104. Zellini F, Niepel G, Tench CR, Constantinescu CS. Hypothalamic involvement assessed by T1 relaxation time in patients with relapsing-remitting multiple sclerosis. *Mult Scler* (2009) **15**:1442–9. doi:10.1177/1352458509350306
105. Hanken K, Eling P, Kastrup A, Klein J, Hildebrandt H. Integrity of hypothalamic fibers and cognitive fatigue in multiple sclerosis. *Mult Scler Rel Dis* (2014). doi:10.1016/j.msard.2014.11.006
106. Hanken K, Eling P, Klein J, Kastrup A, Hildebrandt H. The right insula – cortical area responsible for fatigue in multiple sclerosis? *Zeitschrift für Neuropsychologie* (2014) **25**:177–214.
107. Hesse S, Moeller F, Petroff D, Lobsien D, Luthardt J, Regenthal R, et al. Altered serotonin transporter availability in patients with multiple sclerosis. *Eur J Nucl Med Mol Imaging* (2014) **41**:827–35. doi:10.1007/s00259-013-2636-z
108. Pardini M, Bonzano L, Bergamino M, Bommarito G, Feraco P, Murugavel A, et al. Cingulum bundle alterations underlie subjective fatigue in multiple sclerosis. *Mult Scler* (2014). doi:10.1177/1352458514546791
109. Tartaglia MC, Narayanan S, Arnold DL. Mental fatigue alters the pattern and increases the volume of cerebral activation required for a motor task in multiple sclerosis patients with fatigue. *Eur J Neurol* (2008) **15**:413–9. doi:10.1111/j.1468-1331.2008.02090.x

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Subjective cognitive fatigue in multiple sclerosis depends on task length

Joshua Sandry[1,2]*, Helen M. Genova[1,2], Ekaterina Dobryakova[1,2], John DeLuca[1,2,3] and Glenn Wylie[1,2,4]

[1] Neuropsychology and Neuroscience Research, Kessler Foundation, West Orange, NJ, USA
[2] Department of Physical Medicine and Rehabilitation, Rutgers – New Jersey Medical School, Newark, NJ, USA
[3] Department of Neurology and Neurosciences, Rutgers – New Jersey Medical School, Newark, NJ, USA
[4] War Related Illness and Injury Study Center, Department of Veterans Affairs, East Orange, NJ, USA

Edited by:
Christian Dettmers, Kliniken Schmieder Konstanz, Germany

Reviewed by:
Herbert Schreiber, Neurological Practice and NeuroTransData (NTD) Study Group, Germany
Olivia Marie Reinhold Svolgaard, Copenhagen University Hospital Hvidovre, Denmark

***Correspondence:**
Joshua Sandry, Neuropsychology and Neuroscience Research, Kessler Foundation Research Center, 300 Executive Dr., Suite 70, West Orange, NJ 07052, USA
e-mail: jsandry@kesslerfoundation.org

Objective: The objective of this paper is to investigate the interrelationship between subjective and objective cognitive fatigue, information processing domain [processing speed (PS) vs. working memory (WM)], cognitive load (high vs. low), and time on task in Multiple Sclerosis (MS).

Methods: Thirty-two MS participants and 24 healthy controls completed experimental tasks in both the PS and WM domains with different levels of cognitive load. Subjective cognitive fatigue was measured using a visual analog scale at baseline and at multiple time points throughout the experiment.

Results: A mixed model ANOVA revealed that subjective cognitive fatigue was higher for the PS task, increased across time, and was higher in the MS group. These findings were qualified by an interaction demonstrating that the MS group showed a steeper increase in subjective cognitive fatigue over time than the healthy control group. Subjective and objective (i.e., performance) cognitive fatigue were not correlated.

Conclusion: In this study, subjective and objective cognitive fatigue appears to be independent and cognitive fatigue does not depend on cognitive load. Subjective cognitive fatigue increased with time on task and subjective cognitive fatigue increased more steeply for the MS group. These data suggest that cognitive fatigue in MS is a function of time, that is, the longer participants were engaged in a cognitive task, the more likely it was for them to report increases in cognitive fatigue.

Keywords: cognitive fatigue, fatigability, time, processing speed, working memory

INTRODUCTION

Fatigue is perhaps the most common complaint associated with Multiple Sclerosis (MS) (1) with prevalence estimates ranging between 70 and 90% (2–4). Fatigue can be cognitive or motoric and originate at a central level (i.e., the central nervous system) or peripheral level (i.e., peripheral nerve and muscle) (5). Cognitive fatigue can be a result of both cognitive and physical exertion (6). Cognitive fatigue may manifest as subjective sensations or objective changes in performance, fatigue, and fatigability, respectively (7). Treating cognitive fatigue clinically remains difficult, particularly because a basic understanding of the variables that contribute to cognitive fatigue are not well defined. The present paper investigates the task parameters that lead to cognitive fatigue in MS. This knowledge may help to inform future research as well as clinical evaluations of cognitive fatigue in MS. Novel insights into how and why cognitive fatigue manifests may also ultimately lead to improved clinical treatment strategies for cognitive fatigue.

One strong predictor of cognitive fatigue is the amount of time spent on task (time on task); as time on task increases cognitive fatigue also increases (8–11). Interestingly in some instances increased time on task can improve performance (12, 13). Reports are mixed regarding the effect of time on cognitive fatigue in MS. Some researchers have shown that time on task may result in increases in subjective cognitive fatigue but not decreases in objective performance (14). Others have shown time negatively impacts both subjective and objective measures (15). Interestingly, most studies of cognitive fatigue in MS have failed to show a relationship between subjective and objective measures of cognitive fatigue (9, 14–18). Further, high and low levels of fatigue do not map onto changes in cognitive performance (19). Cognitive load is an additional variable to consider when investigating cognitive fatigue.

Tasks high in cognitive load (challenging tasks) often result in greater increases in subjective cognitive fatigue than tasks low in cognitive load (less challenging tasks) (20). High cognitive load can also result in a more rapid onset of subjective cognitive fatigue (21). In past work, Bailey et al. (16) tested the consequences of cognitive load and time on task for cognitive fatigue in a sample of advanced MS participants [Expanded Disability Status Scale (EDSS) of 7–8]. Researchers manipulated high and low cognitive load using the n-back working memory (WM) task, 0-back, and 1-back, respectively. Subjective cognitive fatigue increased across

sessions for the high cognitive load condition in the MS and HC groups and this effect was more pronounced for the MS group, suggesting that patients with advanced stages of MS are more likely to experience cognitive fatigue on challenging tasks.

One unanswered question is whether MS patients are more susceptible to cognitive fatigue in one cognitive domain than in a different cognitive domain. For example, some evidence suggests that impaired processing speed (PS) is the major information processing deficit associated with MS (22, 23) while other evidence suggests that impaired WM is the major information processing deficit associated with MS (24). Based on this past work, it may be the case that tasks that engage different cognitive domains result in different patterns of cognitive fatigue. Cognitive fatigue may be domain specific and when one domain is impaired, e.g., PS, more neural resources must be recruited from other domains. Expending more resources could result in patients reporting higher levels of cognitive fatigue. At this point, it remains unclear how cognitive fatigue manifests in MS as a function of different cognitive domains and different degrees of cognitive load associated with those domains. What is also unclear is how time, arguably the strongest predictor of cognitive fatigue, interacts with these variables.

The purpose of the present study was to examine whether cognitive fatigue (both objective and subjective) is influenced by type of cognitive task (i.e., PS vs. WM) in MS. Based on the reviewed literature, three competing hypotheses that influence cognitive fatigue can be directly tested: (1) *the cognitive load hypothesis* (16), (2) *the cognitive domain hypothesis* (22–24), and (3) *the temporal fatigue hypothesis* (8–11). Particularly strong support for any hypothesis and its relationship with MS will come from an interaction between group and the related main effect. If the Cognitive Load hypothesis is correct, then reported fatigue will be higher as a function of task difficulty: higher reported fatigue in the high cognitive load conditions compared to lower reported fatigue in the low cognitive load conditions. If the Cognitive Domain hypothesis is correct, there will be higher reported fatigue in a particular information processing domain (PS or WM). If the Temporal Fatigue hypothesis is correct, then cognitive fatigue will increase as the length of the task increases, and not depend on task difficulty.

Because the three hypotheses are not mutually exclusive and various interactions are possible, the present experiments are somewhat exploratory. Support for any of the competing hypotheses will help to provide information about the manifestation of cognitive fatigue in MS. The accompanying evidence will be useful in identifying whether cognitive fatigue in MS is domain general or domain specific, whether cognitive fatigue in MS depends on high or low cognitive load, and whether cognitive fatigue increases as time increases.

MATERIALS AND METHODS

PARTICIPANTS

Fifty-six right-handed individuals; 24 healthy controls (HC; 16 female); and 32 (30 female) clinically definite (25) MS patients participated. MS participants were at least 1 month from their most recent exacerbation and reported no current corticosteroid use. Disease duration was available for 30 MS participants and was 11.91 (±7.05) years. Disease subtype was available for 29 MS patients; 24 relapsing-remitting, 1 primary-progressive, 3 secondary progressive, and 1 progressive relapsing. The Ambulatory Index (AI) score was available for 27 MS participants and was 2.44 (±2.53) representing mild to moderate disease progression. All participants had self-reported normal or corrected-to-normal visual acuity and normal color vision. Participants with a history of diagnosed psychological and psychiatric problems (i.e., resulting in patient hospitalization for these disorders) including: epilepsy, learning disability, diagnosis of substance abuse/dependence, brain injury, or loss of consciousness (lasting 30 or more minutes) were excluded. MS and HC groups did not differ in the years of education. The HC group was disproportionately Male and MS group was disproportionately Female, and the MS group was older than the HC group at the time of testing (see **Table 1**). This study was approved by the Institutional Review Board at the Kessler Foundation, and all participants provided informed consent prior to enrollment.

NEUROPSYCHOLOGICAL TESTING

The following specific neuropsychological tests (and differences between them) were particularly relevant to the present investigation and part of a larger neuropsychological testing session (see **Table 1** for additional neuropsychological assessment scores). The MS and HC groups did not differ on WM (Digit Span Total), however, the MS group was significantly impaired on PS [Symbol-Digit Modalities Test (SDMT)]. The MS group reported higher depression (Chicago Multi-scale Depression Inventory) and higher fatigue on the Fatigue Severity Scale and all subscales of the Modified Fatigue Impact Scale. Additionally, because fatigue was the main focus of this study, we computed the percentage of the MS sample that report high fatigue (≥1.5 SDs above the HC mean) on the FSS and MFIS subscales (**Table 1**).

EXPERIMENTAL DESIGN

The experiment was conducted over two separate testing sessions, within a 2-week time period. Each session involved different cognitive domains; either a PS or WM task. Experiments were conducted concomitantly with an *f*MRI scan (imaging results to be reported separately). The order of testing sessions and order of tasks within the testing sessions were counterbalanced across participants. All participants received all manipulations within subjects. Stimuli were presented using E-prime software and response time (RT) and accuracy was recorded.

PROCESSING SPEED

The modified SDMT (mSDMT) (26, 27) and a visual matching control task were manipulated within participants resulting in high and low cognitive load, respectively. The sessions were separated by a 10-min break in order to allow the participants time to rest and reorient themselves to the new task before beginning the second part of the experiment. The entire experiment consisted of 8 blocks, 4 blocks for each task, and each block consisted of 55 trials. During the mSDMT, participants viewed a 2×9 grid of exemplar stimuli (i.e., the key). The upper and lower rows of the exemplar grid contained symbols and digits, respectively. A 1×2 grid probe was positioned below the key and participants

Table 1 | Available demographic information and neuropsychological performance characteristics.

	HC group			MS group				*t*
	Mean	**SD**	***N***	**Mean**	**SD**	***N***	**% Impaired**	
Age (years)	37.74	11.09	24	48.23	9.66	32		3.71*
Education (years)	16.13	1.96		15.77	2.33			0.6
Percent female	67%			94%				7.02 (X^2)*
DST scaled score	11.91	2.97	23	10.87	4.30	31		1
SDMT z	0.32	1.19	23	−0.71	1.32	31		2.95*
PASAT 2 z	0.01	0.90	23	−0.57	1.13	30		2.05*
PASAT 3 z	0.08	0.81	23	−0.58	1.16	30		2.32*
CVLT-II LDFR z	0.02	1.14	23	−0.40	1.26	31		1.28
BVMT-R DR T	58.43	9.10	23	48.20	13.21	30		3.18*
JLO corrected score	28.05	3.44	22	25.87	5.53	31		1.64
CMDI Total *t*-score	45.47	7.88	18	54.15	8.48	27		3.47*
FSS raw	2.12	0.93	18	5.09	1.47	27	74%	7.63*
MFIS total	9.56	9.06	18	44.86	16.46	28	89%	8.31*
Physical	3.61	3.62	18	21.32	8.44	28	89%	8.4*
Cognitive	5.06	5.09	18	21.00	7.68	28	75%	7.77*
Psychosocial	0.89	1.08	17	4.32	2.06	28	57%	6.52*

*$p < 0.05$.

Independent samples t-tests comparisons between MS and HC groups. Percent (%) high fatigue calculated based on a cut-off value with scores 1.5 SD greater than the HC mean interpreted as high fatigue. DST, digit span total; SDMT, symbol-digit modality test; PASAT 2, paced auditory serial addition test 2 s; PASAT 3, paced auditory serial addition test 3 s; CVLT-II LDFR, California verbal learning test – II long delay free recall; BVMT-R DR, brief visuospatial memory test – revised delayed recall; T, JLO, judgment of line orientation; CMDI, Chicago multi-scale depression inventory; FSS, fatigue severity scale; MFIS, modified fatigue impact scale total score, and physical, cognitive, and psychosocial subscales.

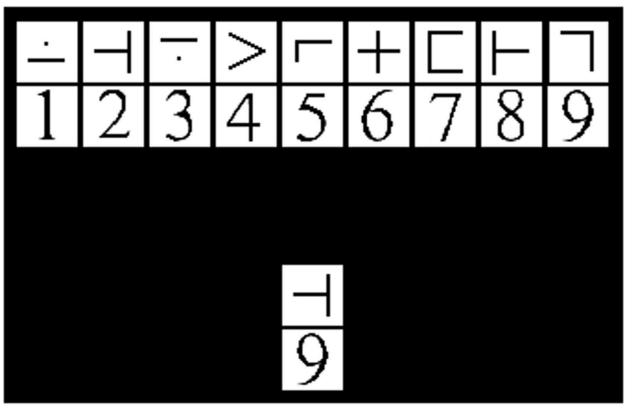

FIGURE 1 | Example of the stimuli used during the mSDMT. Target represents a no-match trial.

were instructed to respond "match" or "no-match" as fast and accurately as possible. The match/no-match decision depended on whether the probe corresponded to the exemplar stimuli in the key positioned above (**Figure 1**). The paired stimuli and probe remained on the screen for 3500 ms. To minimize learning and practice effects, the exemplar symbol-digit combination in the key randomly changed with each trial. In the visual matching control task, participants were presented with the same 2×9 grid; however, they responded when the test-probe was a "7."

WORKING MEMORY

The 2-back and 0-back version of the n-back task were manipulated within participants resulting in high and low cognitive load, respectively. The sessions were separated by a 10-min break to allow participants time to rest and reorient themselves before beginning the second half of the experiment. The entire experiment consisted of 8 blocks, 4 blocks for each task, and each block consisted of 65 trials. A series of single letters were sequentially presented and participants responded when the target letter was a "K" (0-back) or when the target letter matched the letter from two trials prior (2-back). Stimuli remained on the screen for 1500 ms.

MEASURING SUBJECTIVE COGNITIVE FATIGUE

State fatigue (28) was measured one time before the experiment began (establishing baseline) and once after each block (run) using the Visual Analog Scale (VAS) for Fatigue. The VAS is a valid and reliable instrument used to measure self-reported fatigue in MS (29, 30). Participants orally reported how mentally fatigued they felt "right now at this moment," on a scale of 0–100. This measurement provides an online assessment of fatigue (state fatigue), rather than an estimate of fatigue over an extended period of time (c.f., FSS, MFIS, trait fatigue) (28), allowing quantifications of the level of fatigue resulting from the different tasks across blocks. Additionally, we asked participants to focus on their feelings of fatigue at that moment and disregard prior feelings of fatigue.

STATISTICS

Group differences on demographics and neuropsychological performance were evaluated using independent sample *t*-tests.

Three separate mixed model ANOVA's were conducted on the VAS, Accuracy, and Response Time data, respectively, to investigate the effect of the independent variables on the dependent measures. Age, gender, and depression scores were initially included as covariates in all models, however, scores on these variables did not significantly covary, thus the reported analyses described below do not include age, gender, or depression scores as covariates in the models. Pearson correlation coefficients were used to investigate any relationships between subjective (VAS scores) and objective (performance) cognitive fatigue. Alpha was set at 0.05 for all comparisons except where noted. All statistical analyses were computed with IBM SPSS Statistics Release 21.0.0.1.

RESULTS

SUBJECTIVE COGNITIVE FATIGUE: VAS

Visual analog scale cognitive fatigue measurements taken after each block were subtracted from the initial VAS baseline measurements to control for baseline cognitive fatigue. VAS scores were analyzed using a 2 (Group: MS vs. HC) × 2 (Cognitive Domain: PS vs. WM) × 2 (Cognitive Load: High vs. Low) × 4 (Run: 1, 2, 3, 4) Mixed ANOVA. The main effect of Cognitive Domain was significant, $F(1,54) = 5.50$, $p = 0.02$, $\eta_p^2 = 0.09$, with higher VAS scores reported for the PS ($M = 8.13$) than WM ($M = 5.12$) Domain. The main effect of Run was significant, $F(3,162) = 17.98$, $p < 0.001$, $\eta_p^2 = 0.25$, with a significant linear trend, $F(1,54) = 37.18$, $p < 0.001$, $\eta_p^2 = 0.41$, the VAS scores increased as a function of Run suggesting that subjective cognitive fatigue increased over time. The main effect of Cognitive Load was not significant, $F(1,54) = 2.53$, $p = 0.12$. The main effect of Group was significant, $F(1,54) = 6.45$, $p = 0.01$, $\eta_p^2 = 0.11$, with higher VAS scores, and higher reported subjective cognitive fatigue, for the MS group ($M = 8.95$) than HCs ($M = 4.30$). The Run by Group interaction was also significant, $F(3,162) = 2.71$, $p = 0.047$, $\eta_p^2 = 0.05$. The significant Run by Group interaction suggests that the MS group showed higher VAS scores (higher fatigue) across runs (**Figure 2**). This finding supports the Temporal Fatigue Hypothesis.

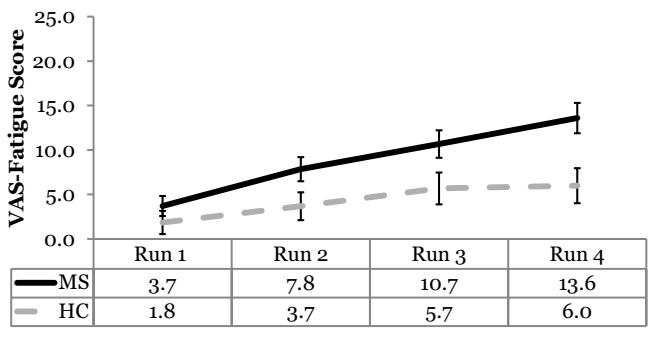

FIGURE 2 | VAS scores as a function of run and group. The MS group showed higher fatigue than the HC group across runs. Error bars represent standard error.

Subjective cognitive fatigue: VAS

High vs. low trait fatigue in MS. The MS patients were divided by fatigue group and identified as being either high or low in trait fatigue as measured by the FSS and MFIS. MS patients were classified as high fatigue if their FSS or MFIS score were ≥1.5 SD above the HC mean (see **Table 1** and Neuropsychological Testing). The analysis reported above was recomputed using *MS Fatigue Group* as the between subjects variable. This helped to identify whether patients who reported high compared to low trait fatigue differed in their pattern of state fatigue (VAS scores). High trait fatigue patients were compared to low trait fatigue patients using a 2 *MS Fatigue Group* (MS High Fatigue vs. MS Low Fatigue) × 2 Cognitive Domain × 2 Cognitive Load × 4 Run Mixed ANOVA.

The main effect of MS Fatigue Group was not significant and there were no interactions between MS Fatigue Group and any of the other independent variables. This was true when classifying patients' trait fatigue using the FSS (all p's > 0.40) and when classifying patients' trait fatigue using the MFIS (all p's > 0.13). These supplementary analyses on the quasi variables of high and low fatigue should be interpreted cautiously because the proportion of patients classified as low fatigue was small. The majority of the sample reported high levels of fatigue when classified by the FSS and MFIS trait fatigue measures (**Table 1**).

Subjective cognitive fatigue: VAS

Correlation between state and trait fatigue. We also investigated the correlations between measures of trait (MFIS and FSS scores) and state fatigue (VAS scores) in the MS group. The FSS and MFIS scores were positively correlated with each other, $r(27) = 0.46$, $p = 0.02$. Because of the high number of correlational comparisons, alpha was adjusted using a Bonferroni correction for each set of comparisons (alpha = 0.006). None of the correlations between the trait (FSS or MFIS) and state (VAS scores) fatigue measures was significant. Additional correlations were computed between the MFIS *cognitive fatigue subscale* and VAS scores. This was done to determine whether there was a noticeable relationship between state and trait cognitive fatigue using the more specific subscale of the MFIS. No correlations between the MFIS cognitive fatigue subscale and VAS scores reached significance.

The lack of a correlation between the trait and state fatigue measures suggest that trait and state fatigue may be independent or that state fatigue is not well captured by the trait fatigue measures. No observable correlations may also be because the state fatigue measure (VAS scores) captured online cognitive fatigue "right now" and the trait fatigue measures captured general fatigue over the past week (FSS) or past 4 weeks (MFIS). Further, the FSS and MFIS include items that may not directly capture cognitive fatigue, rendering the scores more representative of general fatigue. Even the specific items on the MFIS cognitive subscale seem ambiguous in this regard.

OBJECTIVE COGNITIVE FATIGUE: ACCURACY

Due to a programing malfunction, only a subset of behavioral data recorded and was available for data analysis (HC = 12; MS = 18). Accuracy was analyzed using the same 2 × 2 × 2 × 4 Mixed ANOVA. The main effect of Cognitive load was significant,

$F(1,28) = 34.42$, $p < 0.001$, $\eta_p^2 = 0.55$, with lower accuracy in the high ($M = 0.93$) compared to low ($M = 0.99$) load condition. The main effect of Run was significant, $F(3,84) = 3.36$, $p = 0.02$, $\eta_p^2 = 0.11$, with a significant quadratic trend, $F(1,28) = 4.72$, $p = 0.04$, $\eta_p^2 = 0.14$. The quadratic trend was driven by low accuracy on the first run and an increase and plateau in accuracy for runs 2, 3, and 4. The main effect of Group was not significant, $F(1, 28) = 0.19$, $p = 0.67$. The Domain × Cognitive Load interaction was significant, $F(1,28) = 4.19$, $p = 0.05$, $\eta_p^2 = 0.13$, with accuracy lower for WM under a high load than the other conditions.

Objective cognitive fatigue: accuracy

High vs. low trait fatigue in MS. Multiple sclerosis Fatigue Group comparisons were not conducted for MS patients because of the missing accuracy data.

OBJECTIVE COGNITIVE FATIGUE: RT

Response time was analyzed for accurate trials only using the same $2 \times 2 \times 2 \times 4$ Mixed ANOVA on a subset of the data (HC = 10; MS = 17). The main effect of Domain was significant, $F(1,25) = 168.36$, $p < 0.001$, $\eta_p^2 = 0.87$, with slower RTs for PS ($M = 1237$) than WM ($M = 700$). The main effect of Cognitive Load was significant, $F(1,25) = 188.89$, $p < 0.001$, $\eta_p^2 = 0.88$ with slower RTs in the High ($M = 1194$) than Low Load ($M = 742$) condition. The main effect of Group was significant, $F(1,25) = 15.63$, $p < 0.001$, $\eta_p^2 = 0.39$, with slower RTs for MS ($M = 1078$) than HCs ($M = 859$). The Domain × Group interaction was significant, $F(1,25) = 4.50$, $p = 0.04$, with the MS group showing a larger difference between Domains than HCs. The Domain × Load interaction was significant, $F(1,25) = 162.86$, $p < 0.001$, $\eta_p^2 = 0.87$, with the High Load condition of the PS task resulting in substantially slower RTs than the other conditions. This effect was further augmented by the Domain × Load × Group interaction, $F(1,25) = 6.87$, $p = 0.02$, $\eta_p^2 = 0.22$, with a larger difference in RTs between the MS and HC groups in the High Load condition of the PS task. The Load × Run × Group interaction was significant, $F(1,25) = 4.65$, $p = 0.005$, $\eta_p^2 = 0.16$, along with the four-way interaction $F(3,75) = 3.28$, $p = 0.03$, $\eta_p^2 = 0.12$. The MS group was slower during early runs but showed improvement across runs and this was true only in the high Cognitive Load condition.

Objective cognitive fatigue: RT

High vs. low trait fatigue in MS. Multiple sclerosis Fatigue Group comparisons were not conducted for MS patients because of the missing RT data.

CORRELATIONS BETWEEN SUBJECTIVE AND OBJECTIVE COGNITIVE FATIGUE

Correlations were computed between the VAS scores and RTs to better understand the relationship between subjective and objective fatigue. Correlations were not computed for accuracy because the tasks did not differ between MS and HCs. After a Bonferroni correction, none of the correlations between VAS scores and RTs reached significance. We further explored these same correlations using only responses from the MS group and found no correlations reached significance.

DISCUSSION

Irrespective of Cognitive Load, subjective cognitive fatigue increased as the length of the task increased. The present data support the Temporal Fatigue hypothesis over the Cognitive Load hypotheses. There was some support for higher reported fatigue in the PS domain than in the WM domain, however, this was observed in both the MS and HC groups.

Correlations used to investigate the relationship between subjective and objective cognitive fatigue were not significant, suggesting subjective and objective cognitive fatigue are independent and supportive of prior work (9, 14–19). Subjective and objective cognitive fatigue may continuously fail to correlate because behavior and performance may not be the ideal measure of fatigue (9). The often replicated lack of a relationship between subjective and objective cognitive fatigue (9, 14–18) may suggest researchers pursue alternative objective measures of cognitive fatigue. Importantly, cognitive fatigue does not have to result in changes in behavior or performance deficits, thus a relationship may not be supported in large part because the intuitive assumption that cognitive fatigue and performance will be related is inaccurate. Additionally, measurement of trait (FSS and MFIS) and state fatigue (VAS) was uncorrelated suggesting trait measures may not capture state fatigue.

Neuroimaging may be one potential direction that may help identify the mechanisms associated with fatigue. Several investigations highlight the involvement of the fronto-striatal network in cognitive fatigue in a variety of clinical populations, including MS (31). In MS, fMRI studies have also found the fronto-striatal network to be associated with fatigue during task performance (26) and tracked brain activity as a function of on-task fatigue (28). Interestingly, the pattern of activation also appeared to be independent of behavioral performance in that study (28).

The present findings suggest that MS participants experience subjective cognitive fatigue as the time of the task increased, regardless of the cognitive domain, and regardless of the cognitive load associated with the task. To our knowledge, no other studies have made direct comparisons between cognitive fatigue resulting from a PS task compared with a WM task in MS. In past work, Bailey et al. (16) reported higher fatigue during the 1-back component for participants with advanced MS. Cognitive load was arguably higher (2-back) in the present study and there was no difference found in cognitive fatigue between the MS and HC groups. This may be because the Bailey et al. study limited their sample to what they referred to as advanced MS. That is, patients who scored between 7 and 8 on the EDSS. EDSS scores were not available in the present study; however, AI scores were available for most of the MS group. AI scores are highly correlated with EDSS [$r = 0.89$; DeLuca et al. (32)] and the AI scores of the present sample suggested mild to moderate disease severity. The present sample was likely less extreme than the Bailey et al. sample and mainly comprised of relapsing-remitting MS participants. It is possible that the experience of cognitive fatigue is greater at higher cognitive loads during advanced stages of the disease or different disease subtypes. This is one avenue for future work.

Multiple sclerosis participants who experience cognitive impairment [either WM (24) or PS (22, 23) impairments] might be more susceptible to cognitive fatigue during cognitive task

performance that is related to the impaired cognitive domain. We could not investigate this hypothesis with the current data. None of the MS participants in the present sample showed impairments in WM and only six MS participants scored 1.5 standard deviations or more below the mean on the SDMT [supporting (22, 23)]. Similar to the current design that manipulated cognitive load, cognitive domain, and time, future work should also differentiate the groups based on cognitive impairment. MS participants with cognitive impairment (WM or PS) should be compared to MS participants without cognitive impairment. The cognitive fatigue profile may differ for these participants.

There are limitations associated with the present study restricting the generalizability of the findings. First, the MS sample and HC sample were disproportionately female and male, respectively and the HC group was slightly younger in age and reported lower depression. After controlling for age, gender, and depression in our main analysis, we found no covariance. Nonetheless, these differences should be kept in mind when making comparisons across studies and generalizing the MS community in general. Second, the duration of the decision screen of the PS task was somewhat longer than the decision screen of the WM task because the PS decision required more time, rendering the PS task somewhat longer than the WM task. Typically MS participants are more familiar with neuropsychological tests, given they may undergo assessment at different intervals as the disease progresses. It is possible that MS patient familiarity with the test procedures increased their overall performance, masking noticeable differences between the HC and MS group. Importantly, familiarity with the different tests remains unknown in this study.

Additionally, the MS group may have had to work harder than the HC group to achieve equivalent performance, and this extra effort resulted in higher fatigue. It remains possible that cognitive fatigue increased as a result of cognitive load or cognitive domain; however, this may have resulted in participants exerting more effort to maintain efficient performance. Such a relationship may show no change in objective performance scores but will show an increase in reported fatigue. The subjective–objective relationship may resemble a complex feedback loop between cognitive effort and cognitive fatigue that goes unnoticed by objective performance-based measures. The relationship may be one whereby cognitive effort results in increases in cognitive fatigue and those increases in cognitive fatigue result in additional cognitive effort – *ad infinitum* – until the cognitive task is discontinued. The present findings cannot directly rule out this complimentary theoretical explanation describing the relationship between subjective and objective cognitive fatigue. It may be possible to disentangle this account in future research if valid and reliable measures of cognitive effort are correlated with cognitive fatigue [perhaps physiological measures of pupillometry will be one viable approach, c.f., Hess and Polt (33)]. Presently, the assumptions associated with this theoretical perspective remain open to further empirical investigation.

CONCLUSION

Irrespective of cognitive load, subjective cognitive fatigue increased as a time increased and this was magnified for the MS group. The independence of subjective and objective cognitive fatigue replicates past work in MS. These data suggest a temporal nature of cognitive fatigue in MS. Researchers should consider sustained task length as an important variable to control for when designing and conducting studies investigating cognitive fatigue and consider measuring subjective fatigue at multiple specific intervals. It remains possible that subjective cognitive fatigue may manifest differently in other neurological populations and other MS disease subtypes. This hypothesis will need to be further evaluated in future research.

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REFERENCES

1. Minden S, Frankel D, Hadden L, Perloff J, Srinath K, Hoaglin D. The Sonya Slifka longitudinal multiple sclerosis study: methods and sample characteristics. *Mult Scler* (2006) **12**(1):24–38. doi:10.1191/135248506ms1262oa
2. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray T. The impact of fatigue on patients with multiple sclerosis. *Can J Neurol Sci* (1994) **21**(1):9–14.
3. Freal J, Kraft G, Coryell J. Symptomatic fatigue in multiple sclerosis. *Arch Phys Med Rehabil* (1984) **65**(3):135–8.
4. Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. *Arch Neurol* (1988) **45**(4):435. doi:10.1001/archneur.1988.00520280085020
5. Chaudhuri A, Behan PO. Fatigue and basal ganglia. *J Neurol Sci* (2000) **179**(1):34–42. doi:10.1016/S0022-510X(00)00411-1
6. Claros-Salinas D, Dittmer N, Neumann M, Sehle A, Spiteri S, Willmes K, et al. Induction of cognitive fatigue in MS patients through cognitive and physical load. *Neuropsychol Rehabil* (2013) **23**(2):182–201. doi:10.1080/09602011.2012.726925
7. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses proposal for a unified taxonomy. *Neurology* (2013) **80**(4):409–16. doi:10.1212/WNL.0b013e31827f07be
8. Ackerman PL. 100 years without resting. In Ackerman PL, editor. *Cognitive Fatigue: Multidisciplinary Perspectives on Current Research and Future Applications*. Washington, DC: American Psychological Association (2011). p. 11–37.
9. DeLuca J. Fatigue, cognition and mental effort. In: DeLuca J, editor. *Fatigue as a Window to the Brain*. Cambridge: MIT Press (2005). p. 37–57.
10. Kanfer R. Determinants and consequences of subjective cognitive fatigue. In Ackerman PL, editor. *Cognitive Fatigue: Multidisciplinary Perspectives on Current Research and Future Applications*. Washington, DC: American Psychological Association (2011). p. 189–208.
11. Van Dongen HPA, Belenky G, Krueger JM. Investigating the temporal dynamics and underlying mechanisms of cognitive fatigue. In: Ackerman PL, editor. *Cognitive Fatigue: Multidisciplinary Perspectives on Current Research and Future Applications*. Washington, DC: American Psychological Association (2011). p. 127–47.
12. Ackerman PL, Kanfer R. Test length and cognitive fatigue: an empirical examination of effects on performance and test-taker reactions. *J Exp Psychol* (2009) **15**(2):163. doi:10.1037/a0015719
13. Jensen JL, Berry DA, Kummer TA. Investigating the effects of exam length on performance and cognitive fatigue. *PLoS One* (2013) **8**(8):e70270. doi:10.1371/journal.pone.0070270
14. Johnson SK, Lange G, DeLuca J, Korn LR, Natelson B. The effects of fatigue on neuropsychological performance in patients with chronic fatigue syndrome, multiple sclerosis, and depression. *Appl Neuropsychol* (1997) **4**(3):145–53. doi:10.1207/s15324826an0403_1
15. Krupp LB, Elkins LE. Fatigue and declines in cognitive functioning in multiple sclerosis. *Neurology* (2000) **55**(7):934–9. doi:10.1212/WNL.55.7.934
16. Bailey A, Channon S, Beaumont J. The relationship between subjective fatigue and cognitive fatigue in advanced multiple sclerosis. *Mult Scler* (2007) **13**(1):73–80. doi:10.1177/1352458506071162

17. Paul RH, Beatty WW, Schneider R, Blanco CR, Hames KA. Cognitive and physical fatigue in multiple sclerosis: relations between self-report and objective performance. *Appl Neuropsychol* (1998) **5**(3):143–8. doi:10.1207/s15324826an0503_5
18. Schwartz CE, Coulthard-Morris L, Zeng Q. Psychosocial correlates of fatigue in multiple sclerosis. *Arch Phys Med Rehabil* (1996) **77**(2):165–70. doi:10.1016/S0003-9993(96)90162-8
19. Parmenter BA, Denney DR, Lynch SG. The cognitive performance of patients with multiple sclerosis during periods of high and low fatigue. *Mult Scler* (2003) **9**(2):111–8. doi:10.1191/1352458503ms859oa
20. Ackerman PL. Determinants of individual differences during skill acquisition: cognitive abilities and information processing. *J Exp Psychol* (1988) **117**(3):288. doi:10.1037/0096-3445.117.3.288
21. Cameron C. A theory of fatigue. *Ergonomics* (1973) **16**(5):633–48. doi:10.1080/00140137308924554
22. DeLuca J, Chelune GJ, Tulsky DS, Lengenfelder J, Chiaravalloti ND. Is speed of processing or working memory the primary information processing deficit in multiple sclerosis? *J Clin Exp Neuropsychol* (2004) **26**(4):550–62. doi:10.1080/13803390490496641
23. Genova HM, Hillary FG, Wylie G, Rypma B, DeLuca J. Examination of processing speed deficits in multiple sclerosis using functional magnetic resonance imaging. *J Int Neuropsychol Soc* (2009) **15**(03):383–93. doi:10.1017/S1355617709090535
24. Berrigan LI, LeFevre J-A, Rees LM, Berard J, Freedman MS, Walker LA. Cognition in early relapsing-remitting multiple sclerosis: consequences may be relative to working memory. *J Int Neuropsychol Soc* (2013) **19**(08):938–49. doi:10.1017/S1355617713000696
25. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* (2011) **69**(2):292–302. doi:10.1002/ana.22366
26. DeLuca J, Genova HM, Hillary FG, Wylie G. Neural correlates of cognitive fatigue in multiple sclerosis using functional MRI. *J Neurol Sci* (2008) **270**(1):28–39. doi:10.1016/j.jns.2008.01.018
27. Rypma B, Berger JS, Prabhakaran V, Martin Bly B, Kimberg DY, Biswal BB, et al. Neural correlates of cognitive efficiency. *Neuroimage* (2006) **33**(3):969–79. doi:10.1016/j.neuroimage.2006.05.065
28. Genova HM, Rajagopalan V, DeLuca J, Das A, Binder A, Arjunan A, et al. Examination of cognitive fatigue in multiple sclerosis using functional magnetic resonance imaging and diffusion tensor imaging. *PLoS One* (2013) **8**(11):e78811. doi:10.1371/journal.pone.0078811
29. Benito-León J, Martínez-Martín P, Frades B, Martínez-Ginés M, De Andrés C, Meca-Lallana J, et al. Impact of fatigue in multiple sclerosis: the fatigue impact scale for daily use (D-FIS). *Mult Scler* (2007) **13**(5):645–51. doi:10.1177/1352458506073528
30. Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. *Psychiatry Res* (1991) **36**(3):291–8. doi:10.1016/0165-1781(91)90027-M
31. Dobryakova E, DeLuca J, Genova HM, Wylie GR. Neural correlates of cognitive fatigue: cortico-striatal circuitry and effort–reward imbalance. *J Int Neuropsychol Soc* (2013) **19**(08):849–53. doi:10.1017/S1355617713000684
32. DeLuca J, Gaudino EA, Diamond BJ, Christodoulou C, Engel RA. Acquisition and storage deficits in multiple sclerosis. *J Clin Exp Neuropsychol* (1998) **20**(3):376–90. doi:10.1076/jcen.20.3.376.819
33. Hess EH, Polt JM. Pupil size in relation to mental activity during simple problem-solving. *Science* (1964) **143**(3611):1190–2. doi:10.1126/science.143.3611.1190

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Fatigue in multiple sclerosis compared to stroke

*Claudia Lukoschek[1], Annette Sterr[2,3,4], Dolores Claros-Salinas[1,5], Rolf Gütler[1] and Christian Dettmers[1,5,6]**

[1] Kliniken Schmieder Konstanz, Konstanz, Germany, [2] University of Surrey, Guildford, UK, [3] University of Freiburg, Freiburg im Breisgau, Germany, [4] Department of Neurology, University of São Paulo, São Paulo, Brazil, [5] Lurija Institute, Kliniken Schmieder Allensbach, Allensbach, Germany, [6] Department of Psychology, University of Konstanz, Konstanz, Germany

Objectives: Fatigue is typically associated with multiple sclerosis (MS), but recent studies suggest that it is also a problem for patients with stroke. While a direct comparison of fatigue in, e.g., Stroke and MS is desirable, it is presently not easily possible because of different definitions and assessment tools used for the two conditions. In the present study, we therefore assessed fatigue in Stroke and MS using a generic, not disease-specific instrument to allow transdiagnostic comparison.

Method: A total of 137 patients with MS and 102 patients with *chronic* stroke completed the SF-36, a generic questionnaire assessing health related quality of life. Fatigue was measured through the vitality scale of the SF-36. The vitality scale consists of two positive items ("lot of energy," "full of life") and two negative ones ("worn out," "tired"). The two negative ones were scaled in reverse order. The vitality scale has been recommended as reciprocal index of fatigue.

Results: Normalized vitality scores in MS (35.3) and stroke (42.1) were clearly lower than published reference values from the SF-36 in age-matched healthy controls. The sum score of the vitality items was lower in MS than in stroke patients. This difference could not be explained by age, gender, or the Physical Functioning Scale of the SF-36. Both patient groups showed no positive correlation between fatigue and physical functioning. Fatigue – as determined with the vitality scale of the SF-36 – correlated with the estimated working capacity in MS patients, but not in stroke patients.

Conclusion: These findings confirm high fatigue in MS and stroke patients with higher values in MS. Fatigue has a higher impact on working capacity in MS than in stroke. Fatigue in both patient groups is not a direct consequent of physical functioning/impairment. Vitality score of the SF-36 is a suitable transdiagnostic measure for the assessment of fatigue in stroke and MS.

Keywords: assessment, fatigue, multiple sclerosis, questionnaire, SF-36, stroke, vitality

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****Correspondence:***
Christian Dettmers, Kliniken Schmieder Konstanz, Eichhornstr. 68, Konstanz 78464, Germany
c.dettmers@kliniken-schmieder.de

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Introduction

Fatigue is a prominent and frequent symptom in multiple sclerosis (MS), and affects 60–90% of patients (1, 2). Fatigue is often experienced as the most disabling and limiting symptom, and greatly contributes to the degradation of general well-being, quality of life, and social participation (3, 4). Moreover, the impact of fatigue in the workplace can be severe and frequently triggers early

retirement, even in the early phase of the disease (5). In contrast to the importance of fatigue for patients, treatment options are limited and efficacy varies substantively across patients (6) (see also Khan et al., this special issue). Understanding and distinguishing different pathophysiological mechanisms might improve individually tailored treatment options.

While fatigue is most prominent in MS, it is also observed in other conditions. This is particularly for patients with Stroke, where fatigue has been identified as "a major yet neglected issue" (7). This perspective has spearheaded more research in this arena (8–10), but the characteristics of fatigue in stroke have yet to be fully determined. It is further unclear to what extent fatigue in MS and Stroke share similarities in their impact on the individual, and whether fatigue is equally prevalent in the two conditions.

Because fatigue is by far best characterized in MS, benchmarking fatigue characteristics of other conditions against MS is important. However, such comparisons are challenging because the majority of assessment instruments, such as the Fatigue Severity Scale (11) and the Fatigue Scale for Motor and Cognitive Functions (FSMC) (12), have been specifically developed for MS, and might therefore not be equally sensitive in other neurological conditions. Moreover, a recent review on fatigue measures in neurological conditions concluded that the FSMC and the Unidimensional Fatigue Impact Scale (13, 14) are best suited for measuring fatigue in MS, while the Profile of Mood States Fatigue subscale (POMS-F) is the optimal measure for stroke (15).

If fatigue characteristics and fatigue prevalence are to be compared across neurological conditions, it is necessary to use a generic, disease-unspecific measure, which allows the transdiagnostic comparison of fatigue prevalence. Such a generic measure has been derived from the vitality subscale of the short form SF-36 (15). The SF-36 is a well-validated and accepted measure of health, which is used in a wide range of health care settings and research (16). Its vitality subscale has already been used to assess fatigue in patients with myocardial infarction (17). The present study therefore used the vitality subscale to contrast fatigue in 137 MS and 102 Stroke patients. Based on the prevailing notion that the fatigue affects the majority of MS patients, we predicted a more severe manifestation and a higher impact on working capacity in MS compared to Stroke.

Materials and Methods

Participants

Data from 137 patients with MS (aged 47.3 ± 8.8, 51 males) and 102 patients with chronic stroke (aged 54.3 ± 12.0, 58 males), admitted to the hospital between January 2011 and March 2012, were included in the study. The data were retrospectively extracted from the database of the Kliniken Schmieder Konstanz, a specialized inpatient rehabilitation center in southern Germany. Kliniken Schmieder provides care for a wide range of neurological conditions but the largest patient groups comprise MS (800 patients per year), subacute, and chronic stroke (about 300 stroke patients per year). Patients typically stay in the clinic for 3–6 weeks. At the beginning of the stay, every patient completes the SF-36, a health related, generic questionnaire (16). All participants had a Barthel Index of >70 (qualifying for "Phase D" in the German rehabilitation system), and were able to independently exercise personal care.

For MS, the inclusion criteria comprised the confirmed diagnosis of MS, based on the McDonald criteria (18), for 12 months or longer. No further selection criteria were employed. The inclusion criteria for stroke encompassed hemorraghic or ischemic stroke which had occurred at least 12 months prior to testing. Transient ischemic attack (TIA) was not accepted as inclusion criterion. For both groups, exclusion criteria included (1) other neurological disorders such as head trauma, M. Parkinson, brain tumor, neuromuscular disorder, (2) history of psychiatric disorders, (3) major depression, and (4) cancer. In order to evaluate and compare the degree of impairment in both patient groups, the Physical Functioning Scale of the SF-36 and the participants' retirement/employment and insurance status (for details, see next paragraph) were analyzed.

Assessment

The SF-36 [German translation, version 1, (16)] was applied to all patients within 2 days of admittance to Kliniken Schmieder. The SF-36 is a psychometrically well-characterized (19) and widely used questionnaire to assess functional health and well-being. It contains 36 questions, which cover the following eight domains: vitality, physical functioning, bodily pain, general health perceptions, role physical functioning, role emotional, social functioning, and mental health. Scores on each item range from 0 to 100, with higher scores reflecting better functioning.

Fatigue was measured through the scores of the vitality domain (items 9a: "Did you feel full of life," 9e: "Did you have a lot of energy," 9g: "Did you feel worn out," and 9i: "Did you feel tired"). These items are rated on a six-step Likert scale, and assigned values between 1 and 6. Because items 9a and 9e are positively scored, the respective raw scores were reversed prior to the transformation into standardized scores [transformed score $= 100 \times$ (raw value$-$minimal value)/range]. The average vitality (VT) score was calculated as the mean standardized scores of the VT items 9a, e, g, and i.

The level of physical disability was measured through the Physical Functioning Scale of the SF-36. This scale comprises 10 items (3a:vigorous activities, 3b: moderate activities, 3c: lift, carry groceries, 3d: climb several flights, 3e: climb one flight, 3f: bend, kneel, 3g: walk a mile, 3h: walk several blocks, 3i: walk one block, 3j: grooming and bathing). Responses are categorized according to the following options on a three-step Likert scale ($1 =$ strongly impaired, $2 =$ moderately impaired, and $3 =$ not at all impaired), and transformed into standard scores ranging from 0 to 100 as described above.

Unfortunately at the time of admittance, we did not apply a standardized stroke scale for our patients like the NIH Stroke Scale or the Modified Ranking Scale (mRS) to describe characteristics of our patient population. But even if we had done so, it would have been difficult to compare these characteristics to MS patients, which are measured or scaled with different tools, most often with the Expanded Disability Status Scale (EDSS, see below).

In order to compare the handicap in both patient groups, the categorization of their working capacity assessment was taken from the discharge letters. In agreement with the work capacity

classification system of German pension funds, the capacity for full time is defined as $\geq$6 h a day and part time as 3 to <6 h a day. A working capacity of <3 h a day corresponds to retirement. The working capacity is a medical prognostic judgment of the degree to which patients will be able to work after finishing sick leave. This judgment is independent of the actual employment status (i.e., all potentially eligible patients receive this judgment whether they are in employment or not). This categorization is not developed as a research tool, but is well standardized and affords excellent socioeconomic validity. It is also not specific for one diagnostic group, but allows for transdiagnostic comparison of restrictions in the working field.

The party covering the cost of the rehabilitation (pension funds in case of preserved working capacity and health insurance company in case of retirement) was determined. The working capacity measure is used uniformly across the range of health conditions and therefore provides a comparable real-world index of the capacity to work in both groups. Vitality and Physical Functioning were calculated for each working capacity category for both groups (**Table 3**).

The EDSS is documented in patients with MS. EDSS represents a common scale to quantify disability in MS patients, ranging from 0 to 10. Zero means no symptoms, 10 means dead due to MS. It is commonly used in clinical studies to characterize MS patients, and was therefore included in this study. The measure, however, is not meaningful to apply in patients with stroke, and is therefore reported for MS only.

Statistics

Statistical analysis was conducted with SPSS version 19. Normal distribution of the variables was investigated using the Kolmogoroff–Smirnov test. Homogenous distribution of variances was confirmed by the Levene-test. Independent *t*-test was used to determine differences between vitality scores in stroke and MS patients. An ANOVA was calculated to look for interaction between diagnostic group and fatigue. A Pearson correlation was performed to analyze the correlation between fatigue and physical functioning. An ANCOVA was applied to investigate whether the difference between both patient groups was independent of age, sex, and physical functioning.

Results

Patients

The final sample comprised 102 patients with chronic stroke (mean age 54.3 ± 12.0 years) and 137 patients with MS (mean age 47.3 ± 8.8 years). Age was significantly different in both groups ($t[177] = -5.02$; $p = 0.0005$; $\eta^2 = 0.096$). The gender balance in the two patient groups was different with 62.8% females in the MS group and 43.1% in the stroke group (χ^2 [1] = 9.1; $p = 0.003$). In addition, scores on the Physical Functioning subscale of the SF-36 indicated significantly greater levels of disability in the MS group (17.8 ± 5.0) than in the stroke group (20.1 ± 5.6; $t[183] = -3.2$, $p = 0.002$). The EDSS – a scale developed for MS patients and not applicable in stroke patients – indicated a score of 4 reflecting moderate disability (3 refers to the border between light and moderate disability, 6 means depended on a walking aid to walk 100 m without rest). Although great care was taken only to include chronic stroke patients, time since onset of symptoms was longer in MS patients (15.5 years ± 9.3) than in stroke patients (5.2 years ± 6.0) due to its natural and chronic course.

Analysis of the employment status revealed that 70% of MS patients were funded by the pension fund compared to 76.5% in the stroke group (**Table 1**). These are the patients still working and those still under consideration for returning to work by the pension fund. At the time of discharge, almost 50% in both groups (46% of MS and 50% of stroke patients) were categorized as qualifying for a full time job. Almost 40% of the MS patients fell in the category for part-time work compared to 25% of stroke patients. In the stroke group, more patients had reached the status of being unable to work (25%) compared to the MS patients (14%) (**Table 1**).

Fatigue Score

Mean values on the normalized vitality subscale of the SF-36 were 35.4 ± 12.1 in MS patients and 42.1 ± 12.7 in stroke patients (compare **Table 2**). These means are well below the vitality data available through the German Health Survey 1998 (20).

TABLE 1 | Demographics and patients' characteristics.

	Patients with MS	Patients with stroke	Sign. level
N	137	102	
Female	63%	43%	<0.05
Mean age (range)	47.3 (20–69)	54.3 (21–80)	<0.05
Mean EDSS (SD)	4.1 (1.6)	Not applicable	
Range	0–8		
Years since onset, mean (SD)	15.5 (9.3)	5.2 (6.0); 1–33.6	<0.05
Range	1–49		
Party paying the rehabilitation			
Pension fund (%)	70	76.5	
Health insurance company (%)	30	23.5	
Estimated working capacity			
>6 h	46.2%	50.8%	
3–6 h	39.5%	24.6%	
<3 h	14.3%	24.6%	
Physical Functioning Scale from SF-36 (SD)	17.8 (5.0)	20.1 (5.6)	<0.05

EDSS, Expanded Disability Status Scale.
Paying party: as long as the pension fund pays for rehabilitation, the client is still in the category of being or becoming potentially able to work. "Estimated working capacity" displays the number of full-time (>6 h) and part-time (3–6 h) workers as well as the number of those being unable to work anymore. The paying party and the estimated working capacity indicate that disability in both groups was similar.

TABLE 2 | Normalized Vitality scores of the vitality subscale of the SF-36 from the present investigation compared to normal values from the German Health Survey 1998 (20).

Patients/reference group	Mean	SD	Comment Original publication
MS	35.4	12.1	Present data
Stroke	42.1	12.7	Present data
Male, age 40–49	64.2	16.3	German Health Survey 1998 (20) (*N* = 6964 participants, age 18–80)
Male, age 50–59	61.5	18.1	German Health Survey 1998 (20)
Female, age 40–49	57.4	18.8	German Health Survey 1998 (20)
Female, age 50–59	57.7	18.8	German Health Survey 1998 (20)

TABLE 3 | Vitality and Physical Functioning in relation to working capacity in MS and stroke patients.

Estimated working capacity	Vitality			10-item Physical Functioning		
	N	Mean (SD; range)	Median	*N*	Mean (SD; range)	Median
Patients with MS						
>6 h	43	38.2 (15.8; 5–75)	40	41	52.1 (26.1; 5–100)	50
3–6 h	36	32.8 (21.3; 0–80)	30	33	30.8 (26.9; 0–100)	35
<3 h	13	25.0 (10.0; 5–40)	25	11	30.0 (13.2; 5–45)	35
Patients with stroke						
>6 h	32	44.8 (18.4; 15–85)	42.5	32	64.2 (24.1; 15–100)	67.5
3–6 h	15	31.7 (13.2; 10–60)	30	14	56.8 (23.7; 20–95)	60
<3 h	16	41.6 (22.4; 0–80)	40	16	37.2 (31.0; 0–100)	30

Vitality appears to be proportional to working capacity in MS, but not in stroke patients. Working capacity had been estimated from the medical doctor at the time of discharge only in those patients, whose rehabilitation had been paid from the pension funds (92 patients with MS, 62 patients with stroke).

Statistical analysis of the vitality scores further suggested a highly significant group difference ($F = 7.49$; $p = 0.007$), reflecting higher levels of fatigue in MS than Stroke. This group difference remained when age, sex, and Physical Functioning were factored in as covariates ($F[1,236] = 4.59$; $p = 0.033$; $\eta^2 = 0.02$ for age; $F[1,236] = 5.96$; $p = 0.015$; $\eta^2 = 0.03$ for sex; $F[1,213] = 9.19$; $p = 0.003$; $\eta^2 = 0.04$ for Physical Functioning). Both groups did not show positive correlations between fatigue and physical functioning as determined by question three of the SF-36 (Pearson correlation).

Separate calculation of the vitality scores for each category of estimated working capacity further revealed that vitality was closely related to working capacity in MS patients ($r = 0.25$; $p = 0.02$; Pearson correlation), but not in stroke patients. By contrast, Physical Functioning is associated to the estimated working capacity in stroke patients but not in MS patients. These data are summarized in **Table 3**.

Discussion

The present study used the vitality score derived from the SF-36 as an index of fatigue. The data shows that the vitality scores derived in patients with MS and stroke are lower than normal values of population based studies. This suggests that patients with stroke and patients with MS suffer greater fatigue than their healthy peers. The data further suggests that fatigue is a substantive issue in both patient groups.

This study allows for a direct comparison between the SF-36 vitality score as a proxy for fatigue in stroke and MS patients. The SF-36 is a widely evaluated generic patient-assessed health outcome measure (21). The generic character of the questionnaire enables transdiagnostic comparison of patients with different conditions. In the present study, the comparison was conducted for fatigue and showed that fatigue in stroke patients falls within a similar range as in MS patients. This is an important finding since fatigue, recognized as a major issue in clinical practice, is much less recognized in patients with stroke.

However, fatigue in MS patients is still higher than in stroke patients. This might have been expected at least from health professionals and cares dealing with MS patients.

It appears remarkable to us that there is an association of fatigue and working capacity in MS patients, but that there is not such an association in stroke patients. In our view, this confirms the clinical impression that fatigue has a high clinical impact on MS patients, but less so in stroke patients. In other words: the close association of fatigue with working capacity in MS patients suggests that fatigue directly affects working capacity in MS patients. This is not the case in stroke patients; here, working capacity is more related to Physical Functioning.

The data confirm that fatigue is more prominent in MS than stroke. This is a very important finding; since to our knowledge, only few publications have investigated fatigue in MS and stroke patients using the same assessment tool. Naess et al. obtained the Nottingham Health Profile in 191 ischemic stroke patients and compared it to 337 MS patients (22). It was concluded that stroke patients often report pain and problems with sleepiness, while MS patients often report more problems with fatigue. Using alertness as a marker of fatigue in MS and stroke patients, Claros-Salinas et al. (23) demonstrated an increase in reaction time during the course of the day, highlighting the similarity between these two patient groups. At the same time, the decline of performance in MS patients appeared slightly greater than in stroke suggesting more pronounced fatigue in MS patients compared to stroke patients. In contrast, no decline was found for age matched controls. Mills and colleagues further developed a new fatigue index for MS patients (24), and validated the instrument for assessment of fatigue in stroke patients (25). They concluded that "post-stroke fatigue appeared to be qualitatively similar to that of MS fatigue, including, for example, features associated with physical and cognitive aspects" (25). The present study therefore provides further evidence that fatigue is an important symptom in the chronic phase of stroke. Whether the pathophysiological mechanisms underlying fatigue in stroke and MS are similar or not, however, it needs to be determined in future research.

Importantly, neither patient group showed a positive association between the vitality subscale and the Physical Function subscale. It is remarkable that the degree of fatigue reported here cannot be explained by a simple effect of limitations in physical functioning. Our results suggest that fatigue is not a consequence of the accumulation of tissue damage. This is in line with recent observations showing that the Motricity index as well as the Stroke Impact Scale are not predictive of fatigue (9). Similarly, structural computer tomography variables (atrophy, white matter lesions, or previous vascular lesions) were not associated with fatigue at 1 month (26). Previous investigations could not confirm a significant correlation between EDSS and fatigue (27, 28). This

stands in contrast to other studies reporting a correlation between fatigability and motor ("pyramidal") involvement and disability (29, 30). While it may be plausible that patients have more fatigue in the advanced stage, there seems to be no *close* correlation between physical impairment and fatigue. Our data confirm that fatigue is not a direct consequence of physical impairment in MS or stroke.

Study Limitations

While the use of a general health questionnaire has the advantage of being applicable in two different patient groups, it has the obvious disadvantage that it is not a precise instrument, which can capture fatigue in all its facets. In other words, the benefit of comparability comes at the cost of accuracy with which fatigue is assessed. Although stroke and MS patients rated their vitality in a similar range, confronting patients with a more elaborate questionnaire or *measuring* reaction time as a surrogate marker of fatigue before and after a cognitive challenging task (31) might provoke different results and might show larger discrepancies between stroke and MS patients. Although fatigue falls in a similar range in both entities, in our opinion the question remains, whether or not fatigue in stroke patients is as disabling as in MS patients. We assume that the vitality score is not elaborate enough to capture the complete phenomenon of fatigue and to compare the disabling impact of fatigue in both diseases. Nevertheless, the SF-36 is widely applied, easy to handle, and allows for transdiagnostic comparison between different patient groups.

Another limitation might be the selection of our MS and stroke patients. We did not include severely affected stroke patients, who require further assistance in daily activities. Neither did we include stroke patients with a very good prognosis, who do not require any rehabilitation. The present findings might therefore not be generalizable to the whole range of longer term outcome present in stroke survivors.

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References

1. Freal JE, Kraft GH, Coryell JK. Symptomatic fatigue in multiple sclerosis. *Arch Phys Med Rehabil* (1984) **65**(3):135–8.
2. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. *Can J Neurol Sci* (1994) **21**(1):9–14.
3. Krupp LB. Fatigue in multiple sclerosis: definition, pathophysiology and treatment. *CNS Drugs* (2003) **17**(4):225–34. doi:10.2165/00023210-200317040-00002
4. Simmons RD. Life issues in multiple sclerosis. *Nat Rev Neurol* (2010) **6**(11):603–10. doi:10.1038/nrneurol.2010.143
5. Simmons RD, Tribe KL, McDonald EA. Living with multiple sclerosis: longitudinal changes in employment and the importance of symptom management. *J Neurol* (2010) **257**(6):926–36. doi:10.1007/s00415-009-5441-7
6. Kos D, Kerckhofs E, Nagels G, D'Hooghe MB, Ilsbroukx S. Origin of fatigue in multiple sclerosis: review of the literature. *Neurorehabil Neural Repair* (2008) **22**(1):91–100. doi:10.1177/1545968306298934
7. Staub F, Bogousslavsky J. Fatigue after stroke: a major but neglected issue. *Cerebrovasc Dis* (2001) **12**(2):75–81. doi:10.1159/000047685
8. Radman N, Staub F, Aboulafia-Brakha T, Berney A, Bogousslavsky J, Annoni JM. Poststroke fatigue following minor infarcts: a prospective study. *Neurology* (2012) **79**(14):1422–7. doi:10.1212/WNL.0b013e31826d5f3a
9. van Eijsden HM, van de Port IG, Visser-Meily JM, Kwakkel G. Poststroke fatigue: who is at risk for an increase in fatigue? *Stroke Res Treat* (2012) **2012**:863978. doi:10.1155/2012/863978
10. Naess H, Lunde L, Brogger J. The effects of fatigue, pain, and depression on quality of life in ischemic stroke patients: the Bergen Stroke Study. *Vasc Health Risk Manag* (2012) **8**:407–13. doi:10.2147/VHRM.S32780
11. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* (1989) **46**(10):1121–3. doi:10.1001/archneur.1989.00520460115022
12. Penner IK, Raselli C, Stocklin M, Opwis K, Kappos L, Calabrese P. The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult Scler* (2009) **15**(12):1509–17. doi:10.1177/1352458509348519
13. Doward LC, Meads DM, Fisk J, Twiss J, Hagell P, Oprandi NC, et al. International development of the Unidimensional Fatigue Impact Scale (U-FIS). *Value Health* (2010) **13**(4):463–8. doi:10.1111/j.1524-4733.2010.00706.x
14. Meads DM, Doward LC, McKenna SP, Fisk J, Twiss J, Eckert B. The development and validation of the Unidimensional Fatigue Impact Scale (U-FIS). *Mult Scler* (2009) **15**(10):1228–38. doi:10.1177/1352458509106714
15. Elbers RG, Rietberg MB, van Wegen EE, Verhoef J, Kramer SF, Terwee CB, et al. Self-report fatigue questionnaires in multiple sclerosis, Parkinson's disease and stroke: a systematic review of measurement properties. *Qual Life Res* (2012) **21**(6):925–44. doi:10.1007/s11136-011-0009-2
16. Bullinger M. German translation and psychometric testing of the SF-36 Health Survey: preliminary results from the IQOLA Project. International Quality of Life Assessment. *Soc Sci Med* (1995) **41**(10):1359–66. doi:10.1016/0277-9536(95)00115-N
17. Fink AM, Eckhardt AL, Fennessy MM, Jones J, Kruse D, VanderZwan KJ, et al. Psychometric properties of three instruments to measure fatigue with myocardial infarction. *West J Nurs Res* (2010) **32**(7):967–83. doi:10.1177/0193945910371320
18. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald criteria". *Ann Neurol* (2005) **58**(6):840–6. doi:10.1002/ana.20703
19. Haley SM, McHorney CA, Ware JE Jr. Evaluation of the MOS SF-36 physical functioning scale (PF-10): I. Unidimensionality and reproducibility of the Rasch item scale. *J Clin Epidemiol* (1994) **47**(6):671–84. doi:10.1016/0895-4356(94)90215-1
20. Ellert U, Bellach BM. [The SF-36 in the Federal Health Survey – description of a current normal sample]. *Gesundheitswesen* (1999) **61**(Spec No):S184–90.
21. Garratt A, Schmidt L, Mackintosh A, Fitzpatrick R. Quality of life measurement: bibliographic study of patient assessed health outcome measures. *BMJ* (2002) **324**(7351):1417. doi:10.1136/bmj.324.7351.1417
22. Naess H, Beiske AG, Myhr KM. Quality of life among young patients with ischaemic stroke compared with patients with multiple sclerosis. *Acta Neurol Scand* (2008) **117**(3):181–5. doi:10.1111/j.1600-0404.2007.00923.x
23. Claros-Salinas D, Bratzke D, Greitemann G, Nickisch N, Ochs L, Schroter H. Fatigue-related diurnal variations of cognitive performance in multiple sclerosis and stroke patients. *J Neurol Sci* (2010) **295**(1–2):75–81. doi:10.1016/j.jns.2010.04.018
24. Mills RJ, Young CA, Pallant JF, Tennant A. Development of a patient reported outcome scale for fatigue in multiple sclerosis: The Neurological Fatigue Index (NFI-MS). *Health Qual Life Outcomes* (2010) **8**:22. doi:10.1186/1477-7525-8-22
25. Mills RJ, Pallant JF, Koufali M, Sharma A, Day S, Tennant A, et al. Validation of the Neurological Fatigue Index for stroke (NFI-Stroke). *Health Qual Life Outcomes* (2012) **10**:51. doi:10.1186/1477-7525-10-51
26. Kutlubaev MA, Shenkin SD, Farrall AJ, Duncan FH, Lewis SJ, Greig CA, et al. CT and clinical predictors of fatigue at one month after stroke. *Cerebrovasc Dis Extra* (2013) **3**(1):26–34. doi:10.1159/000347113
27. Bakshi R, Shaikh ZA, Miletich RS, Czarnecki D, Dmochowski J, Henschel K, et al. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. *Mult Scler* (2000) **6**(3):181–5. doi:10.1191/135245800701566052

28. Flachenecker P, Kumpfel T, Kallmann B, Gottschalk M, Grauer O, Rieckmann P, et al. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. *Mult Scler* (2002) **8**(6):523–6. doi:10.1191/1352458502ms839oa
29. Iriarte J, Subira ML, Castro P. Modalities of fatigue in multiple sclerosis: correlation with clinical and biological factors. *Mult Scler* (2000) **6**(2):124–30. doi:10.1191/135245800678827572
30. Colosimo C, Millefiorini E, Grasso MG, Vinci F, Fiorelli M, Koudriavtseva T, et al. Fatigue in MS is associated with specific clinical features. *Acta Neurol Scand* (1995) **92**(5):353–5. doi:10.1111/j.1600-0404.1995.tb00145.x
31. Neumann M, Sterr A, Claros-Salinas D, Gutler R, Ulrich R, Dettmers C. Modulation of alertness by sustained cognitive demand in MS as surrogate measure of fatigue and fatigability. *J Neurol Sci* (2014) **340**(1–2):178–82. doi:10.1016/j.jns.2014.03.024

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Difference in motor fatigue between patients with stroke and patients with multiple sclerosis: a pilot study

Aida Sehle[1,2], Manfred Vieten[1], Annegret Mündermann[1,3] and Christian Dettmers[2,4]*

[1] *Division of Sport Science, University of Konstanz, Konstanz, Germany*
[2] *Lurija Institute, Kliniken Schmieder Allensbach, Allensbach, Germany*
[3] *Department of Orthopaedics, University Hospital Basel, Basel, Switzerland*
[4] *Kliniken Schmieder Konstanz, Konstanz, Germany*

Edited by:
John DeLuca, Kessler Foundation, USA

Reviewed by:
Peter Feys, University of Hasselt, Belgium
Randall L. Jensen, Northern Michigan University, USA

****Correspondence:***
Christian Dettmers, Kliniken Schmieder Konstanz, Eichhornstraße 68, Konstanz 78464, Germany
e-mail: c.dettmers@kliniken-schmieder.de

Fatigue is often reported in stroke patients. However, it is still unclear if fatigue in stroke patients is more prominent, more frequent or more "typical" than in patients with multiple sclerosis (MS) and if the pathophysiology differs between these two populations. The purpose of this study was to compare motor fatigue and fatigue-induced changes in kinematic gait parameters between stroke patients, MS patients, and healthy persons. Gait parameters at the beginning and end of a treadmill walking test were assessed in 10 stroke patients, 40 MS patients, and 20 healthy subjects. The recently developed Fatigue index Kliniken Schmieder (FKS) based on change of the movement's attractor and its variability was used to measure motor fatigue. Six stroke patients had a pathological FKS. The FKS (indicating the level of motor fatigue) in stroke patients was similar compared to MS patients. Stroke patients had smaller step length, step height and greater step width, circumduction with the right and left leg, and greater sway compared to the other groups at the beginning and at the end of test. A severe walking impairment in stroke patients does not necessarily cause a pathological FKS indicating motor fatigue. Moreover, the FKS can be used as a measure of motor fatigue in stroke and MS and may also be applicable to other diseases.

Keywords: multiple sclerosis, stroke, motor fatigue, gait analysis, attractor, fatigue index, questionnaire assessment, physical performance

INTRODUCTION

Fatigue is a frequent symptom in many neurologic diseases (1) and especially common and disabling in patients with multiple sclerosis (MS) (2, 3). Moreover, fatigue is often the reason for early retirement and hence represents a high economic burden (4). Despite the high prevalence of fatigue in MS of up to 83% (1), its pathophysiology is largely unknown (5, 6). Nonetheless, several pathophysiological pathways have been proposed: demyelinisation and axonal injury may cause "electric failure" (7); immunological and inflammatory factors such as cytokines may hamper neuronal processing (8); hormonal dysregulation may be caused by failed cortico-hypothalamic loops (9); and reorganization and compensation might add to the ineffectiveness of cerebral control and cause fatigue (10). Moreover, fatigue may be secondary to conditions including depression, sleep disorders, physical deconditioning, anemia, or side effects of medication (3, 11, 12).

In the last decade, reports of fatigue in neurological conditions other than MS, such as for instance stroke, have become more frequent (13, 14), and the prevalence of fatigue in patients after stroke ranges from 36 to 77% (1). Fatigue is a common and debilitating symptom even in patients with good recovery after stroke (15). Patients' level of fatigue does not change over time (16) and baseline fatigue immediately after a stroke predicts fatigue outcome (17). Staub and Bogousslavsky (18) suspected that primary poststroke fatigue may be caused by minor attentional deficits due to the interruption of neural networks, such as the reticular activating system. Patients use different strategies and coping styles to deal with poststroke fatigue (19). In addition, poststroke fatigue appears to be an independent determinant of not being able to resume paid work following stroke (20).

Currently, there are no widely accepted standard definitions or accepted standardized methods and instruments for assessing fatigue (1). Moreover, fatigue is understood as a multidimensional phenomenon with different aspects including a complex interplay between the underlying disease process, peripheral, and central control systems, as well as environmental factors (21). Its multidimensionality complicates the assessment of fatigue in neurological disorders. Kluger et al. (1) proposed a new taxonomy for fatigue in neurologic diseases and suggested differentiating between fatigue as subjective sensation and fatigability as an objective change in performances. Here, we distinguish between cognitive and motor components, which can occur in isolation or in combination. Commonly, the subjective perception of fatigue is assessed using questionnaires (22), and the measurement properties of fatigue questionnaires in MS have previously been evaluated (23). The most frequently used instruments for measuring fatigue in MS patients are the Fatigue Severity Scale (FSS) (24), the Fatigue Assessment Instrument (FAI) (25), the Fatigue Impact Scale (FIS) (2), the Modified Fatigue Impact Scale (MFIS) (26), the Fatigue

Scale for Motor and Cognitive Functions (FSMC) (27), and the Würzburg Fatigue Inventory in Multiple Sclerosis (WEIMuS) (28). Despite the reported prevalence of fatigue in MS and stroke, few studies used the same tools for assessing fatigue in these two conditions (compare also Lukoschek et al., in this special issue) (23). Moreover, in contrast to MS, there are no fatigue questionnaires that have been developed specifically for measuring fatigue after stroke (29). Often, the following instruments are used: the FSS (24), the Short-form 36/12 vitality questions (30), the Fatigue Assessment Scale (FAS) (31), and the Multidimensional Fatigue Symptom Inventory (MFSI) (14, 32). Overall, fatigue may be assessed quickly using fatigue questionnaires. However, these questionnaires are based on patients' self-assessments and may be distorted (overestimation or underestimation) due to an inaccurate self-perception (33). Moreover, fatigue questionnaires capture patients' general condition during a particular time period (33) and fatigue may also be quickly clinically assessed by physicians or physiotherapists. However, clinical experience suggests that an accurate identification of fatigue and non-fatigue depends on the experience of the therapists and physicians, and in some cases a clear diagnosis of fatigue is difficult. Especially, comorbidities (depression, sleep disorders, physical deconditioning, anemia, or side effects of medication) may cause similar symptoms (33). In these cases, the objective instrument can be extremely helpful for measuring fatigue. A correct diagnosis of fatigue is not only important to define optimal treatment but also when it is used as criterion for early retirement.

In the current study, we focused on the motor dimension of fatigability (here, we used the term motor fatigue as a synonym) in stroke and MS patients. The motor dimension of fatigability has previously been assessed in lower limbs using dynamometry in isometric contractions, sustained maximal contractions, repetitive maximal contractions, and walking as far as 500 m (34, 35) and in upper limbs using static and dynamic contraction tests (36–38) in MS patients. Hence, overall maximal force appeared to decrease either during repeated maximal contraction or during sustained contraction in MS patients. Furthermore, Severijns et al. (38) observed differences in sustained maximal hand grip contraction but not in dynamic contraction between healthy subjects and MS patients with high EDSS ($\geq$6) (38). Schwid et al. (35) proposed that motor fatigue can be measured as a decline in strength during sustained muscle contractions (35). Similarly, Greim et al. (36) proposed that decreases in strength of maximal repetitive muscle contraction and/or decrease of walking speed can be used to measure motor fatigue objectively (36). Post-stroke motor fatigue has previously been assessed in a few studies in upper and lower limbs using transcranial magnetic stimulation, dynamometry, and/or electromyography during the maximal voluntary contraction (MVC), sustained isometric contraction, submaximal contraction, and repetitive eccentric–concentric contraction (39–41). Knorr et al. (40) showed that during fatigue the silent period duration increased significantly in both upper limbs, whereas the motor evoked potential amplitude significantly increased only in the non-paretic limb (40). After fatigue, the reductions in the M wave, twitch peak torque, and MVC peak torque were observed in both limbs. Furthermore, the reduction in voluntary activation was greater in the paretic than in the non-paretic limb (40). Another study concluded that a reduction in work in high-intensity dynamic muscle activity may not be associated with a reduction in mean power frequency (39). Hu et al. (41) suggested that for identifying fatigue associated with neuromuscular transmission failure, the motor unit firing parameters firing rate, minimum inter-pulse interval, and maximum oscillation were more sensitive than the mean power frequency (41).

We recently developed the Fatigue index Kliniken Schmieder (FKS) as an objective tool for assessing motor fatigue in MS based on gait changes in a walking test on the treadmill (33). In this study, the subjects walked on a treadmill under different conditions: in a normal rested state and in an exhausted state or after 60-min walking. We measured the changes in acceleration patterns and acceleration variability of the feet during the walking test at the beginning and at the end of the walking test in MS patients and healthy subjects. Furthermore, in this study, we developed the FKS that is composed of these two components and which makes the distinction between fatigue and non-fatigue. The FKS described the changes in acceleration patterns and acceleration variability during the walking test on the individual level. The advantage of a walking test is that the entire musculature, especially the major muscle groups are required. This task is daily task-oriented and represents a complex movement with many degrees of freedom. In contrast to fatigue questionnaires, this test captures the current state of motor fatigue.

To date, it is still unclear if fatigue is specific to MS or at least to inflammatory disease or if it is an unspecific reaction of the brain after any kind of brain injury (1). The inflammatory etiology is supported by the fact that other inflammatory diseases such as sarcoidosis or cerebral vasculitis can be accompanied by serious fatigue. In stroke, fatigue may be related to reorganization or inefficient/suboptimal fiber tract connections or compensatory effort. Although we were not able to investigate different pathophysiological mechanisms directly by surrogate markers such as cytokines or tumor necrosis factor alpha or by different cerebral activation patterns, the intention of our study was to compare motor fatigue in patients with stroke and MS. This should facilitate better understanding limitations and needs of patients and more accurately define their goals for instance in rehabilitation. Therefore, the aim of our study was to investigate if the amount of change of the gait pattern during an exhausting physical task differs between stroke and MS patients. After propagating the test for identifying motor fatigue in MS (33), this investigation also should clarify if this test and the FKS are feasible for stroke patients and that a severe walking impairment in stroke patients does not necessarily cause a pathological FKS. Data of patients after stroke were collected and compared with previously published data (33) on 40 patients with MS and 20 healthy subjects.

MATERIALS AND METHODS

SUBJECTS

Ten patients who were admitted to a neurological rehabilitation clinic after stroke, met the inclusion criteria, and volunteered to participate between March and October 2012 were included in this study. Inclusion criteria were central hemiparesis affecting the leg, reduced walking capacity, and the ability to walk on a treadmill

without aids or assistance. All stroke patients were chronic (time since the onset of stroke > 12 months). Hemiparesis was left sided in four patients and right sided in six patients. Eight patients had a proportional hemiparesis affecting arm and leg, and two patients were more affected in their legs. Three patients had a haemorrhagic infarction and seven patients an ischemic infarction. One infarct was located in the brainstem, one in the anterior cerebral artery (ACA), and eight in the middle cerebral artery (MCA). Two MCA infarcts showed additional involvement of the ACA.

Data from our previous study (33) involving 20 healthy subjects and 40 patients with definite MS according to the McDonald criteria (42) were used in this study. MS patients and control subjects were recruited between October 2011 and July 2012. The MS patients were admitted to a neurological rehabilitation clinic. Inclusion criterion for MS patients was the ability to walk on a treadmill without aids or assistance. There were no limitations regarding the disease course and disability levels. Subjects were excluded from the study if they had relapses within the preceding three months or received Fampyra® (Fampridin; Biogen Idec Inc., 225 Binney Street, Cambridge, MA 02142). Healthy subjects were recruited from the local population and from clinic staff. Healthy subjects were excluded if they had any neurological or orthopedic disorders. In the previous study, the MS patients were classified into two groups based on the FKS: patients with a FKS > 4 were categorized as having motor fatigue (MS-F), and patients with a FKS ≤ 4 were categorized as having no motor fatigue (MS-NF). According to these criteria, 29 MS patients were in the fatigue group and 11 MS patients in the non-fatigue group.

All participants provided informed written consent prior to participation. The study protocol was approved by the University Ethics Committee and conducted in accordance with the Declaration of Helsinki.

QUESTIONNAIRES

At admission to the study, all subjects answered the Beck Depression Inventory II (BDI-II) to assess the level of subclinical depression (43). Self-reported physical function was assessed by patients using the physical functioning 10 subscale of the Short-form 36 (PF-10; SF-36) and four vitality questions of the SF-36 (44, 45). Vitality questions from the SF-36 have previously been suggested as measures of fatigue (46). These two assessments allowed for comparison of physical impairments and complaints about fatigue between groups.

EXPERIMENTAL PROCEDURE

An exercise task and a functional test were carried out on two different days for each stroke patient. The exercise task included a walking test on a treadmill: patients walked either until they felt physically exhausted [17 – very hard, on the Borg scale (47)]; or for up to 60 min at 10% above their preferred speed or a maximum speed of 5 km/h on a level treadmill. The preferred walking speed was determined at an initial exam where each subject walked on the treadmill to familiarize them with the set-up. An important criterion was that the subjects were able to walk on a treadmill without aids or assistance. The walking speed was limited to a maximum of 5 km/h so that subjects stayed within a comfortable walking speed (48). The treadmill speed was kept constant throughout the test. The participants were repeatedly asked to rate their exhaustion on a Borg scale. The walking test was stopped 1 min after the patient reached 17 on the Borg scale or after 60-min walking on the treadmill. Kinematic gait data were measured for 1 min at the beginning of the walking test (t_1) and for 1 min after reaching 17 on the Borg scale or for the final minute of 60 min (t_2).

The functional test consisted of a 6-min walk test (6MWT) (49). The 6MWT is often used in clinical practice and has been frequently used for measuring the response to therapeutic interventions in various diseases. Heart rate was measured prior to and at the end of the walking test, and lactate concentration was measured prior to and immediately after walking. We used the 4 mmol/L lactate threshold originally described by Mader et al. (50).

TECHNICAL EQUIPMENT

The AS200 system (80 Hz; LUKOtronic, Lutz Mechatronic Technology e.U., Innsbruck, Austria) was used to record the gait data. This system consists of a three line-scanning camera system and 10 active markers attached bilaterally to the subjects' body: centered on the margo medialis; the highest point of the ilium; the posterior aspect of the knee; on the shoes on top of the calcaneus and on the rod attached at the level of the ankle.

Videos were recorded with a HD digital camera synchronized with the motion analysis system (Exilim EX-F1, digital camera, Casio Computer Co. Ltd., Tokyo, Japan). Heart rate was captured using a chest strap and a gage (Garmin Forerunner 305, Garmin Ltd., KS, USA). Lactate levels in the blood were detected using a lactate analyzer and lactate strips (Arkray Lactate Pro LT-17810, Kyoto, Japan).

CALCULATION OF THE FATIGUE INDEX KLINIKEN SCHMIEDER

For each stroke patient, the change in the movement pattern described by the attractor (δM) and change in movement variability (δD) of the acceleration of the feet between t_1 and t_2 were calculated (**Figures 1** and **2A,B**). This new method has recently been described in detail by Vieten et al. (51) and used to detect motor fatigue in patients with MS (33). The changes in movement acceleration patterns and variability were used as indicators of motor fatigue. It is well known that human walking in the absence of disturbances is characterized by a stable movement pattern and consistent movement control. We kept the walking situation unchanged throughout the walking test, and hence changes in attractor and movement variability indicated an alteration of the gait mechanism, which by ruling out other reasons, we identified as acute motor fatigue. The calculation of FKS was based on both feet. The FKS was defined as the changes in δM and δD between the beginning and the end of walking (51) and represented as

$$\delta F = \delta M \cdot \delta D$$

The FKS was calculated for each stroke patient. These patients were then classified according to the FKS in a fatigue and non-fatigue group. This method allows analyzing fatigue on the individual patient level and on the group level. Based on FKS, stroke patients with FKS ≤ 4 were identified as having no motor fatigue (stroke-NF) and stroke patients with FKS > 4 were identified as having

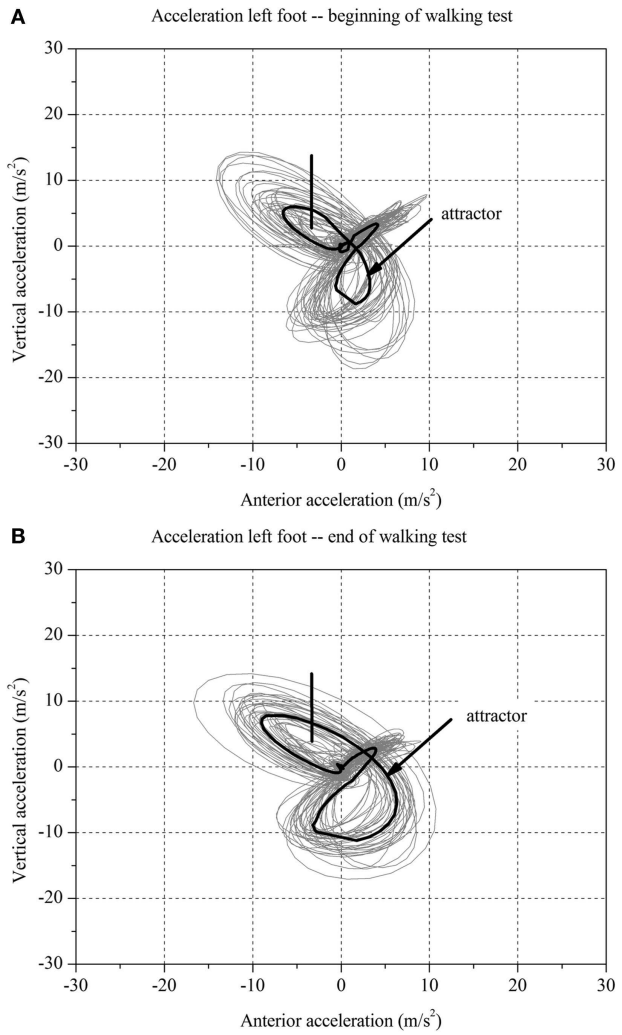

FIGURE 1 | Two-dimensional graph of the acceleration data of a subject's left foot for one minute (A) at the beginning and (B) at the end of the walking test for one stroke patient with fatigue.

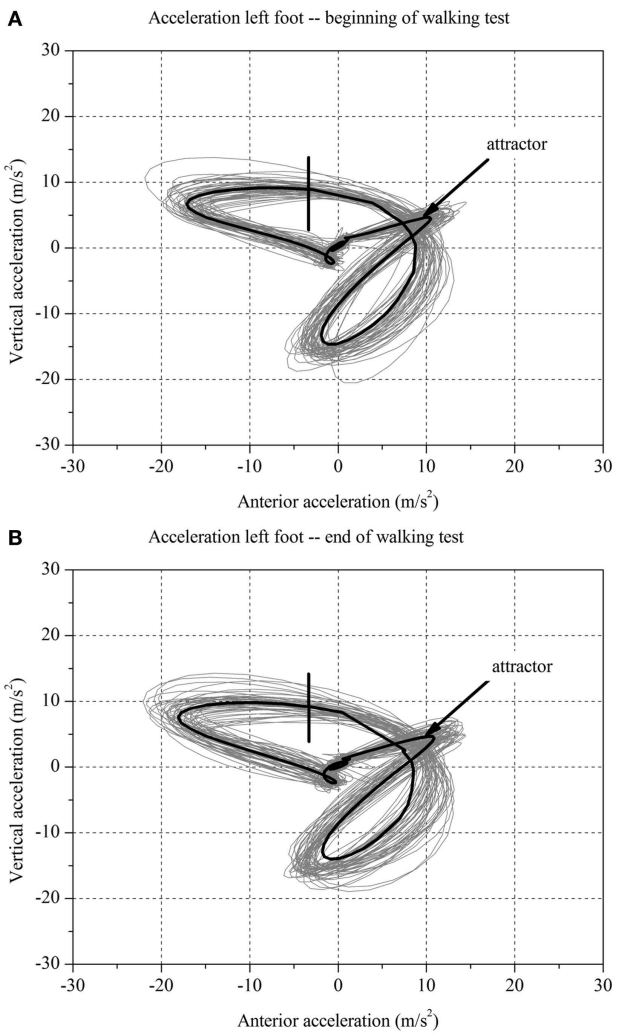

FIGURE 2 | Two-dimensional graph of the acceleration data of a subject's left foot for one minute (A) at the beginning and (B) at the end of the walking test for one stroke patient without fatigue.

motor fatigue (stroke-F). The FKS cut-off of 4 was calculated in our previous study in the following order: first, using the group medians calculated using traditional methods (neurologist rating) to find the threshold between normal and fatigue (33). Second, the FKS of healthy individuals was used as a benchmark test. Third, all subjects were classified according to the FKS values into the fatigue and the non-fatigue groups.

CONVENTIONAL GAIT ANALYSIS

Spatial parameters were calculated: step length, step width, step height, maximum circumduction of the right and left leg, and medio-lateral sway of the upper body were calculated using three-dimensional co-ordinates of the active markers. This analysis allowed comparisons between different groups on the group level.

EVALUATION OF THE VIDEO RECORDINGS

The subjects' movement patterns were recorded on videos captured during t_1 and t_2 from the side and from the back. Videos were evaluated by two experienced physiotherapists from the rehabilitation clinic. The order of the videos was randomized, and thus the physiotherapists did not know which video had been captured at the beginning and which at the end of walking test when attempting to correctly assign the videos to the corresponding time period. The physiotherapists did not evaluate the details regarding the modality of movement.

STATISTICAL ANALYSIS

Data of stroke patients were compared to those of MS patients and healthy control subjects (33). All statistical tests were performed using StatFree Version 8.0.0.9 (VietenDynamics, University of Konstanz, Germany) and Stata Version 11.0 (StatCorp LP, College Station, TX, USA). Differences in non-normally distributed parameters between groups were detected using Kruskal–Wallis test with Mann–Whitney *U* test as *post hoc* tests. For categorical variables, we used the χ^2-test. Pearson correlation coefficients

were used to detect significant associations between the changes in the movement pattern and changes in movement variability as well as between FKS and the results of BDI-II. The significance level for all statistical tests was set *a priori* to.05.

RESULTS

DIFFERENCES BETWEEN STROKE PATIENTS, MS PATIENTS, AND HEALTHY SUBJECTS

Table 1 presents descriptive characteristics for stroke patients, MS, and healthy subjects. Significant differences between stroke and MS patients were found for sex, age, height, and mass. Furthermore, the PF-10 and vitality score of the SF-36 differed significantly between the stroke and MS groups with a higher physical impairment and higher vitality level in stroke patients ($p < 0.04$ and $p < 0.02$, respectively). In contrast, no significant differences were detected between stroke patients and healthy subjects with the exception of age.

Based on the BDI-II questionnaire, one patient was affected by minimal depression and one patient was affected by slight depression in the stroke group. All other patients with stroke were not affected by depression. Moreover, 65% of MS patients and 15% of healthy subjects were affected by depression.

PHYSICAL PERFORMANCE IN STROKE PATIENTS COMPARED WITH MS PATIENTS AND HEALTHY SUBJECTS

Table 2 shows the physical performance in three groups. The stroke patients walked significantly slower than the healthy subjects ($p < 0.001$) and a shorter distance than MS patients and

Table 1 | Mean (1 standard deviation) characteristics of participants.

Characteristic	Stroke	MS	Healthy subjects	*p*-value
Sex male/female	7/3	13/27	9/11	0.03[a]
Age	51.6 (8.3)	45.9 (7.0)	43.1 (8.6)	0.03[a]
				0.01[b]
Height (cm)	177.2 (7.7)	171.4 (10.7)	173.4 (8.4)	0.04[a]
Mass (kg)	84.5 (16.5)	74.1 (15.6)	80.4 (21.3)	0.04[a]
SF-36, PF-10	16.3 (4.8)	21.0 (4.3)	Not collected	0.04[a]
SF-36, vitality	15.8 (2.2)	11.1 (3.5)	Not collected	0.02[a]
BDI-II (% of patients with depression)	20.0	65	15.0	0.02[a]
EDSS	Not applicable	3.4 (1.3)	Not applicable	
Disease duration (years)	8.3 (7.9)	10.8 (7.2)	Not applicable	

MS, MS patients; SF-36, PF-10, 10 items of the physical functioning (ranging from 10 to 30, where low values indicate strong impairment, high values low impairment); SF-36, vitality scale, four items each ranging from 1 (low vitality/high fatigue) and to six (high vitality/low fatigue); BDI-II, Beck Depression Inventory II; EDSS, Extended Disability Status Scale ranging from 0 (no symptoms) to 10 (death through MS).

[a] *Significantly different between stroke and MS.*

[b] *Significantly different between stroke and healthy subjects. Only the significant differences are indicated.*

Table 2 | Mean (1 standard deviation) gait and physiological parameters of the walking test.

Parameters	Stroke	MS	Healthy subjects	*p*-value Kruskal–Wallis test	*p*-value *Post hoc* test
Walking distance (km)	1.9 (0.9)	2.5 (1.6)	5.3 (0.3)	0.001	0.001[a]
Walking speed (km/h)	2.2 (0.8)	3.4 (1.4)	5.0 (0.0)	0.001	0.01[b]
					0.001[a]
6MWT (km)	0.30 (0.11)	0.51 (0.10)	0.68 (0.10)	0.001	0.001[b]
					0.001[a]
Lactate (mmol/L)					
t_1	0.7 (0.6)	1.1 (0.6)	0.8 (0.6)	0.04	0.02[b]
t_2	0.2 (0.4)	0.6 (0.5)	0.6 (0.6)		
Heart rate (bpm)					
t_1	70.0 (10.8)	79.2 (11.0)	79.4 (20.7)		
t_2	99.9 (13.2)	104.8 (16.8)	108.8 (20.8)		
Borg scale	14.0 (1.7)	16.0 (2.6)	10.0 (2.5)	0.001	0.001[b]
					0.001[a]

Stroke, stroke patients; MS, MS patients; 6MWT, 6-min walk test.

[a] *Significantly different between stroke and MS.*

[b] *Significantly different between stroke and healthy subjects.*

healthy persons ($p < 0.01$) in the walking test on the treadmill. Walking distance ranged from 1.0 to 3.4 km and walking speed ranged from 1.0 to 3.3 km/h in stroke patients. In MS patients, walking distance ranged from 0.2 to 5.6 km and walking speed ranged from 0.9 to 5.0 km/h. In healthy subjects, walking distance ranged from 5.0 to 6.0 km and walking speed was 5 km/h. The stated speed refers to the speed with which subjects walked on the treadmill after the familiarization phase and in which all data were collected. Some subjects walked slower in the familiarization phase and then they increased their speed. The important criterion was that the subjects do not walk over 60 min in the test. In the 6MWT, stroke patients walked a significantly shorter distance than the other groups ($p < 0.001$).

All subjects remained below the aerobic-anaerobic threshold (lactate concentration below 4 mmol/L) during the walking test and had a heart rate below the maximal heart rate. At the end of the test, the level of exertion on the Borg scale was significantly lower in stroke patients than in MS patients ($p < 0.001$). In contrast, stroke patients had greater levels of exertion than healthy subjects ($p < 0.001$).

CONVENTIONAL GAIT ANALYSIS IN STROKE PATIENTS COMPARED WITH MS PATIENTS AND HEALTHY SUBJECTS

Significant group differences in gait parameters were observed at t_1 and at t_2 ($p < 0.001$). The results of the *post hoc* tests revealed that stroke patients had shorter step lengths and greater step widths than the other groups both at t_1 and t_2 ($p < 0.001$). Furthermore, the stroke patients had lower step height than the MS patients and healthy persons at t_1 and t_2 ($p < 0.001$). Circumduction with the right and left legs as well as the sway were significantly greater in the stroke group than in the other groups at t_1 and t_2 ($p < 0.009$).

VIDEO ANALYSIS

One physiotherapist correctly classified 6 of 20 (30%) and the other physiotherapist 8 of 20 (40%) videos of stroke patients indicating that they were correct just by chance and did not recognize increasing gait abnormality at the end compared to the beginning of the walking test. In contrast, the physiotherapists classified most of the videos correctly in the MS group 68 of 80 (85%) and 64 of 80 (80%), respectively. In healthy subjects, the physiotherapists properly classified 26 of 40 (65%) and 34 of 40 (85%) videos, respectively.

FATIGUE INDEX KLINIKEN SCHMIEDER COMPARISON BETWEEN GROUPS

Based on the FKS scores, six stroke patients were classified into the fatigue group (stroke-F) and four patients into the non-fatigue group (stroke-NF). The FKS in the stroke-F group ranged from 5.3 to 15.3 (δM: 4.1–9.3; δD: 1.1–1.9) and in the stroke-NF group from 2.2 to 3.2 (δM: 1.8–3.6; δD: 0.6–1.4). The FKS in the MS-F group ranged from 4.2 to 125 (δM: 2.8–30.4; δD: 0.9–4.1) and in the MS-NF group from 0.5 to 3.4 (δM: 1.0–3.6; δD: 0.4–1.0). The FKS in the healthy subjects ranged from 0.3 to 3.9 (δM: 0.6–4.3; δD: 0.3–1.5) (**Figure 3**). The FKS differed significantly between stroke patients and healthy persons ($p < 0.001$) but not between stroke and MS patients ($p = 0.44$). In the subgroups, the FKS differed significantly between the stroke-F and the stroke-NF, MS-NF, and healthy groups ($p < 0.01$). Mean FKS in the stroke-F group was smaller than that in the MS-F group, but this difference did not reach statistical significance (8.7 versus 17.5; $p = 0.18$). In all groups, subjects with greater changes in movement patterns also showed greater changes in movement variability ($r = 0.66$, $p < 0.001$) (**Figure 4**). The differences in changes in movement patterns and changes in movement variability between groups corresponded to the differences in FKS between groups. Furthermore, FKS did not correlate significantly with the results of BDI-II ($r = 0.27$, $p < 0.09$).

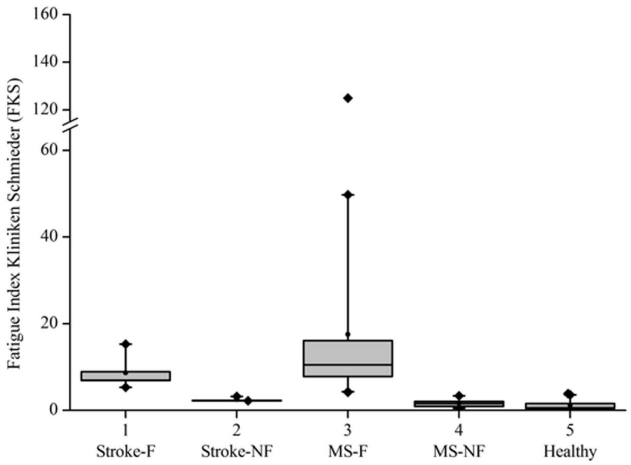

FIGURE 3 | Boxplot for FKS values in all groups.

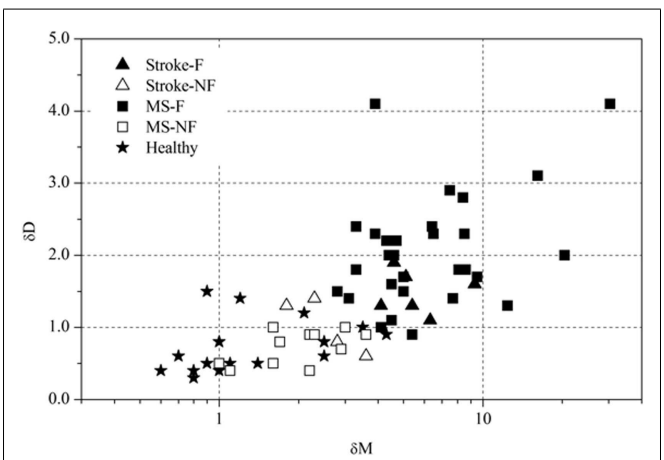

FIGURE 4 | Scatterplot between changes in movement pattern and movement variability.

DISCUSSION

The purpose of this study was to compare motor fatigue in stroke and MS patients by analyzing changes in movement patterns and their variability. In this pilot study, we observed no significant difference in FKS values between stroke and MS patients as well as in their subgroups: between stroke patients with fatigue symptom and MS patients with fatigue symptom. Hence, fatigue induced

similar changes in the movement patterns and variability in both patient groups. Furthermore, the results of our study showed that the FKS can also be used in stroke patients for objectively measuring motor fatigue.

We intended to verify that severe walking impairment in stroke patients does not cause a pathological FKS. During the walking test on the treadmill, stroke patients rated their fatigue on the Borg scale significantly lower than the MS patients. Interestingly, despite lower perception of fatigue on the Borg scale, the stroke patients had greater physical impairment. All stroke patients had a hemiparesis affecting the leg. A higher level of impairment was observed using kinematic gait analysis, PF-10 of SF-36, and physical performance. Using conventional kinematic gait analysis of a few single stride cycles, we observed very clear differences in all gait parameters between the stroke patients and the other groups at t_1 and t_2. Generally, the stroke patients showed smaller step length, step height and greater step width, circumduction with the right and left leg, and greater sway compared to MS patients and healthy subjects. These results are in agreement with other studies (52, 53). The reduced step length and greater step width in stroke patients indicate an unsteady gait and the attempt to improve their stability to avoid falling while walking. The altered gait pattern already present at the beginning of the walking test on the treadmill, compared to the other groups, is presumably caused by the hemiparesis in this patient group. The reduction of walking speed and walking distance in stroke patients compared to the other groups as measured in our study are well established (53, 54).

Although stroke patients had higher physical impairment on PF-10 of SF-36 than MS patients, they showed greater vitality scores on the SF-36 than MS patients. These results point toward a conceptual and pathophysiological difference between impairment and fatigue. While it can be disputed whether or not fatigue should be rated as impairment, the neurological exam or the PF-10 of SF-36 do not assess fatigue.

The origin of peripheral or muscle fatigue is outside the central nervous system (CNS). For example, the peripheral fatigue can be caused by an increased blood lactate accumulation and hydrogen ions, accumulation of ammonia, loss of water, an accumulation of Pi (inorganic phosphate), and an accumulation of H+ ions in the sarcoplasm (55). There are several objective methods for measuring peripheral fatigue. Among others, muscle fatigue can be detected using surface electromyography (sEMG) and mechanomyography (MMG) (56). Previous studies investigated manifestations of fatigue in prolonged activities involving repetitive low force work tasks. In contrast to our study, they used task duration of more than 1 h with an intensity of 20% maximum voluntary contraction in an isolated movement with few active muscles (57). For example, they measured fatigue using electromyography of a descending part of the trapezius muscle. In our study, walking is a complex movement with involvement of many muscle groups and several degrees of freedom. Based on the results of our previous studies, we expected that patients with fatigue would be exhausted in less than 60 min (33, 58). One of the most popular cost-efficient and quick measurement of muscle fatigue is the analysis of blood lactate during exhaustive exercises. We used this method in our study. All subjects walked on the treadmill without reaching their lactate threshold, which reflects the rate at which a person can work aerobically without accumulation of acid substances associated with muscular fatigue (59). However, some patients have reached exhaustion as these patients reported 17 (very hard) on the Borg scale and/or the FKS was >4. None of the healthy persons reached exhaustion in the walking test determined using the Borg scale and the FKS. Hence, it seems unlikely that motor fatigue was not associated with muscular fatigue.

A strong relationship between depression and fatigue has been described in both patient groups (3, 18). Moreover, depression is considered one of the most confounding factors associated with fatigue; it can be hard to disentangle depression and fatigue in a patient. In the present study, the depression was more common in MS groups than in the stroke or healthy subjects. Epidemiological studies reported that depression is common in MS with annual prevalence rates as high as 20% and a lifetime prevalence of up to 50% (60–62), which is approximately three times higher than in healthy people (61). Approximately one-third of all patients with stroke experience depression symptoms and the prevalence only slightly decreases within the first 2 years after stroke (63, 64). In our study, the FKS did not correlate with BDI-II. The FKS is an important tool for detecting motor fatigue objectively and independent of the presence or absence of depression.

It may be speculative and beyond the scope of the present investigation, but the motor fatigue in stroke and MS patients probably suggests different underlying pathophysiological mechanisms. Ischemic lesions occur according to the all-or-nothing principle: if oligemia causes an ischemic lesion, it results in a complete lesion of the tissue finally ending up in the chronic stage as a substantial cyst (simply speaking as a hole in the brain). Fatigue in this case may be related to compensation or use of alternative, less efficient, or reorganized pathways. Inflammation in MS might cause demyelination or partial impairment of neural pathways. Neuronal function may be partially preserved, but under high demand or long or highly repetitive requirements function might slowly decline. Further or additional compensation does not seem to be possible, and it is unclear if this is due to loss of K^+ as suggested in the literature explaining the function of 4-aminopyridine (65). Completely different pathomechanisms may be related to inflammatory substances such as cytokines or tumor necrosis factor alpha (TNF-α) (Hacken et al., this special issue) (8). Increased cytokines, however, are not a prominent finding in the liquor of chronic stroke patients, and hence fatigue is expected to have a different pathomechnism in stroke. Different pathomechanisms of fatigue would require different treatment options (8, 66). For instance, compensation in stroke patients may be enhanced by training, and electric failure in MS lesions may be ameliorated by substances such as 4-aminopyridine or inhibitors of TNF-α (67, 68).

Most standardized fatigue questionnaires are based on patients' self-assessments and often used for rating fatigue symptoms. However, because these questionnaires are based on the patients' subjective impressions, they may be distorted because of an inaccurate self-perception. Currently, most of the fatigue questionnaires are disease specific and have been specifically developed to assess fatigue in MS (29). Elbers et al. (23) recommended the FSMC for the multidimensional assessment of fatigue in MS patients (23).

In contrast, the FSS is the most commonly used instrument to measure fatigue in stroke patients (69), which was also recommended by Elbers et al. (23). Since most of the motor scores are disease specific, it is not easy to compare the degree of impairment in stroke and MS patients. For instance, the Motricity Index (70), the Fugl-Meyer test (71), or Rivermead Motor Assessment (72) are evaluated for stroke, whereas the application of the Expanded Disability Status Scale (73) is restricted to MS, and there is no common measure for both entities. To overcome this difficulty, we used the Physical Functioning Scale of the SF-36 to assess daily life motor activities and their restrictions. This allowed for some rough comparison of motor impairment and disabilities in daily life. Currently, there is a validated scale for fatigue in both MS and stroke patients (74), which was not available at the time of data collection.

The estimation error may occur in the clinical assessment of the patient by physicians and physiotherapists. Some patients are hard to classify into fatigue and non-fatigue groups based on patient's survey and traditional clinical tests carried out by physicians and therapists. The results of the FKS largely agreed with the results of the video analysis in MS patients. The physiotherapists assigned videos of the beginning and end correctly in 80–85% of MS patients. Such classification was difficult for stroke patients and healthy subjects. In general, the MS patients have almost an unremarkable gait pattern at the beginning of walking. In the state of fatigue, the gait changed greatly. Thus, it can be clearly seen in most cases. However, it depends on the experience of the physiotherapist. In contrast to MS, the stroke patients had an impaired gait pattern at the beginning of walking test. All stroke patients had a hemiparesis and hence an abnormal gait pattern at both time points. It is possible that the raters cannot be distinguishing between the abnormal gait characteristics caused by the hemiparesis and those caused by motor fatigue. This could lead to difficulties to assess the changes in gait pattern. Even if this evaluation was very successful for these cases, the analysis is subjective and depends on many factors and particularly on the therapists' experience. These results emphasize the importance of an objective measure of motor fatigue that is independent of the subjective assessment of a rater.

The FKS is an objective measure. As acknowledged above in many cases, a neurologist can detect the presence of fatigue in patients with MS using "classic" instruments. However, in some cases, a physician cannot be sure of the diagnosis of the fatigue syndrome, and in these cases, the FKS can be extremely helpful for objectively measuring motor fatigue. The correct diagnosis of fatigue is especially important when it is used as criterion for early retirement emphasizing the relevance of this test. For example, the most important differential diagnosis may be depression. In some instances, it may not be easy to disentangle both phenomena. Treatment may be similar involving antidepressive agents, increasing regular physical activity, acceptance of limitations, energy conservation programs, etc. However, the patient will feel more accepted and understood, if the therapist and neurologist are able to discriminate, explain, and treat different components of his complex symptom. Moreover, the FKS can be used both for diagnosis and for the evaluation of the course of treatment.

CONCLUSION

Using FKS, a new and objective tool for identifying and quantifying motor fatigue, we found that fatigue was similarly pronounced in both patient groups. We observed that a more severe walking impairment in stroke patients at baseline is not associated with a pathologically higher FKS. The objective assessment of motor fatigue via the FKS allows the comparison of motor fatigue between stroke patients, MS patients, and healthy persons.

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REFERENCES

1. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology* (2013) **80**(4):409–16. doi:10.1212/WNL.0b013e31827f07be
2. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. *Can J Neurol Sci* (1994) **21**(1):9–14.
3. Romani A, Bergamaschi R, Candeloro E, Alfonsi E, Callieco R, Cosi V. Fatigue in multiple sclerosis: multidimensional assessment and response to symptomatic treatment. *Mult Scler* (2004) **10**(4):462–8. doi:10.1191/1352458504ms1051oa
4. Simmons RD, Tribe KL, McDonald EA. Living with multiple sclerosis: longitudinal changes in employment and the importance of symptom management. *J Neurol* (2010) **257**(6):926–36. doi:10.1007/s00415-009-5441-7
5. Kos D, Kerckhofs E, Nagels G, D'Hooghe MB, Ilsbroukx S. Origin of fatigue in multiple sclerosis: review of the literature. *Neurorehabil Neural Repair* (2008) **22**(1):91–100. doi:10.1177/1545968306298934
6. Mills RJ, Young CA. A medical definition of fatigue in multiple sclerosis. *QJM* (2008) **101**(1):49–60. doi:10.1093/qjmed/hcm122
7. Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. *Mult Scler* (2003) **9**(3):219–27. doi:10.1191/1352458503ms904oa
8. Heesen C, Nawrath L, Reich C, Bauer N, Schulz K, Gold S. Fatigue in multiple sclerosis: an example of cytokine mediated sickness behaviour? *J Neurol Neurosurg Psychiatry* (2006) **77**(1):34–9. doi:10.1136/jnnp.2005.065805
9. Tellez N, Alonso J, Rio J, Tintore M, Nos C, Montalban X, et al. The basal ganglia: a substrate for fatigue in multiple sclerosis. *Neuroradiology* (2008) **50**(1):17–23. doi:10.1007/s00234-007-0304-3
10. Liepert J, Mingers D, Heesen C, Bäumer T, Weiller C. Motor cortex excitability and fatigue in multiple sclerosis: a transcranial magnetic stimulation study. *Mult Scler* (2005) **11**(3):316–21. doi:10.1191/1352458505ms1163oa
11. Labuz-Roszak B, Kubicka-Baczyk K, Pierzchala K, Machowska-Majchrzak A, Skrzypek M. Fatigue and its association with sleep disorders, depressive symptoms and anxiety in patients with multiple sclerosis. *Neurol Neurochir Pol* (2012) **46**(4):309–17. doi:10.5114/ninp.2012.30261
12. Braley TJ, Chervin RD, Segal BM. Fatigue, tiredness, lack of energy, and sleepiness in multiple sclerosis patients referred for clinical polysomnography. *Mult Scler Int* (2012) **2012**:673936. doi:10.1155/2012/673936
13. Naess H, Lunde L, Brogger J. The effects of fatigue, pain, and depression on quality of life in ischemic stroke patients: the Bergen Stroke Study. *Vasc Health Risk Manag* (2012) **8**:407–13. doi:10.2147/vhrm.s32780
14. Lerdal A, Bakken LN, Kouwenhoven SE, Pedersen G, Kirkevold M, Finset A, et al. Poststroke fatigue – a review. *J Pain Symptom Manage* (2009) **38**(6):928–49. doi:10.1016/j.jpainsymman.2009.04.028
15. Zedlitz AMEE, van Eijk M, Kessels RPC, Geurts ACH, Fasotti L. Poststroke fatigue is still a neglected issue: findings from an internet-based study on the need for information and treatment in the Netherlands. *ISRN Stroke* (2012) **2012**:629589. doi:10.5402/2012/629589
16. Lerdal A, Lee KA, Bakken LN, Finset A, Kim HS. The course of fatigue during the first 18 months after first-ever stroke: a longitudinal study. *Stroke Res Treat* (2012) **2012**:126275. doi:10.1155/2012/126275
17. Snaphaan L, van der Werf S, de Leeuw FE. Time course and risk factors of poststroke fatigue: a prospective cohort study. *Eur J Neurol* (2011) **18**(4):611–7. doi:10.1111/j.1468-1331.2010.03217.x
18. Staub F, Bogousslavsky J. Post-stroke depression or fatigue. *Eur Neurol* (2001) **45**:3–5. doi:10.1159/000052081

19. Kirkevold M, Christensen D, Andersen G, Johansen SP, Harder I. Fatigue after stroke: manifestations and strategies. *Disabil Rehabil* (2012) **34**(8):665–70. doi:10.3109/09638288.2011.615373
20. Andersen G, Christensen D, Kirkevold M, Johnsen SP. Post-stroke fatigue and return to work: a 2-year follow-up. *Acta Neurol Scand* (2012) **125**(4):248–53. doi:10.1111/j.1600-0404.2011.01557.x
21. Chaudhuri A, Behan PO. Fatigue in neurological disorders. *Lancet* (2004) **363**(9413):978–88. doi:10.1016/S0140-6736(04)15794-2
22. Braley TJ, Chervin RD. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. *Sleep* (2010) **33**(8):1061–7.
23. Elbers RG, Rietberg MB, van Wegen EE, Verhoef J, Kramer SF, Terwee CB, et al. Self-report fatigue questionnaires in multiple sclerosis, Parkinson's disease and stroke: a systematic review of measurement properties. *Qual Life Res* (2012) **21**(6):925–44. doi:10.1007/s11136-011-0009-2
24. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* (1989) **46**(10):1121–3. doi:10.1001/archneur.1989.00520460115022
25. Schwartz JE, Jandorf L, Krupp LB. The measurement of fatigue: a new instrument. *J Psychosom Res* (1993) **37**(7):753–62. doi:10.1016/0022-3999(93)90104-N
26. Guidelines MSCfCP. *Fatigue and Multiple Sclerosis*. Washington, DC: Paralyzed Veterans Association (1998). Available at: www.pva.org
27. Penner IK, Raselli C, Stocklin M, Opwis K, Kappos L, Calabrese P. The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult Scler* (2009) **15**(12):1509–17. doi:10.1177/1352458509348519
28. Flachenecker P, Muller G, Konig H, Meissner H, Toyka KV, Rieckmann P. ["Fatigue" in multiple sclerosis. Development and and validation of the "Wurzburger Fatigue Inventory for MS"]. *Nervenarzt* (2006) **77**(2):165–6. doi:10.1007/s00115-005-1990-x
29. Acciarresi M, Bogousslavsky J, Paciaroni M. Post-stroke fatigue: epidemiology, clinical characteristics and treatment. *Eur Neurol* (2014) **72**(5–6):255–61. doi:10.1159/000363763
30. Fink AM, Eckhardt AL, Fennessy MM, Jones J, Kruse D, VanderZwan KJ, et al. Psychometric properties of three instruments to measure fatigue with myocardial infarction. *West J Nurs Res* (2010) **32**(7):967–83. doi:10.1177/0193945910371320
31. Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: the Fatigue Assessment Scale. *J Psychosom Res* (2003) **54**(4):345–52. doi:10.1016/S0022-3999(02)00392-6
32. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* (1995) **39**(3):315–25. doi:10.1016/0022-3999(94)00125-O
33. Sehle A, Vieten MM, Sailer S, Mundermann A, Dettmers C. Objective assessment of motor fatigue in multiple sclerosis: the Fatigue Index Kliniken Schmieder (FKS). *J Neurol* (2014) **261**(9):1752–62. doi:10.1007/s00415-014-7415-7
34. Surakka J, Romberg A, Ruutiainen J, Virtanen A, Aunola S, Mäentaka K. Assessment of muscle strength and motor fatigue with a knee dynamometer in subjects with multiple sclerosis: a new fatigue index. *Clin Rehabil* (2004) **18**(6):652–9. doi:10.1191/0269215504cr781oa
35. Schwid SR, Thornton CA, Pandya S, Manzur KL, Sanjak M, Petrie MD, et al. Quantitative assessment of motor fatigue and strength in MS. *Neurology* (1999) **53**(4):743–50. doi:10.1212/WNL.53.4.743
36. Greim B, Benecke R, Zettl UK. Qualitative and quantitative assessment of fatigue in multiple sclerosis (MS). *J Neurol* (2007) **254**:II58–64. doi:10.1007/s00415-007-2014-5
37. Iriarte J, de Castro P. Correlation between symptom fatigue and muscular fatigue in multiple sclerosis. *Eur J Neurol* (1998) **5**(6):579–85. doi:10.1046/j.1468-1331.1998.560579.x
38. Severijns D, Lamers I, Kerkhofs L, Feys P. Hand grip fatigability in persons with multiple sclerosis according to hand dominance and disease progression. *J Rehabil Med* (2014). doi:10.2340/16501977-1897
39. Svantesson UM, Sunnerhagen KS, Carlsson US, Grimby G. Development of fatigue during repeated eccentric-concentric muscle contractions of plantar flexors in patients with stroke. *Arch Phys Med Rehabil* (1999) **80**(10):1247–52. doi:10.1016/S0003-9993(99)90024-2
40. Knorr S, Ivanova TD, Doherty TJ, Campbell JA, Garland SJ. The origins of neuromuscular fatigue post-stroke. *Exp Brain Res* (2011) **214**(2):303–15. doi:10.1007/s00221-011-2826-5
41. Hu XL, Tong KY, Hung LK. Firing properties of motor units during fatigue in subjects after stroke. *J Electromyogr Kinesiol* (2006) **16**(5):469–76. doi:10.1016/j.jelekin.2005.09.005
42. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* (2001) **50**(1):121–7. doi:10.1002/ana.1032
43. Kuhner C, Burger C, Keller F, Hautzinger M. [Reliability and validity of the Revised Beck Depression Inventory (BDI-II). Results from German samples]. *Nervenarzt* (2007) **78**(6):651–6. doi:10.1007/s00115-006-2098-7
44. Bullinger M, Morfeld M, Kohlmann T, Nantke J, van den Bussche H, Dodt B, et al. [SF-36 Health Survey in Rehabilitation Research. Findings from the North German Network for Rehabilitation Research, NVRF, within the rehabilitation research funding program]. *Rehabilitation (Stuttg)* (2003) **42**(4):218–25. doi:10.1055/s-2003-41645
45. Mead GE, Graham C, Dorman P, Bruins SK, Lewis SC, Dennis MS, et al. Fatigue after stroke: baseline predictors and influence on survival. analysis of data from UK patients recruited in the international stroke trial. *PLoS One* (2011) **6**(3):e16988. doi:10.1371/journal.pone.0016988
46. Fennessy M, Fink A, Eckhardt A, Jones J, Kruse D, VanderZwan K, et al. Gender differences in fatigue associated with acute myocardial infarction. *J Cardiopulm Rehabil Prev* (2010) **30**(4):224–30. doi:10.1097/HCR.0b013e3181d0c493
47. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* (1982) **14**(5):377–81. doi:10.1249/00005768-198205000-00012
48. Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. *Age Ageing* (1997) **26**(1):15–9. doi:10.1093/ageing/26.1.15
49. Laboratories ACoPSfCPF. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* (2002) **166**(1):111–7. doi:10.1164/ajrccm.166.1.at1102
50. Mader A, Liesen H, Heck H, Philippi H, Rost R, Schürch P, et al. Zur beurteilung der sportartspezifischen ausdauerleistungsfähigkeit im labor. *Sportarzt Sportmed* (1976) **27**(80):199.
51. Vieten MM, Sehle A, Jensen RL. A novel approach to quantify time series differences of gait data using attractor attributes. *PLoS One* (2013) **8**:e71824. doi:10.1371/journal.pone.0071824
52. Chen G, Patten C, Kothari D, Zajac F. Gait differences between individuals with post-stroke hemiparesis and non-disabled controls at matched speeds. *Gait Posture* (2005) **22**(0966–6362):51–6. doi:10.1016/j.gaitpost.2004.06.009
53. Olney SJ, Richards C. Hemiparetic gait following stroke. Part I: characteristics. *Gait Posture* (1996) **4**(2):136–48. doi:10.1016/0966-6362(96)01063-6
54. Sosnoff JJ, Sandroff BM, Motl RW. Quantifying gait abnormalities in persons with multiple sclerosis with minimal disability. *Gait Posture* (2012) **36**(1):154–6. doi:10.1016/j.gaitpost.2011.11.027
55. Ament W, Verkerke GJ. Exercise and fatigue. *Sports Med* (2009) **39**(5):389–422. doi:10.2165/00007256-200939050-00005
56. Xie HB, Zheng YP, Jing-Yi G. Detection of chaos in human fatigue mechanomyogarphy signals. *Conf Proc IEEE Eng Med Biol Soc* (2009) **2009**:4379–82. doi:10.1109/IEMBS.2009.5333485
57. de Looze M, Bosch T, van Dieën J. Manifestations of shoulder fatigue in prolonged activities involving low-force contractions. *Ergonomics* (2009) **52**(4):428–37. doi:10.1080/00140130802707709
58. Sehle A, Mundermann A, Starrost K, Sailer S, Becher I, Dettmers C, et al. Objective assessment of motor fatigue in multiple sclerosis using kinematic gait analysis: a pilot study. *J Neuroeng Rehabil* (2011) **8**:59. doi:10.1186/1743-0003-8-59
59. Pariser G, Madras D, Weiss E. Outcomes of an aquatic exercise program including aerobic capacity, lactate threshold, and fatigue in two individuals with multiple sclerosis. *J Neurol Phys Ther* (2006) **30**(2):1524–7. doi:10.1097/01.NPT.0000282572.63297.3d
60. Patten S, Beck C, Williams JVA, Williams J, Barbui C, Metz L. Major depression in multiple sclerosis: a population-based perspective. *Neurology* (2003) **61**(11):1524–7. doi:10.1212/01.WNL.0000095964.34294.B4
61. Patten S, Williams J, Lavorato D, Koch M, Metz L. Depression as a predictor of occupational transition in a multiple sclerosis cohort. *Funct Neurol* (2013) **3**:1–6. doi:10.1212/01.WNL.0000095964.34294.B4
62. Siegert R, Abernethy D. Depression in multiple sclerosis: a review. *J Neurol Neurosurg Psychiatry* (2005) **76**(4):469–75. doi:10.1136/jnnp.2004.054635
63. Egeto P, Fischer C, Ismail Z, Smith E, Schweizer T. Lacunar stroke, deep white matter disease and depression: a meta-analysis. *Int Psychogeriatr* (2014) **26**(7):1101–9. doi:10.1017/S1041610214000568

64. House A. Depression after stroke. *Br Med J (Clin Res Ed)* (1987) **294**(6564):76–8. doi:10.1136/bmj.294.6564.76
65. Sherratt R, Bostock H, Sears T. Effects of 4-aminopyridine on normal and demyelinated mammalian nerve fibres. *Nature* (1980) **283**(5747):570–2. doi:10.1038/283570a0
66. Flachenecker P, Bihler I, Weber F, Gottschalk M, Toyka K, Rieckmann P. Cytokine mRNA expression in patients with multiple sclerosis and fatigue. *Mult Scler* (2004) **10**(2):165–9. doi:10.1191/1352458504ms991oa
67. Goodman A, Cohen J, Cross A, Vollmer T, Rizzo M, Cohen R, et al. Fampridine-SR in multiple sclerosis: a randomized, double-blind, placebo-controlled, dose-ranging study. *Mult Scler* (2007) **13**(3):357–68. doi:10.1177/1352458506069538
68. Goodman A, Stone R. Enhancing neural transmission in multiple sclerosis (4-aminopyridine therapy). *Neurotherapeutics* (2013) **10**(1):106–10. doi:10.1007/s13311-012-0156-3
69. Lerdal A, Gay CL. Fatigue in the acute phase after first stroke predicts poorer physical health 18 months later. *Neurology* (2013) **81**(18):1581–7. doi:10.1212/WNL.0b013e3182a9f471
70. Demeurisse G, Demol O, Robaye E. Motor evaluation in vascular hemiplegia. *Eur Neurol* (1980) **19**(6):382–9. doi:10.1159/000115178
71. Sanford J, Moreland J, Swanson LR, Stratford PW, Gowland C. Reliability of the Fugl-Meyer assessment for testing motor performance in patients following stroke. *Phys Ther* (1993) **73**(7):447–54.
72. Lincoln N, Leadbitter D. Assessment of motor function in stroke patients. *Physiotherapy* (1979) **65**(2):48–51.
73. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* (1983) **33**(11):1444–52. doi:10.1212/WNL.33.11.1444
74. Mills RJ, Pallant JF, Koufali M, Sharma A, Day S, Tennant A, et al. Validation of the Neurological Fatigue Index for stroke (NFI-Stroke). *Health Qual Life Outcomes* (2012) **10**:51. doi:10.1186/1477-7525-10-51

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Is personality profile a relevant determinant of fatigue in multiple sclerosis?

Herbert Schreiber [1,2] ***, Michael Lang*** [1,2] ***, Kristina Kiltz*** [3] ***and Charlotte Lang*** [4]

[1] *Neuropoint Patient Academy, Neurological Practice Center, Ulm, Germany*
[2] *Neuro Trans Data (NTD) Study Group on Multiple Sclerosis, Neuburg, Germany*
[3] *Department of Neurology, Marienhospital Stuttgart, Stuttgart, Germany*
[4] *Department of Neurology, Marienhospital Düsseldorf, Düsseldorf, Germany*

Edited by:
John DeLuca, Kessler Foundation, USA

Reviewed by:
Timo Partonen, National Institute for Health and Welfare, Finland
Reinhard Reuß, BKH Bayreuth, Germany

****Correspondence:***
Herbert Schreiber, Neurological Practice Center Ulm, Pfauengasse 8, Ulm D-89073, Germany
e-mail: schreiber@neurologie-ulm.de

The origin and pathophysiological background of multiple sclerosis (MS)-associated fatigue is poorly understood. There is no unifying concept of its nature and its determinants to date. This paper reviews possible influences of factors determining personality profile on fatigue in MS. Likewise, the role of psychological factors and their interaction with personality to promote fatigue is discussed. Current data suggest that fatigue, especially in early MS states, may be influenced by vulnerable personality traits and personality-associated features. Among them are depressive disease coping, avoidance behavior and inhibition, irritability, less extraversion, neuroticism, lower reward responsiveness, and somatization behavior. However, among the validated personality factors, no genuine influences that are independent of depression have been documented. From a psychological perspective, depressiveness, anxiety, and somatization may be relevant mediators of fatigue. Interesting to note that in early MS, a psychiatric diagnosis is significantly more likely than on a later stage of the disease and that fatigue and motivation might share neural circuits. It is hypothesized that psychological factors promote fatigue in MS by psychological distress and sustained neuroendocrine and neurovegetative stress response. Despite the limitations of data discussed in the paper, personality research might help to disentangle specific promoting factors of fatigue in MS. Further research efforts are warranted since they might open ways to early psychological intervention of MS-associated fatigue. This is all the more important since medication is insufficient until now.

Keywords: multiple sclerosis, fatigue, personality assessment, depression, coping behavior, anxiety

INTRODUCTION

Fatigue is one of the most prevalent symptoms of multiple sclerosis (MS). It may already be present at early stages and is often the cause for psychosocial and occupational problems. It even happens that otherwise unaffected MS patients cannot work anymore because of fatigue. Fatigue can be defined as either a feeling, i.e., a subjective lack of physical and/or mental energy that is experienced by the individual or caregiver to interfere with usual or desired activities (1), or as a performance decrement, i.e., an inability to complete mental or physical tasks at normal performance level (2). Mental fatigue, in this context, is a transient decrease in optimal cognitive performance resulting from prolonged periods of cognitive activity and manifesting as concentration deficit and cognitive slowing. Motor fatigue, or muscle fatigue, is the inability of a muscle to perform continuously in the sense of a "use-dependent conduction block" (3). The onset of muscle fatigue during physical activity is mostly gradual, and it can be reversed by rest. The same is true for mental fatigue. With respect to basic mechanisms, fatigue can be attributed to the temporary loss of power to respond in sensory receptors, motor end organs, or complex behavioral networks induced by continued stimulation.

Fatigue may have physical, mental, and probably psychological causes. However, insight in its pathophysiology is very limited to date, and there is no unifying concept of its nature and its determinants until today. Even its definition remains controversial among clinicians and researchers since most questionnaires and studies rely on subjective evaluation, i.e., patient self-report. Thus, progress continues to be hampered by unsolved questions related to terminology and assessment (4).

When looking at the multitude of influences that have been claimed to cause fatigue, MS-associated fatigue is less likely a unitary symptom than a construct integrating multiple facets that might emanate from different mechanisms of origin (2, 5). Pro-inflammatory cytokines, autonomic and neuroendocrine dysfunction, a.o. blunted hypothalamic–pituitary–adrenal axis (HPA) axis, nerve conduction block, and inadequate cortical and subcortical activation patterns have been implicated as the pathophysiological key factors. But it seems true that a highly complex interplay of pathophysical, behavioral, and psychological factors contributes to the appearance of fatigue in MS. The most influential candidates in the psychological domain are depression, anxiety, and disease coping. Moreover, there is growing evidence that personality traits interact as behavioral determinants. Personality research in fatigue has been triggered by early studies suggesting a link between premorbid personality characteristics and fatigue in healthy individuals (6, 7).

Despite different concepts, personality is most commonly defined as "that pattern of characteristic thoughts, feelings, and behaviors that distinguishes one person from another and that persists over time and situations" (8, 9). Thereby, the term "personality trait" is thought to refer to enduring personal characteristics that are revealed in a particular pattern of thoughts, feelings, and behavioral modes in a variety of situations. Since personality traits are relatively stable over time, rather specific among individuals and influential predictors of behavior, they are also used to get insight in the patients' individual response to challenging disease experiences.

RELATIONSHIPS BETWEEN VALIDATED PERSONALITY TRAITS AND MS FATIGUE

There are only a few studies addressing the relationship between MS-associated fatigue (MSF) and personality traits so far. Merkelbach et al. (10) found a higher prevalence of altered personality factors, i.e., higher neuroticism scores and reduced extraversion in relapsing-remitting multiple sclerosis (RRMS) versus healthy controls (HC). MS patients with fatigue (MS-F) presented more emotionally instable, hypersensitive, and introverted compared to those with lower fatigue scores. The authors concluded that personality factors contribute to fatigue in MS and even may exert more influence than physical deficits. Penner et al. (11) also found higher scores of neuroticism and reduced extraversion related to fatigue in 41 MS patients and 41 controls. Likewise, depression turned out to be a main influencing factor of fatigue, the association between mental fatigue and depression being particularly strong. When including depression as a covariate into the regression analysis, the significant influence of personality traits on fatigue was no longer present. On the other hand, a decreased level of action control, i.e., the ability of maintaining own aims and goals against competing external stimuli, persisted as significant influential factor on fatigue. The authors concluded that in MS patients with fatigue, cognitive and motivational control of behavior might work less efficiently and be controlled to a higher degree by situational triggers, as is the case in state orientation behavior. Since no relation was found between fatigue and action control within the control group, the authors speculated that disturbances of action control might be specific for MS-related fatigue (MSF). Kiltz et al. (12) by evaluating physical, cognitive, and psychological dimensions of fatigue in 102 early MS patients, among them 48 MS-F, 54 MS-NF, and 29 HC, revealed highly significant differences between fatigued and non-fatigued MS patients in various aspects of personality and disease coping. The respective personality traits correlating with fatigue were: less performance orientation, minor self-content, more inhibition, irritability and aggressiveness, more demand and physical complaints, less extraversion, and more neuroticism. The respective disease coping factors were significantly higher depressive coping and more extenuation/wishful thinking. The authors concluded that premorbid, not intrinsically MS-related factors (personality, disease coping) might be essential contributors to fatigue, especially in the early phase of MS. Since fatigue also scored higher with more severe disease, future task would be to disentangle the contributions of central nervous system (CNS) deficit and psychological factors, especially personality, disease coping, depression, and anxiety, to the expression of fatigue in MS. In a subsequent longitudinal study, when monitoring the identical parameters in the same group of patients and re-evaluating them by multivariate analysis after 2 years (13, 14), it was found that none of cognitive parameters was differentially expressed between groups. But it were the same personality traits, disease coping factors, and depression that again discriminated between MS-F and MS-NF patients. Moreover, the personality profile remained unchanged over time despite the experience of a chronic disease. Analysis with mixed linear models provided evidence that fatigue was not only correlated to but also directly influenced by several personality traits (i.e., performance orientation, demand, extraversion), depression, disease coping, and disease status as assessed by Expanded Disability Status Scale (EDSS), but not by disease duration. The fact that most fatigued patients expressed both dimensions of fatigue (physical and cognitive) prompted the authors to conclude that both fatigue dimensions are rather complementary than independent entities.

In sum, the currently available studies suggest that fatigue, especially in early MS, may be influenced by vulnerable personality traits. Since personality traits are commonly seen as enduring determinants of behavior, it is probable that these characteristics in personality profile are not intrinsically linked to MS. This would mean that they should be able to cause comparable reactions in other chronic diseases. Alternatively, they might also be a consequence of disease coping. But due to a lack of valid premorbid data, this question cannot be settled to date.

However, current data cannot prove a genuine influence of personality factors on fatigue that is independent of depression. Personality seems to interfere with or work through psychological factors (depression, anxiety) that generate fatigue. This is outlined in more detail later. A limitation of all current data is the fact that they are based on subjects' subjective experience indexing trait fatigue over longer time periods as assessed by self-report questionnaires. No objective performance measurement of fatigue and no validation of the characteristic MS-related performance decrement have been done in correlation to personality traits so far. Therefore, present data on the personality profile in MS fatigue may primarily index psychological facets of fatigue, i.e., its "trait" character, while fatigue caused by functional brain alterations may represent more "state" forms of fatigue.

RELATIONSHIP BETWEEN PERSONALITY-ASSOCIATED FEATURES AND FATIGUE IN MS

The assessment of personality-associated features in MS patients is relevant because they may represent part of the "intermediate phenotypes" of fatigue in MS. This concept is a modification of that of "endophenotypes," which comes from genetic epidemiology and is mainly used in psychiatric genetics to converge behavioral symptoms to phenotypes with straight genetic background. Both concepts are closely related to one another representing approaches to find basic genetic–pathophysiological factors and psychological–behavioral drives of complex syndromes.

The intermediate phenotype (endophenotype) construct is therefore an appropriate approach in the field of behavioral neurology to index those basic neuropsychological and behavioral processes that might play a role in the development of the complex

syndrome "fatigue." Moreover, such an approach might shed light on (mal-)adaptive coping behavior and therefore contribute to explain fatigue states with respect to personality influences. The literature contains a few studies related to MS. Van der Werf et al. (15) explored the role of helplessness as a mediator between neurological disability and psychobehavioral factors. They found that more neurological impairment and more emotional instability created more helplessness, the latter being associated with more experienced fatigue and depressive mood. In support of this, emotional instability that characterizes the personality trait neuroticism has repeatedly been related to fatigue. Hyphantis et al. (16) claim that specific personality features, especially defense style and ego strength, may be considered as indicators of premature exhaustion of patients' vital energy. Interestingly, they found that the odds of being assessed with a psychiatric diagnosis were 9.3 times higher among patients with recent-onset MS compared to those with long-term disease. This highlights the problem of disease coping after revealing the diagnosis of MS to patients. Jopson and Moss-Morris (17) and Skerret and Moss-Morris (18) suggest that the work-up of a strong "disease identity," i.e., of a high internal representation, is an important predictor of physical and cognitive fatigue. They argue that the more MS patients tend to subjectively attribute every deficit and misfeeling to the MS, the more they are fatigued. One can speculate that such a behavior is dependent on personality features, but a direct correlation to objectively assessed personality traits has not been investigated to date. Also the role of spiritual beliefs, control beliefs, and personality in MS fatigue has been studied. Thus, Wahlig (19) found in a doctoral dissertation that fatigue in MS patients was inversely correlated with "I feel peaceful" during an observation period of 3.5 years. However, the relationship between spiritual beliefs and personality has not been specified. Recent work of Pardini et al. (20) has focused on the motivational system of MS patients evaluating behavioral activation and inhibition on the basis of Gray's theory of personality (21). It conceptualizes personality as being represented by two basic dimensions of activity control, i.e., a behavioral activation system (BAS) and a behavioral inhibition system (BIS). Greater BAS sensitivity is thought to foster engagement in goal-directed efforts, while BIS is thought to be aversive causing negative experiences during goal-directed activity. Thus, when assessing fatigued MS patients' reward perception as important part of the BAS, Pardini's group showed lower reward responsiveness to be present in fatigued MS compared to fatigue-free patients. And lower reward responsiveness scores were found to be associated with Modified Fatigue Impact Scale (MFIS) scores at baseline and to correlate with minor fatigue reduction after treatment. The authors conclude that disturbed reward-related cognition may be one of the "key cognitive underpinnings" of MSF. These findings add to the literature of possible relationships between different personality features and fatigue in MS. Other studies also provide evidence for an overlap between motivational system and fatigue level. Thus, in fatigued subjects, an increased reward for the completion of a task has been shown to reduce some of the effects of fatigue in behavioral performance and neurophysiological testing of centralized fatigue (22, 23). In this context, it is interesting to note that fatigue and the motivational system might share some common neural circuits. For instance, lesions in the ventromedial prefrontal cortex could be related to increased fatigue perception levels and also to deficits in the evaluation of outcomes as rewarding or non-rewarding (24). Most interestingly, depression has been excluded as a relevant confounding factor in Pardini's MS patients who were required to show normal Hospital Anxiety and Depression Scale scores (HADS) to enter the study. Therefore, motivational testing in the context of reward perception seems to represent a distinct entity that is not merely an efflux of depression.

It sum, it can be said that the studies hitherto available on personality features in MS-associated fatigue provide promising first approaches to the field. However, more systematic research is warranted to further substantiate how and to which extent personality-associated intermediate phenotypes might contribute to the generation of fatigue in MS and other diseases. Again, however, it seems to be only the trait variant of fatigue that can be addressed in this context. Methodological limitations remain and imply also the fact that not all personality features investigated to date are sufficiently validated. Nevertheless, the currently available data give a first impression of the possible significance of a covertly vulnerable personality structure that results in the development of MSF by causing "maladaptive" disease coping and psychological distress.

INTERACTION OF DEPRESSION AND PERSONALITY TRAITS IN MS-ASSOCIATED FATIGUE

A decisive question is whether we are essentially assessing some sort of state depression instead of enduring personality traits when evaluating personality structure in MSF. This is relevant because both disorders share a high prevalence among MS patients, which makes coincidence in individuals probable, and it may be difficult to differentiate between coincidence and interaction. Moreover, no reliable data are available to date with respect to the premorbid personality structure of fatigued MS patients. Accordingly, their personality profile as assessed after the onset of the disease might not be "genuine" but already be altered by adaptive behavior and depression. Supporting evidence for a high interference of certain personality traits with depressiveness can be drawn from observations with patient groups other than MS. In patients with chronic fatigue syndrome (CFS), the subgroup with concomitant depressive disorder accounted for most of the personality pathology (25). And neuroticism was found to account for 22% of the variance of depression in MS patients after 3.5 years follow-up (19). Likewise, Penner et al. (11) defined depression as an influential factor of personality traits. Various personality changes being related to MS fatigue were no longer significant after control of depression as a covariate. Also in the patient sample of our group, MSF was significantly influenced by the factor depression. But when looking at individual expressions of depression in fatigued patients, it turned out that, despite higher mean values, depression in nearly all cases scored below the clinically relevant threshold raising the question of clinical relevance (14).

These observations suggest that fatigue and depression in MS, despite interacting with each other, are essentially distinct entities. The opinion that MSF is a mere expression of a somatic depression with vital deficit is also not compatible with clinical experience. First, MSF is mostly of shorter duration, in contrast to more persistent fatigue associated with depression, and it is

closely activity-related, i.e., shows performance decrement. Second, its aggravation by heat is rather unique for MS and not seen in depression. Against this background, it is comprehensible that no consistent beneficial effect of antidepressant drugs in MS has been found so far.

It can be hypothesized from the current data that MS-associated fatigue is not congruent with depression, but that depressive mood may promote fatigue. In line with this hypothesis, MS-related mental fatigue has been shown to be preceded by reduced motivation and emotional distress (26). In the proportion of MS patients that are fatigued, depression and anxiety may be the "interface" between a vulnerable personality structure facilitating maladaptive disease coping behavior, and fatigue. Interpretation of current data, that are not fully consistent, suggests that a personality characterized by emotional lability (neuroticism), inhibition/avoidance, inflexible cognitions, and less open-mindedness (extraversion) is more prone to "maladaptive" disease coping behavior, anxiety, and depression, than a resilient personality. Depression, in turn, may aggravate feelings of fatigue that again are the primary pick-up criterion of conventional fatigue questionnaires. It is interesting to note in this context that anxiety, depression, and fatigue are not only highly prevalent in MS but tend to cluster together. A recent study has emphasized that the prevalence of the three factors is high in MS, with depression rarely occurring alone or without concurrent anxiety and/or fatigue (27). Notably, the psychological dimension of fatigue has especially been advocated for fatigue feelings over extended time (trait fatigue) and in early MS when structural and functional brain deficits are not prevalent. In later disease stages, physical dimensions of fatigue, more linked to performance decrement (4) may gain importance.

PERSONALITY PROFILE IN MS-RELATED FATIGUE AND CHRONIC FATIGUE SYNDROME

When discussing the personality profile of fatigued MS patients, it is rewarding to look at the CFS. It is a disorder without obvious neural damage and without a consistent biological marker that, at first glance, shares striking similarities with MSF in clinical picture including vital deficit beyond fatigue, sleep disorder, and attention deficit. Unlike many depressed MS patients, fatigued MS patients are usually not dominated by negative affect (28) resembling CFS subjects who tend to make physical attributions for their deficit (29). And the dominant symptom of CFS is pervasive fatigue, but interestingly, less performance decrement is occurring in CFS patients than seen in fatigued MS patients.

The question, whether there are similarities in the personality profile between fatigued MS and CFS patients, has been addressed in a few studies. Early work concentrated on psychiatric aspects. Thus, Pepper et al. (30) found no differences concerning personality disturbances between CFS and MS fatigue patients, but more frequent depression in CFS, especially following the onset of the disease. A study comparing relative rates of personality disturbance in CFS, fatigued MS, and depressed patients revealed higher rates of personality disorders in all three patient groups compared to controls with depressed patients showing the highest scores and MFS and CFS patients medium scores. However, personality alterations in the CFS group did not differ from that exhibited by MS patients (25). Christodoulou et al. (31) evaluated personality profiles on the basis of Cloninger's four basic dimensions of personality in CFS compared to MS patients and HC. MS patients were unique in terms of having lower Persistence Level than CFS patients and HC, and comparable with CFS patients in terms of increased sensitivity to negative stimuli (i.e., higher levels of Harm Avoidance) and lower levels of Reward Dependence as compared to HC. The reduced Persistence Level in MS patients has been interpreted by the authors according to Cloninger's theory as the tendency of the individual to persevere in behaviors that have been previously associated with reward or relief from punishment. Taillefer et al. (32) examined personality, depression, and illness worry in CFS versus MS outpatients and detected no differences with respect to neuroticism and depressive symptoms. On the other hand, CFS patients showed a significantly higher illness worry index than MS patients. The latter, however, were not all in a state of fatigue.

Summing up, current data do not substantiate any essential differences concerning personality profiles in CFS and fatigued MS patients. Alternatively, CFS patients could be distinguished from depressed patients on clinical grounds and psychometric testing. In a study comparing CFS and depression, the CFS patients were characterized by lower ratings of their health status, stronger illness identity, making external attributions of their illness, and distortions in thinking that were specific to somatic experiences. They were more likely than depressed patients to cope with their illness by limiting activity levels, and somatic illness identity turned out to be the most significant predictor of ongoing fatigue (33). In view of such findings, it has been suggested that CFS and MSF might share similarities as a somatization disorder. But the body of data on this issue is mostly speculative to date so that valid conclusions cannot be drawn. Otherwise, there is growing evidence to implicate somatic mechanisms (causative or adaptive) in CFS, especially abnormalities of the HPA axis with altered hormonal stress response. This involves reduced adrenocorticoid hormone (ACTH) response, hypocortisolism, and increased serotonin neurotransmission that, very noteworthy, are contrasting with patterns observed in depressed patients (34). It can be concluded from the data that psychological and somatic factors coexist and may interact to produce the complex behavioral correlate of fatigue in CFS.

HOW MAY PERSONALITY TRAITS AND PERSONALITY-ASSOCIATED FACTORS CONTRIBUTE TO MS-RELATED FATIGUE?

One important pathway by which personality factors may provoke fatigue is "maladaptive" disease coping. This may cause psychological distress and, prompt various psychological, neuroendocrine, and neurovegetative dysregulations that ultimately result in fatigue. The term maladaptive is thought to index coping behavior that is not primarily based on problem-solving but on emotional reactions involving negative feelings, anxiety, exaggerations, and negative cognitions. Personality is known to determine to a high degree the choice of coping strategies (35), although the impact of situative factors is acknowledged as well. Thus, coping strategies have been found to differ between disease populations and HC (36). Since MS is a chronic and potentially disabling

disease that affects patients primarily in younger age, the confrontation with such a diagnosis has to be considered an extremely stressful event that requires adequate coping. In such situations, personality factors that might provoke inadequate modes of adaptation are detrimental. In this context it is important to highlight early work of Folkman and Lazarus (37) who stressed the significance of emotional coping strategies for challenges that act outside of subjects' control (severe disease) and the importance of cognitive coping strategies for challenges within subjects' control (for real problem-solving). In MS disease, emotional coping strategies have been found to prevail in the early stages, while rational (cognitive) strategies gain importance in later stages (38). In support of this, Goretti et al. (39), when exploring coping strategies among MS patients, found that problem-focused strategies are less likely used and avoiding strategies adopted more often.

It can be concluded from this that emotional coping and avoidance behavior entail more risk of psychological distress than cognitive coping strategies, and pave the way to sustained stress responses and ultimately fatigue. This view is supported by recent work of Nielsen-Prohl et al. (40) providing evidence that personality-related volitional coping competences required by daily stressful situations are a relevant factor for depressive mood in individual MS patients. The crucial role of personality traits for the development of psychological problems in MS has also been advocated by other authors (16, 41–43). Especially Rabinowitz and Arnett (43) were able to show in a longitudinal study that depression in MS is dependent on coping styles and that psychological and cognitive status and coping behavior affect each other. Thus, "adaptive" coping protected MS patients from experiencing depression, but when individuals used maladaptive coping, coexisting cognitive dysfunction put them even more at risk for depression. Results suggest that tertiary problems, for example cognitive dysfunction, add to the risk of depression due to an independent negative effect on coping. A personality profile described in the literature as accentuated by inhibition/avoidance, irritability, and aggressiveness, i.e., showing less extraversion and more emotional lability ("neuroticism"), would fit into this model. Such personalities, though not being pathological in terms of a personality disorder, may soon come to a state of psychological distress entailing irritability, depressiveness, and anxiety when facing the diagnosis of MS.

In this context, it may also be asked whether somatization behavior might play a role in fatigue. Despite being speculative, there are several analogies to consider. First, the nosological and etiological boundaries of patients with complaints of chronic fatigue have not been clearly delineated so far. Various disorders are subsumed and patients with chronic fatigue are likely to have comorbid affective, anxiety, and somatoform symptoms (44). Second, somatization patients have a tendency of being hypersensitive to stimuli and more aware of bodily sensations, thinking catastrophically about their physical sensations, and having increased emotional distress, all of which may enhance physical symptoms. Their state of increased reactivity has even been documented neuro-physiologically (45). Third, an association of fatigue and somatization disorder with hypocortisolism has repeatedly been reported (46) with the most consistent correlate being reduced cortisol response from dysregulation of the HPA axis (47). A possible cause of patients' hypersensitivity may be repeated or prolonged exposure to stress. Therefore, it has been argued that somatization patients overstrain their stress response system for a long time resulting in blunted HPA axis function (48). HPA dysfunction again represents the final pathway that has been implicated as an important pathophysiological cause of fatigue (49).

From a psychological perspective, it can be summarized that depressiveness, anxiety, and somatization may be relevant mediators and interfaces to fatigue in MS. But current research suggests that this psychological interface is less likely to act by means of a full-scale somatic depression than by influencing a more complex network of psychological and somatic factors. These involve maladaptive disease coping, inadequate stress response, altered central immune mechanisms (pro-inflammatory cytokines), and neuroendocrine changes (HPA axis). The latter, in turn, may directly be influenced by demyelinating lesions, axonal damage, and altered immune status (upregulation of pro-inflammatory cytokines). The assumption that pro-inflammatory cytokines may pathogenetically be relevant for fatigue relies on laboratory findings that (1) pro-inflammatory cytokines (IL-1, IL-6, TNF-alpha, and Il-12) were positively correlated with fatigue in MS (50–52), (2) TNF-alpha was correlated with the severity of fatigue in MS (52), and (3) TNF-alpha in animal experiments was able to trigger a fatigue syndrome (53). Again there are cytokine–neuroendocrine interactions by which central immune reactions gain influence on the HPA axis.

Thus, psychological and somatic factors seem to converge to final pathways to create fatigue. MS fatigue according to this concept would integrate complementary somatic and psychological causes and be the end-product of an interplay of multiple factors that, in the individual case, change in loading and composition according to disease stage.

CONCLUSION

Current data suggest that fatigue, especially in early MS states, may be influenced by vulnerable personality traits and personality-associated features that are premorbid factors and not intrinsically linked with MS. Among them are depressive disease coping, avoidance behavior, inhibition, irritability, less extraversion, neuroticism, disturbed reward responsiveness, and somatization behavior. However, among the validated personality factors no genuine influences being independent of depression have been found. From a psychological perspective, depressiveness, anxiety, and somatization behavior may therefore be relevant mediators of fatigue promoting it by psychological distress and sustained neuroendocrine and neurovegetative stress response.

Personality research on fatigue in MS is attractive because it might open ways to early psychological intervention targeting unfavorable disease cognitions and coping. This is all the more important since medication is insufficient to date. Further research on the expression and interaction of personality profiles, depressive mood, anxiety states, and disease coping orientations seem to be a promising concept to disentangle psychosocial determinants of fatigue in MS. Such knowledge would allow to improve the non-drug therapy and care of fatigued MS patients by development of adequate coping skills (in coping with stressful experience, timely

diagnosis), of emotional distress and anxiety, also through psychotherapeutic and behavioral interventions, and the creation of social networks to support patients (54).

However, there are several limitations of currently available personality findings. First, we have no reliable premorbid data on personality structure in individuals suffering from MSF. Therefore, we do not know whether the personality profile as assessed after the onset of MS has not been influenced by depressive mood and/or other disease-related factors. Stressful situations as seen in MS may enhance or alter pre-existing personality traits and features and even lead to pathological states in terms of a personality disorder (54). Longitudinal study designs are needed to substantiate whether and possibly how personality structure is altered by MS disease. Second, data relating personality profile to fatigue are solely based on subjective ratings reported in fatigue questionnaires, i.e., assessed as subjective fatigue or fatigability over extended time (trait fatigue), but not on performance measurement after challenging mental and physical effort (state fatigue). This favors a bias towards psychological and trait aspects of fatigue. It remains to be established whether personality profiles show any correlation with test settings including objective measures of fatigue, i.e., reaction times, grip tests, and effort-related changes in performance.

When trying to draft a unifying hypothesis from the current findings, one could argue that there are two types of fatigue: (1) primary fatigue (intrinsically disease-related) and (2) a secondary form related to comorbid conditions. Fatigue in initial stages of MS might largely be driven by factors associated with disease coping while fatigue in later stages should predominantly be caused by inflammatory influence on the brain and functional consequences of brain lesions. Then, the two main subtypes of fatigue states, one "psychosocial" in origin and one characterized by "altered brain function" as formulated by S. Johnson (55) should be coexisting entities in the individual patient thus integrating multiple sources of origin. The main psychological factors interacting with fatigue that have been delineated so far are depression, anxiety, and inadequate disease coping. They seem to be related to personality profile and foster "maladaptive" reactions to MS diagnosis. On the other hand, disease status and disease progression are important physical factors. Therefore, disease-intrinsic determinants and extrinsic ones, that are not directly disease-related, might interact in the generation of fatigue in MS. Finally, psycho-biological models of fatigue (56), integrative physiological concepts like that of "central fatigue" (57) stressing the importance of abnormal patterns of activation in specific brain areas (58, 59) as well as the concept of enhanced cognitive reserve as a putative protective factor (60) are not exclusive, but complementary explanatory models of fatigue in MS. Their contribution to fatigue may change in every individual fatigued MS patient. Thus, the dichotomy of "physical" and "psychological" determinants of MS fatigue and the hitherto conflicting results may be reconciled by the view of fatigue representing a "multifaceted syndrome" with different mechanisms of origin (61).

REFERENCES

1. Multiple Sclerosis Council for Clinical Practice Guidelines. *Fatigue and Multiple Sclerosis: Evidence-Based Management Strategies for Fatigue in Multiple Sclerosis.* Washington, DC: Paralyzed veterans of America (1998).
2. Iriatre J, Subira ML, Castro P. Modalities of fatigue in multiple sclerosis: correlation with clinical and biological factors. *Mult Scler* (2000) **6**:124–30. doi:10.1177/135245850000600212
3. Dettmers C, Sulzmann M, Gütler R, Lange R, Weiller C, Vieten M. Motorische fatigue bei multipler sklerose. In: Penner IK, editor. *Fatigue Bei Multipler Sklerose.* Bad Honnef: Hippokampus Verlag (2009). p. 53–62.
4. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a modified taxonomy. *Neurology* (2013) **80**(4):409–16. doi:10.1212/WNL.0b013e31827f07be
5. DeLuca J. Fatigue, cognition and mental effort. In: De Luca J, editor. *Fatigue as a Window to the Brain.* Cambridge, MA: The MIT Press (2005). p. 37–57.
6. Montgomery GK. Uncommon tiredness among college undergraduates. *J Consult Clin Psychol* (1983) **51**:517–25. doi:10.1037/0022-006X.51.4.517
7. Magnusson AE, Nias DKB, White PD. Is perfectionism associated with fatigue? *J Psychosom Res* (1996) **41**:377–83. doi:10.1016/S0022-3999(96)00189-4
8. Phares EJ, Chaplin WF. *Introduction to Personality.* 4th ed. New York, NY: Longman (1997).
9. Feist J, Gregory J. *Theories of Personality.* 7th ed. Boston, MA: McGraw Hill Higher Education (2009).
10. Merkelbach S, König J, Sittinger H. Personality traits in multiple sclerosis (MS) patients with and without fatigue experience. *Acta Neurol Scand* (2003) **107**:195–201. doi:10.1034/j.1600-0404.2003.02037.x
11. Penner IK, Bechtel N, Raselli C, Söcklin M, Opwis K, Kappos L, et al. Fatigue in multiple sclerosis: relation to depression, physical impairment, personality and action control. *Mult Scler* (2007) **13**:1161–7. doi:10.1177/1352458507079267
12. Kiltz K, Lang M, Flachenecker P, Meissner H, Kohler A, Freidel M, et al. Physical, cognitive and psychological dimensions of fatigue in patients with relapsing-remitting multiple sclerosis – a multi-center study. *Mult Scler* (2009) **15**(9 Suppl):S31–S150/S116. doi:10.1177/1352458509106962
13. Lang C, Lang M, Flachenecker P, Meissner H, Freidel M, Herbst H, et al. Fatigue, cognition and personality in patients with relapsing-remitting multiple sclerosis (RRMS) – a longitudinal study. *Mult Scler* (2011) **17**(10 Suppl):S53–S276/S433. doi:10.1177/1352458511422300
14. Schreiber H, Lang C, Kiltz K, Lang M, Flachenecker P, Meissner H, et al. Multivariate analysis of clinical, behavioural and psychological influences on fatigue and cognition in patients with relapsing-remitting multiple sclerosis. *Mult Scler* **18**(4 Suppl):S55-277/S436. doi:10.1177/1352458512459019
15. Van der Werf SP, Evers A, Jongen PJ, Bleijenberg G. The role of helplessness as mediator between neurological disability, emotional instability, experienced fatigue and depression. *Mult Scler* (2003) **9**:89–94. doi:10.1191/1352458503ms854oa
16. Hyphanthis TN, Christou K, Kontoudaki S, Mantas C, Papamichael G, Goulia P, et al. Disability status, disease parameters, defense styles, and ego strength associated with psychiatric complications of multiple sclerosis. *Int J Psychiatry Med* (2008) **38**(3):307–27. doi:10.2190/PM.38.3.g
17. Jopson NM, Moss-Morris R. The role of illness severity and illness representations in adjusting to multiple sclerosis. *J Psychosom Res* (2003) **54**:503–11. doi:10.1016/S0022-3999(02)00455-5
18. Skerret TN, Moss-Morris R. Fatigue and social impairment in multiple sclerosis: the role of patients' cognitive and behavioral responses to their symptoms. *J Psychosom Res* (2006) **61**:587–93. doi:10.1016/j.jpsychores.2006.04.018
19. Wahlig EL. Health outcomes in multiple sclerosis: the role of beliefs and personality in cognitive function, depression, fatigue, and quality of life. *Diss Abstr Int* (2006) **66**(12–B):6966.
20. Pardini M, Capello E, Krueger F, Mancardi G, Uccelli A. Reward responsiveness and fatigue in multiple sclerosis. *Mult Scler* (2013) **19**(2):233–40. doi:10.1177/1352458512451509
21. Gray JA. The psychophysiological basis of introversion-extraversion. A modification of Eysenck's theory. In: Nebylitsyn VD, Gray JA, editors. *The Biological Basis of Individual Behavior.* San Diego, CA: Academic Press (1972). p. 182–205.
22. Boksem MA, Tops M. Mental fatigue: cost and benefits. *Brain Res Rev* (2008) **59**:125–39. doi:10.1016/j.brainresrev.2008.07.001
23. Boksem MA, Meijman TF, Lorist MM. Mental fatigue, motivation and action monitoring. *Biol Psychol* (2006) **72**:123–32. doi:10.1016/j.biopsycho.2005.08.007
24. O'Doherty JP. Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Curr Opin Neurobiol* (2004) **14**:769–76. doi:10.1016/j.conb.2004.10.016

25. Johnson SK, deLuca J, Natelson BH. Personality dimensions in the chronic fatigue syndrome: a comparison with multiple sclerosis and depression. *J Psychiatr Res* (1996) **30**:9–20. doi:10.1016/0022-3956(95)00040-2
26. Schreurs KM, De Ridder DT, Bensing JM. Fatigue in multiple sclerosis: reciprocal relationships with physical disabilities and depression. *J Psychosom res* (2002) **53**:775–81. doi:10.1016/S0022-3999(02)00326-4
27. Wood B, van der Mei IAF, Ponsonby AL, Pittas F, Quinn S, Dwyer T, et al. Prevalence and concurrence of anxiety, depression and fatigue over time in multiple sclerosis. *Mult Scler* (2012) **19**(2):217–24. doi:10.1177/1352458512450351
28. Patten SB, Metz LM. Fatigue and depression in multiple sclerosis. *Can J Psychiatry* (2000) **45**:84–5.
29. Johnson S, deLuca J. Chronic fatigue syndrome and the brain. In: de Luca J, editor. *Fatigue as a Window to the Brain*. Cambridge, MA: The MIT Press (2007). p. 137–56.
30. Pepper CM, Krupp LB, Friedberg F, Doscher C, Coyle PK. A comparison of neuropsychiatric characteristics in chronic fatigue syndrome, multiple sclerosis, and major depression. *J Neuropsychiatry Clin Neurosci* (1993) **5**(2):200–5. doi:10.1176/jnp.5.2.200
31. Christodoulou C, DeLuca J, Johnson SK, Lange G, Gaudino EA, Natelson BH. Examination of Cloninger's basic dimension of personality in fatiguing illness: chronic fatigue syndrome and multiple sclerosis. *J Psychosom Res* (1999) **47**(6):597–607. doi:10.1016/S0022-3999(99)00063-X
32. Taillefer SS, Kirmayer L, Robbins JM, Lasry JC. Correlates of illness worry in chronic fatigue syndrome. *J Psychosom Res* (2003) **54**(4):331–7. doi:10.1016/S0022-3999(02)00332-X
33. Moss-Morris R, Petrie KJ. Discriminating between chronic fatigue syndrome and depression: a cognitive analysis. *Psychol Med* (2001) **31**:469–79. doi:10.1017/S0033291701003610
34. Cleare AJ, Bearn J, McGregor A, Allain T, Wessely S, Murray RM, et al. Contrasting neuroendocrine responses in depression and chronic fatigue syndrome. *J Affect Disord* (1995) **35**:283–9. doi:10.1016/0165-0327(95)00026-J
35. Cloninger CR, Svrakic PM, Prybeck TR. A psychobiological model of temperament and character. *Psychiatr Clin North Am* (1993) **50**:975–90.
36. Ratsep T, Kallasmaa T, Pulver A, Gross-Paju K. Personality as a predictor of coping efforts in patients with multiple sclerosis. *Mult Scler* (2000) **6**:397–402. doi:10.1191/135245800701566386
37. Folkman S, Lazarus RS. An analysis of coping in a middle-aged community sample. *J Health Soc Behav* (1980) **1980**(21):219–39. doi:10.2307/2136617
38. Aikens JE, Fischer JS, Namey M, Rudick RA. A replicated prospective investigation of life stress, coping, and depressive symptoms in multiple sclerosis. *J Behav Med* (1997) **20**:433–45. doi:10.1023/A:1025569214584
39. Goretti B, Portaccio E, Zipoli V, Hakiki B, Siracusa G, Sorbi S, et al. Coping strategies, psychological variables and their relationship with quality of life in multiple sclerosis. *J Neurol Sci* (2009) **30**(1):15–20. doi:10.1007/s10072-008-0009-3
40. Nielsen-Prohl J, Saliger J, Guldenberg V, Breier G, Karbe H. Stress-simulated volitional coping competencies and depression in multiple sclerosis. *J Psychosom Res* (2013) **74**(3):221–6. doi:10.1016/j.jpsychores.2012.11.003
41. Benedict RH, Carone DA, Bakshi R. Correlating brain atrophy with cognitive dysfunction, mood disturbances, and personality disorder in multiple sclerosis. *J Neuroimaging* (2004) **14**:S36–45. doi:10.1177/1051228404266267
42. Benedict RH, Wahlig EL, Topciu RA, Englert J, Schwartz E, Chapman B, et al. Personality traits in women with multiple sclerosis: discrepancy in patient/partner report and disease course. *J Psychosom Res* (2009) **66**:147–54. doi:10.1016/j.jpsychores.2008.09.007
43. Rabinowitz AR, Arnett PA. A longitudinal analysis of cognitive dysfunction, coping and depression in multiple sclerosis. *Neuropsychology* (2009) **23**(5):581–91. doi:10.1037/a0016064
44. Kroenke K, Wood DR, Mangelsdorff AD, Meier NJ, Powell JB. Chronic fatigue in primary care: prevalence, patient characteristics and outcome. *J Am Med Assoc* (1988) **260**:929–34. doi:10.1001/jama.260.7.929
45. James L, Gordon E, Kraiuhin C, Howson A, Meares R. Augmentation of auditory evoked potentials in somatization disorder. *J Psychosom Res* (1990) **24**:155–63. doi:10.1016/0022-3956(90)90055-U
46. Rief W, Auer C. Cortisol and somatization. *Biol Psychol* (2000) **53**:13–23. doi:10.1016/S0301-0511(00)00042-9
47. Ehlert U, Gaab J, Heinrichs M. Psychoneurological contributions to the etiology of depression, posttraumatic stress disorder and stress-related bodily disorders: the role of the hypothalamus-pituitary-adrenal axis. *Biol Psychol* (2001) **57**:141–52. doi:10.1016/S0301-0511(01)00092-8
48. Allen LA, Escobar JI. Fatigue and somatization. In: de Luca J, editor. *Fatigue as a Window to the Brain*. Cambridge, MA: The MIT Press (2005). p. 173–83.
49. Gottschalk M, Kümpfel T, Flachenecker P, Uhr M, Trenkwalder C, Holsboer F, et al. Fatigue and regulation of the hypothalamo-pituitary-adrenal axis in multiple sclerosis. *Arch Neurol* (2005) **62**:277–80. doi:10.1001/archneur.62.2.277
50. Flachenecker P, Bihler I, Weber F, Gottschalk M, Toyka KV, Rieckmann P. Cytokine mRNA expression in patients with multiple sclerosis and fatigue. *Mult Scler* (2004) **10**:165–9. doi:10.1191/1352458504ms991oa
51. Heesen C, Koehler G, Gross R, Tessmer W, Schulz KH, Gold SM. Altered cytokine responses to cognitive stress in multiple sclerosis patients with fatigue. *Mult Scler* (2005) **11**:51–7. doi:10.1191/1352458505ms1129oa
52. Heesen C, Nawrath L, Reich C, Bauer N, Schulz KH, Gold SM. Fatigue in multiple sclerosis: an example of cytokine mediated sickness behaviour? *J Neurol Neurosurg Psychiatry* (2006) **77**:34–9. doi:10.1136/jnnp.2005.065805
53. Sheng WS, Hu S, Kamkin A, Peterson PK, Chao CC. Susceptibility to immunologiclly mediated fatigue in C57/BL/6 versus Balb/c mice. *Clin Immunol Immunopathol* (1996) **81**:161–7. doi:10.1006/clin.1996.0172
54. Stathopoulou A, Christopoulos P, Soubasi E, Gourzis P. Personality characteristics and disorders in multiple sclerosis patients: assessment and treatment. *Int Rev Psychiatry* (2010) **22**(1):43–54. doi:10.3109/09540261003589349
55. Johnson S. Depression and fatigue. In: de Luca J, editor. *Fatigue as a Window to the Brain*. Cambridge, MA: The MIT Press (2007). p. 157–72.
56. Van Kessel K, Moss-Morris R. Understanding multiple sclerosis fatigue: a synthesis of biological and psychological factors. *J Psychosom Res* (2006) **61**:583–5. doi:10.1016/j.jpsychores.2006.03.006
57. Chaudhuri A, Behan PO. Fatigue and basal ganglia. *J Neurol Sci* (2000) **179**:34–42. doi:10.1016/S0022-510X(00)00411-1
58. Filippi M, Rocca MA, Colombo B, Falini A, Scotti G, Comi G. Functional magnetic resonance imaging correlates of fatigue in multiple sclerosis. *Neuroimage* (2002) **15**:559–657. doi:10.1006/nimg.2001.1011
59. DeLuca J, Genova HM, Hillary FG, Wylie G. Neural correlates of cognitive fatigue in multiple sclerosis using functional MRI. *J Neurol Sci* (2008) **270**:28–39. doi:10.1016/j.jns.2008.01.018
60. Sumowski JF, Wylie GR, DeLuca J, Chiaravalloti N. Intellectual enrichment is linked to cerebral efficiency in multiple sclerosis: functional magnetic resonance imaging evidence for cognitive reserve. *Brain* (2010) **133**:362–74. doi:10.1093/brain/awp307
61. DeLuca J. Fatigue, cognition and mental effort. In: de Luca J, editor. *Fatigue as a Window to the Brain*. Cambridge, MA: The MIT Press (2007). p. 37–57.

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Fatigue in multiple sclerosis: a look at the role of poor sleep

Lauren B. Strober[1,2]*

[1] Neuropsychology and Neuroscience Laboratory, Kessler Foundation, West Orange, NJ, USA
[2] New Jersey Medical School, Rutgers, The State University of New Jersey, Newark, NJ, USA

Edited by:
Christian Dettmers, Kliniken Schmieder Konstanz, Germany

Reviewed by:
Annette Sterr, University of Surrey, UK
Iris-Katharina Penner, University of Basel, Switzerland

***Correspondence:**
Lauren B. Strober, 300 Executive Drive, Suite 70, West Orange, NJ 07052, USA
e-mail: lstrober@kesslerfoundation.org

Fatigue is a frequent and debilitating symptom of multiple sclerosis (MS) with rates ranging anywhere from 53 to 90%. Despite its high prevalence and grave impact on overall functioning and quality of life, the accurate definition, quantification, and etiology of fatigue have plagued the MS literature and clinical care for decades. With regard to its etiology, MS-related fatigue has been construed as being either primary or secondary. Primary fatigue is purported to be related to centrally mediated processes of the disease whereas secondary fatigue is thought to be a result of the host of factors that may accompany MS (e.g., depression, sleep disturbance). The present paper focuses on secondary fatigue and the role of sleep disturbance, in particular. Despite the intuitive assumption that sleep problems could contribute to fatigue, sleep problems in MS have gone fairly unrecognized until recently. The present paper provides a brief review of the literature pertaining to the prevalence and nature of sleep problems in MS as well as their association with fatigue. A replication of this author's and others work is presented further demonstrating that sleep disturbance is a significant contributor to fatigue in MS when taking into account disease variables, depression, and sleep disturbance.

Keywords: fatigue, multiple sclerosis, sleep disorders, depression, fatigue management

INTRODUCTION

Since the first report of fatigue being a prevalent and significant problem in multiple sclerosis (MS) (1) the definition, accurate quantification of fatigue in MS, and etiology has perplexed investigators. To date, nearly every article pertaining to MS-related fatigue contains some sort of disclaimer regarding our inadequate definition, lack of appropriate assessment tools, and limited understanding of its etiology (2). The present article is no exception. However, the investigation outlined in this paper is a replication of previous work demonstrating the fact that when attempting to at least better understand the *etiology* of fatigue in MS, consideration should be given to the role that sleep disturbance as it has been proven to be a significant factor (3).

Despite being the most obvious factor, sleep disturbance or disorders, had initially received fairly little attention as a precipitating or exacerbating factor of fatigue in MS. Fortunately, following an editorial by Attarian titled, "Importance of sleep in the quality of life of multiple sclerosis patients: a long under-recognized issue" sleep disturbance and its disorders have received significantly more attention (4). In fact, when conducting a PubMed search with the terms "MS" and "sleep" in the title, 14 articles have been published between the years 1987 and 1997 and 15 articles were dated from 1998 to 2008, suggesting approximately 15 published articles on sleep in MS per decade. However, since Attarian's editorial in 2009 the number of published articles with MS and sleep in the title is 46. Thus, at this rate, the number of published articles on sleep in MS over the past 5 years is one a half times more than what was published in the preceding two decades of the 2009 editorial (see **Figure 1**).

These articles have been published worldwide and span the gamut of looking at the incidence of various sleep disorders to the role of sleep on quality of life and fatigue to the effects of treating sleep problems in MS. While the majority of these studies rely on self-report measurement, some have also included more objective measures including polysomnography. What is to follow is a brief review of fatigue in MS, the prevalence and nature of sleep disorders in MS, and the relationship between the two. Study findings from a recent investigation that replicates previous work demonstrating that sleep disturbance is a significant contributor to fatigue in MS when taking into account disease variables, depression, and sleep disturbance is then presented. Finally, data from a few studies that have demonstrated that effective treatment of such sleep problems can result in reduced fatigue among individuals with MS are provided.

BACKGROUND

FATIGUE IN MS

Fatigue is a frequent and debilitating symptom of MS with rates ranging anywhere from 53 to 90% (1, 5–9). MS-related fatigue has typically been construed as being either primary or secondary. Primary fatigue is purported to be related to centrally mediated processes of the disease, such as demyelination and axonal loss in the central nervous system or immunological factors. Secondary fatigue, on the other hand, is thought to be a result of the host of factors that may accompany MS (e.g., depression, reduced activity, medication side effects, sleep disturbance) (10). The present paper focuses on secondary fatigue and the role of sleep disturbance. However, regardless of the exact etiology, fatigue is known to be extremely detrimental to those with MS with nearly 55% of patients reporting fatigue to be among their worst symptoms (11) and 40% describing it as their most disabling symptom (8). MS-related fatigue has also been shown to have detrimental effects on

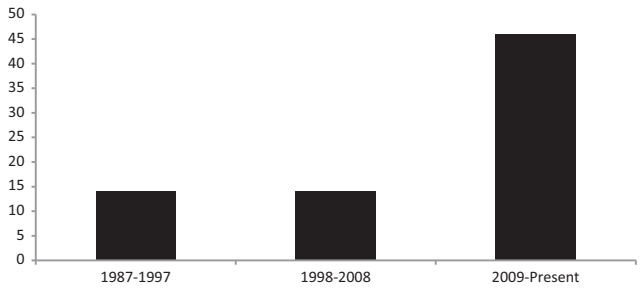

FIGURE 1 | Number of articles published in PubMed with the words "sleep" and "multiple sclerosis" in the title.

daily functioning, social and occupational obligations, and overall well-being. In fact, Freal et al. showed that of the 87% of MS patients complaining of significant fatigue, 67% reported experiencing it on a daily basis and 22% reported that it interfered with their daily functioning (1). Similarly, Iriarte et al. found that fatigue produced limitations in daily functioning in 66% of those who complained of fatigue (12). Of this, 37% reported that it limited their social activities and 61% reported that fatigue limited their work. This is consistent with reports showing that fatigue leads to patients having to cut down on working hours (13) and findings that individuals with MS report fatigue as the one of the greatest culprits related to work difficulty or leaving the workforce (14). Patients also report that their fatigue can result in a lowered sense of self-worth as well as feelings of shame, sorrow, and anger related to their perceptions of their fatigue (15). Similarly, fatigue in MS has been shown to be related to lowered positive affect, psychological distress, and a sense of loss of control (16). Given its grave impact, identification of factors associated with fatigue has been a main priority in research and clinical care among individuals with MS.

SLEEP DISORDERS IN MS

Current research suggests that anywhere from 19 to 67% of individuals with MS experience some sort of sleep difficulty (17–32), with rates as high as 80% in some samples (33). Restless leg syndrome (RLS) (27, 28, 30), periodic limb movement (PLM) (21), narcolepsy–cataplexy syndrome, rapid eye movement (REM) behavior disorder, insomnia, and obstructive sleep apnea (OSA) (34) have all been reported (see **Table 1**).

In general, it is believed that individuals with MS are three times more likely to experience sleep difficulties than controls (36), though the incidence may be greater for some disorders. For instance, in a large study consisting of 861 individuals with MS and 649 healthy controls, it was found that the risk for RLS was 5.4 times greater for individuals with MS (28).

For many sleep disorders, a direct neurological etiology associated with MS has been found. For instance, cervical lesions have been found to be associated with RLS (27) while greater lesion load in the brainstem and cerebellum has been implicated in PLM (21). Narcolepsy in MS has been suggested to be related to focal lesions in the hypothalamus (37). Finally, REM-behavior sleep disorders in MS have been linked to dorsal pontine lesions (37). While these sleep disorders have a direct etiology related to specifically to MS, insomnia, and OSA, which are also common in the general public have been found to be more prevalent in MS. Insomnia in MS has been attributed to a multitude of factors, primarily nocturia, leg spasms, muscle stiffness, pain, depression, and symptomatic MS medication side effects (32, 38). It has been previously shown that individuals report bladder incontinence as the greatest contributor to disturbed sleep, followed by muscle stiffness and leg spasms, in more than 50% of patients (38). Similar findings were found by Stanton et al. in which nocturia was the most common cause of middle insomnia (72%), followed by pain/discomfort (22%). Nocturia was also the greatest contributor to terminal insomnia (40%), while anxiety/racing mind accounted for initial insomnia most often (28%). In general, depression has been shown to be more related to initial insomnia, while nocturia has been found to be the cause of middle and terminal insomnia (32). With regard to OSA, again, reports of OSA in MS are as high as 80% compared to 63% of healthy controls. Causes of OSA in MS may include inactivity due to disability, brainstem lesions that affect the respiratory centers or nucleus ambiguous, or symptomatic medications that relax muscle tone in the pharynx (37). While these sleep disorders are perhaps the most prevalent in MS, they are both amenable to treatment as will be discussed.

RELATIONSHIP OF FATIGUE AND SLEEP IN MS

Nearly all studies examining sleep problems in MS have been an attempt to understand its relationship to secondary fatigue and potential mediating effects, with a few exceptions. In particular, a number of studies in the MS literature have focused on sleep disturbance as a significant contributor to fatigue in MS (23, 24, 30, 32, 39–41). For instance, when comparing fatigued and non-fatigued individuals with MS, Kaynak et al. found that those suffering from fatigue experience greater disturbance in sleep microstructure such as total arousal index (TAI), a measure of sleep fragmentation, and PLM index (24). Such findings are consistent with Chen et al.'s findings in which fatigue scores correlated with PLM index, PLM arousal index, REM latency, and TAI (19). Moriera et al.'s study also found that individuals diagnosed with RLS reported poorer sleep quality, which was in turn related to fatigue (30). Finally, reports on a self-report measure of OSA have also been shown to be related to reports of fatigue with more fatigued individuals being more likely to have elevated scores on this measure, even when items that could be construed as fatigue were removed (18, 20).

When constructing a model of fatigue in MS that took into account disease severity, sleep, and depression, it was found that sleep disturbance was the greatest predictor of fatigue, accounting for 24% of the variance followed by depression (10%) and disease severity (9%) (3). It should be noted that this study utilized measures in which overlapping items of fatigue, sleep, and depression were removed from the measures so as to have the purest constructs. These findings were later replicated by Ghajarzadeh et al. in an Iranian sample in which sleep disturbance accounted for 25% of the variance and depression accounted for an additional 9% (42). Such findings suggest that sleep may be the greatest culprit in the experience of fatigue in MS. Within, present findings demonstrate an additional, third replication of these findings in

Table 1 | Prevalence of sleep disorders in multiple sclerosis (MS).

Reference	Country	Size	Disorder(s)	Prevalence MS	Controls
Bamer et al. (17)	USA	1062	Disturbed sleep[a]	52%	–
Lunde et al. (26, 35)	Norway	90	Poor sleep[b]	67%	44%
Merlino et al. (29)	Italy	120	Poor sleep[b]	48%	–
Chen et al. (19)	China	21	Poor sleep[b]	62%	–
			Initial insomnia	43%	
			Middle insomnia	76%	
			Terminal insomnia	33%	
Pokryszko-Dragan et al. (31)	Poland	100	Initial insomnia	28%	–
			Middle insomnia	33%	
			Terminal insomnia	48%	
Stanton et al. (32)	USA	60	Initial insomnia	42%	–
Braley et al. (33)	USA	30	Obstructive sleep apnea	80%	63%
Kaminska et al. (23)	Canada	62	Obstructive sleep apnea	58%	47%
Dias et al. (20)	USA	103	Obstructive sleep apnea	42%	–
Braley et al. (18)	USA	195	Obstructive sleep apnea	21%	–
Kallweit et al. (22)	Germany	69	Sleep disordered breathing	41%	
Manconi et al. (27)	Italy	861	Restless legs syndrome	19%	4%
Manconi et al. (27)	Italy	82	Restless legs syndrome	37%	–
Moreira et al. (30)	Italy	44	Restless legs syndrome	27%	–
Kaminska et al. (23)	Canada	62	Restless legs syndrome	27%	6%
Kaynak et al. (7, 24)	Turkey	37	Restless legs syndrome	38%	0
Ferini-Strambi et al. (21)	Italy	25	Periodic limb movement	36%	8%
Kaminska et al. (23)	Canada	62	REM sleep behavior	3%	0
Kaminska et al. (23)	Canada	62	Narcolepsy	2%	0

[a] *Based on the medical outcome study sleep (moss) scale.*

[b] *Based on the Pittsburgh sleep quality index.*

hopes of furthering the increase in attention to sleep problems in MS and their contribution to fatigue in MS.

RESEARCH DESIGN AND METHODS

PARTICIPANTS

Participants were recruited from local MS clinics and chapters of the National Multiple Sclerosis Society throughout United States. Participants were enrolled in a larger study examining factors associated with employment in MS and thus were all employed, between the ages of 20 and 64, and diagnosed with definite MS.

PROCEDURES

Participants completed an online survey consisting of several measures assessing disease variables, psychological functioning, well-being, health–behaviors, adjustment and coping to MS, and overall quality of life. All procedures were approved by the Institutional Review Board of the Kessler Foundation. For the purposes of the present study, participants completed the following measures.

MEASURES

Modified fatigue impact scale

Modified fatigue impact scale (MFIS) is modified form of the fatigue impact scale (43) that is based on 21 items derived from interviews with MS patients concerning how fatigue impacts their lives. It consists of three subscales: physical, cognitive, and psychosocial functioning. Patients are asked to rate on a scale of 0–4 their agreement with the statement and how it impacts them with "0" being "Never" and "4" being "Almost always." Recently, it has been recommended that a cutoff of 38 on the MFIS was most indicative of significant fatigue in MS (44). Given the potential overlap of fatigue and depressive symptoms on the psychosocial subscale, the sum of the physical and cognitive subscales was used for the regression analyses. This score has been termed the MFISPC.

Pittsburgh sleep quality index

The Pittsburgh sleep quality index (PSQI) is a measure of sleep disturbance and quality (45). It consists of 19 items that are summed to create seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, daytime dysfunction, and use of sleeping medication. The sum of scores for these seven components yields one global score. A cutoff of "5" on the global score is indicative of being a "poor" sleeper. The global score was used in all analyses.

Chicago multiscale depression inventory

The Chicago multiscale depression inventory (CMDI) was specifically designed to assess depression in MS and other medical groups (46). It consists of three subscales: evaluative, mood, and vegetative. Each subscale contains 14 items and patients are asked to rate on a scale of 1–5 the extent to which each word/phrase describes them during the past week, including today with "1" being "Not

at All" and "5" being "Extremely." For the purpose of this study, ratings on the vegetative scale were removed due to confounds of sleep and fatigue included in the items on this scale. For our sample, depression was measured by a total score of only the combined evaluative and mood subscales. This score has been termed the CMDIME.

STATISTICAL ANALYSES

All statistical analyses were conducted using SPSS 21.0 computer software. Pearson correlations were conducted for all correlational analyses. Independent *t*-tests were conducted to examine group differences between the sleep disturbed and non-sleep disturbed groups on demographics, disease variables, fatigue, and depression. Finally, a stepwise, hierarchical regression was conducted with disease duration, sleep disturbance, and depression as the independent variables and fatigue as the dependent variable.

RESULTS

A total of 107 individuals with definite MS were enrolled in the study. Participants were primarily female ($N = 92$; 86%) with a mean age of 44.71 (±9.76) and mean disease duration of 8.91 (±7.13). Per the global score of the PSQI, 61% of participants were classified as "poor sleepers" and constitute the "sleep disturbed" group. Per the previously recommended cutoff of 38 on the MFIS, approximately half of the sample (47%) experienced significant fatigue (see **Table 2**).

Initial correlations found physical and cognitive fatigue to be significantly correlated with poor sleep ($r = 0.42$ and 0.49, $p < 0.001$, respectively). A slightly lower correlation was found with psychosocial fatigue ($r = 0.30$, $p = 0.001$). Fatigue was also found to be associated with all of the subscales of the CMDI (*r*'s ranging from 0.24 to 0.72), with the highest correlations occurring with the vegetative subscale (*r*'s ranging from 0.47 to 0.72), which is expected given the overlap of fatigue items on the vegetative scale. Finally, sleep was not found to be related to the mood or evaluative subscales of the CMDI but was significant correlated with the vegetative subscale ($r = 0.65$, $p < 0.001$). Again, this is greatly influenced by item overlap. When looking at the measure scores used in the regression analyses (MFISPC and CMDIME) the correlations between fatigue, depression, and sleep remained (see **Table 3**).

Stepwise regression analyses found that sleep disturbance accounted for 25% of the variance in predicting fatigue, followed by depression, which accounted for an additional 7%. Together, they accounted for 32% of the variance, while disease duration did not contribute to predicting fatigue (see **Table 4**).

Such findings are a near replication of previous findings, suggesting that sleep disturbance is the greatest predictor of fatigue in MS when examined among disease variables and depression, and accounts for a quarter of the variance. However, it should be noted that there are limitations of the present data, including the lack of objective measures of disease severity, fatigue, and sleep disturbance and the use of self-report surveys. There is also the lack of information pertaining to participants' medication load. Such factors may also contribute to sleep problems in MS. Though, even with the limitations of the present data, clinical findings, and research supporting, the significant role of sleep on MS-related fatigue should hopefully compel practitioners to consider more routine assessment of sleep and referral to sleep studies, when warranted, or when presented with a patient complaining of significant, debilitating fatigue that may exceed what one expects in MS. Consideration should also be given when there is any indication from the patient or bed partner that they patient may have a concomitant sleep disorder. Lunde et al. provide a very thorough review of how best to begin to assess sleep problems in MS as there are presently no specific guidelines. Practitioners are urged to refer to the full guidelines provided by Lunde et al. when

Table 2 | Participant demographics and group comparisons on disease variables, sleep, fatigue, depression.

	Total sample ($N = 107$) mean (SD)	**Range**	
Age	44.71 (9.76)	23–64	
Disease duration	8.91 (7.13)	0–31	
PSQI total	7.07 (4.07)	1–18	
MFIS physical	17.47 (8.00)	0–35	
MFIS cognitive	16.00 (9.34)	0–38	
MFIS psychosocial	3.40 (1.92)	0–8	
CMDI mood	22.83 (10.07)	14–68	
CMDI evaluative	19.38 (8.19)	14–61	
CMDI vegetative	33.70 (9.72)	17–53	
	Not sleep disturbed ($N = 42$) mean (SD)	**Sleep disturbed ($N = 65$) mean (SD)**	***t*-test, sig.**
Age	46.00 (10.32)	43.88 (9.36)	$t = 1.10$, $p = 0.274$
Disease duration	8.19 (6.07)	9.38 (7.75)	$t = -0.84$, $p = 0.401$
PSQI sleep duration	0.24 (0.43)	0.95 (0.99)	$t = -5.12$, $p < 0.001$
PSQI sleep disturbances	1.12 (0.45)	1.60 (0.49)	$t = -5.18$, $p < 0.001$
PSQI sleep latency	0.50 (0.59)	1.49 (0.89)	$t = -6.93$, $p < 0.001$
PSQI daytime dysfunction	0.74 (0.63)	1.48 (0.77)	$t = -5.42$, $p < 0.001$
PSQI sleep efficiency	0.10 (0.48)	1.11 (1.25)	$t = -5.88$, $p < 0.001$
PSQI sleep quality	0.60 (0.50)	1.65 (0.80)	$t = -8.39$, $p < 0.001$
PSQI sleep medication	0.24 (0.66)	1.20 (1.29)	$t = -5.08$, $p < 0.001$
PSQI global score	3.36 (1.27)	9.48 (3.38)	$t = -1.50$, $p < 0.001$
MFIS physical	14.81 (7.82)	19.18 (7.70)	$t = -2.84$, $p = 0.006$
MFIS cognitive	12.62 (7.47)	18.18 (9.82)	$t = -3.31$, $p = 0.001$
MFIS psychosocial	2.79 (1.88)	3.80 (1.85)	$t = -2.75$, $p = 0.007$
CMDI mood	21.02 (9.85)	24.00 (10.11)	$t = -1.50$, $p = 0.136$
CMDI evaluative	18.26 (8.14)	20.10 (8.20)	$t = -1.14$, $p = 0.257$
CMDI vegetative	28.07 (5.22)	37.34 (10.24)	$t = -6.16$, $p < 0.001$

PSQI, Pittsburgh sleep quality index; MFIS, modified fatigue impact scale; CMDI, Chicago multiscale depression inventory.

Table 3 | Correlations of fatigue, depression, and sleep disturbance.

	Mood	Evaluative	Vegetative	Sleep	MFISPC
Physical	0.32**	0.29**	0.50**	0.42**	–
Cognitive	0.33**	0.24*	0.72**	0.49**	–
Psychosocial	0.37**	0.29**	0.47**	0.30**	–
Mood	–	–	–	0.14	–
Evaluative	–	–	–	0.13	–
Vegetative	–	–	–	0.65**	–
MFISPC	–	–	–	0.51**	–
CMDIME	–	–	–	0.14	0.34**

Physical, MFIS physical subscale; Cognitive, MFIS cognitive subscale; Psychosocial, MFIS psychosocial subscale; Mood, CMDI mood subscale; Evaluative, CMDI evaluative subscale; Vegetative, CMDI vegetative subscale; Sleep, PSQI global score; MFISPC, MFIS Physical + Cognitive score; CMDIME, CMDI Mood + Evaluative score.

**Significant at the 0.05 level.*

***Significant at the 0.01 level.*

Table 4 | Stepwise hierarchical regression predicting fatigue with disease duration, sleep, and depression as the independent variables.

	B	SE (*B*)	β	R^2
Step 1				
PSQI	1.95	0.32	0.51**	0.25
Step 2				
PSQI	1.80	0.31	0.47**	
CMDIME	0.24	0.07	0.28**	0.32

PSQI, Pittsburgh sleep quality index global score; CMDIME, Chicago multiscale depression inventory mood and evaluative subscales.

***Significant at the 0.01 level.*

treating individuals who complain of significant fatigue, daytime sleepiness/dysfunction, and sleep difficulties. We turn now to a brief discussion pertaining to the findings that proper assessment and treatment of sleep problems in MS may result in reduced fatigue.

TREATING SLEEP PROBLEM IN MS

Additional support for addressing sleep problems as an underlying cause of fatigue is more recent findings that effective treatment of sleep problems actually results in reductions in self-reported fatigue and sleepiness in MS. More specifically, in a controlled, non-randomized clinical study, Cote et al. evaluated 62 individuals with MS and referred those suspected of having a sleep disorder for evaluation and treatment at a sleep disorder clinic. Of the 39 (63%) who were diagnosed with a sleep disorder, 21 were treated and 18 were not. Treatment consisted of sleep hygiene advice and then further treatment, which was dependent on the nature of the sleep disorder and included continuous positive airway pressure (CPAP) or other position devices for sleep apnea; treatment of exacerbating factors (e.g., iron or B12 deficiency) and/or pramipexole for RLS; clonazepam for REM behavior disordered sleep; and cognitive behavioral therapy for insomnia. Three months follow-up revealed a significant improvement in fatigue as well as sleepiness, subjective sleep quality, depression, pain, and quality of life among those who were treated. Those not treated did not demonstrate such improvement (39). In another study, progressive muscle relaxation was also shown to improve sleep quality and reports of fatigue in a sample of 32 individuals with MS (47). More specifically, the average score of the fatigue severity scale (48) decreased from 5.75 ± 0.95 (a score above the recommended cutoff of 4) to 3.81 ± 1.30 ($p < 0.001$). Finally, Veauthier et al. evaluated the effectiveness of compliance with treatment imposed by a sleep specialist in 42 individuals with MS. Those who were described as having "good compliance" to the treatment demonstrated a significant, 15-point difference on the MFIS. Such significant findings were not found in those with no to moderate compliance or those without a sleep disorder that were followed over the same time period (40). While it is possible, there may be some expectation bias among those that adhere to their treatment and subsequent ratings of improvement, it should be noted that those who were partially compliant to their treatment also demonstrated an improvement in fatigue, albeit not statistically significant. Together, these findings further stress the importance of proper assessment and effective treatment of sleep problems among individuals with MS complaining of significant fatigue and suggest that effective assessment, referral, and treatment of sleep problems in MS are likely to yield significant results.

In sum, the present paper aimed to again increase our awareness of the prevalence and etiology of sleep problems in MS and more importantly, its contribution to the experience of fatigue, one of the most disabling symptoms associated with MS. The study described within also provides further support of the role of sleep on fatigue and the importance of its assessment. In science, observation is the first step in questioning and aiming to understand a phenomenon. MS-related fatigue has been a construct that has perplexed investigators for decades. Over the past few years, the field has begun to test the hypothesis that sleep may be a significant contributor of fatigue in MS. These observations and subsequent findings have yielded positive results. However, the next, and sometimes neglected aspect of science, is replication. Here, findings show a third replication of study findings that consistently demonstrate that sleep problems account for approximately a quarter of the variance of fatigue in MS.

Based on these findings, further research is warranted in which we continue to examine and model the contributing factors of fatigue and sleep in MS in hopes of indentifying the factors and ultimately, treating them. In doing so, future studies should address some of the methodological limitations of past studies, including reliance on self-report measures of sleep and fatigue. Objective measurement of sleep and fatigue, while time consuming and costly, are likely to yield more substantial findings. A few preliminary studies demonstrating the effects of treating sleep on fatigue were also provided within. Further intervention studies are warranted with larger sample sizes and great characterization of the sleep problems as well as the active ingredients of treatment. With such advances, it is hoped that we will see an increase in the assessment, referral, evaluation, and treatment of sleep problems in MS and ultimately be capable of improving the lives and well-being of individuals with MS.

REFERENCES

1. Freal JE, Kraft GH, Coryell J. Symptomatic fatigue in multiple sclerosis. *Arch Phys Med Rehabil* (1984) **6**:135–8.
2. Mills RJ, Young CA. A medical definition of fatigue in multiple sclerosis. *Q J Med* (2008) **101**:49–60. doi:10.1093/qjmed/hcm122
3. Strober LB, Arnett PA. An examination of four models predicting fatigue in multiple sclerosis (MS). *Arch Clin Neuropsychol* (2005) **20**(5):631–46. doi:10.1016/j.acn.2005.04.002
4. Attarian HP, Brown KM, Duntley SP, Carter JD, Cross AH. The relationship of sleep disturbances and fatigue in multiple sclerosis. *Arch Neurol* (2004) **61**:525–8. doi:10.1001/archneur.61.4.525
5. Colosimo C, Millefiorini E, Grasso MG, Vinci F, Fiorelli M, Koudriavtseva T, et al. Fatigue in MS is associated with specific clinical features. *Acta Neurol Scand* (1995) **92**:353–5. doi:10.1111/j.1600-0404.1995.tb00145.x
6. Ford H, Trigwell P, Johnson M. The nature of fatigue in multiple sclerosis. *J Psychosom Res* (1998) **45**(1):33–8. doi:10.1016/S0022-3999(98)00004-X
7. Kaynak H, Altintas A, Kaynak D, Uyanik O, Saip S, Agaoglu J, et al. Fatigue and sleep disturbance in multiple sclerosis. *Eur J Neurol* (2006) **13**:1333–9. doi:10.1111/j.1468-1331.2006.01499.x
8. Krupp LB, Alvarez L, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. *Arch Neurol* (1988) **45**:435–7. doi:10.1001/archneur.1988.00520280085020
9. Van der Werf SP, Jongen PJH, Lycklama a Nijeholt GJ, Barkhof F, Hommes OR, Bleijenberg G. Fatigue in multiple sclerosis: interrelations between fatigue complaints, cerebral MRI abnormalities, and neurological disability. *J Neurol Sci* (1998) **160**:164–70. doi:10.1016/S0022-510X(98)00251-2
10. DeLuca J. Fatigue: its definition, its study, and its future. In: DeLuca J, editor. *Fatigue as a Window to the Brain*. Cambridge, MA: MIT Press (2005). p. 319–25.
11. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. *Can J Neurol Sci* (1994) **21**:9–14.
12. Iriarte J, Subira ML, de Castro P. Modalities of fatigue in multiple sclerosis: correlation with clinical and biological factors. *Mult Scler* (2000) **6**:124–30. doi:10.1177/135245850000600212
13. Smith MM, Arnett PA. Factors related to employment changes in individuals with multiple sclerosis. *Mult Scler* (2005) **11**(5):602–9. doi:10.1191/1352458505ms1204oa
14. Simmons RD, Tribe KL, McDonald EA. Living with multiple sclerosis: longitudinal changes in employment and the importance of symptom management. *J Neurol* (2010) **257**(6):926–36. doi:10.1007/s00415-009-5441-7
15. Flenser G, Ek AC, Soderhamn O. Lived experience of MS-related fatigue-a phenomenological interview study. *Int J Nurs Stud* (2003) **40**:707–17. doi:10.1016/S0020-7489(03)00010-5
16. Krupp LB. Fatigue in multiple sclerosis: definitions, pathophysiology, and treatment. *CNS Drugs* (2003) **17**(4):225–34. doi:10.2165/00023210-200317040-00002
17. Bamer AM, Johnson KL, Kraft GH, Amtmann D. Sleep problems in multiple sclerosis: assessing prevalence and the association with depression. *Mult Scler* (2007) **13**(S2):S122.
18. Braley TJ, Segal BM, Chervin RD. Obstructive sleep apnea and fatigue in patients with multiple sclerosis. *J Clin Sleep Med* (2014) **10**(2):155–62. doi:10.5664/jcsm.3442
19. Chen J, Liu X, Sun H, Huang Y. Sleep disorders in China: clinical, polysomnography study, and review of the literature. *J Clin Neurophysiol* (2014) **31**(4):375–81. doi:10.1097/WNP.0000000000000067
20. Dias RA, Hardin KA, Rose H, Agius MA, Apperson ML, Brass SD. Sleepiness, fatigue and risk of obstructive sleep apnea using the STOP-BANG questionnaire in multiple sclerosis: a pilot study. *Sleep Breath* (2012) **16**:1255–65. doi:10.1007/s11325-011-0642-6
21. Ferini-Strambi L, Filippi M, Martinelli V, Oldani A, Rovaris M, Zucconi M, et al. Nocturnal sleep study in multiple sclerosis: correlations with clinical and brain magnetic resonance imaging findings. *J Neurol Sci* (1994) **125**:194–7. doi:10.1016/0022-510X(94)90035-3
22. Kallweit U, Baumann CR, Harzheim M, Hidalgo H, Pohlau D, Bassetti CL. Fatigue and disordered breathing in multiple sclerosis: a clinically relevant association? *Mult Scler Int* (2013) **2013**:1–7. doi:10.1155/2013/286581
23. Kaminska M, Kimoff RJ, Benedetti A, Robinson A, Bar-Or A, Lapierre Y, et al. Obstructive sleep apnea is associated with fatigue in multiple sclerosis. *Mult Scler* (2012) **18**(8):1159–69. doi:10.1177/1352458511432328
24. Kaynak H, Altintas A, Kaynak D, Uyanik O, Saip S, Agaoglu J, et al. Fatigue and sleep disturbance in multiple sclerosis. *Eur J Neurol* (2006) **13**:1333–9. doi:10.1111/j.1468-1331.2006.01499.x
25. Lobentanz IS, Asenbaum S, Vass K, Sauter C, Klosch G, Kollegger H, et al. Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue, and sleep quality. *Acta Neurol Scand* (2004) **110**:6–13. doi:10.1111/j.1600-0404.2004.00257.x
26. Lunde HMB, Aae TF, Indrevag W, Aarseth J, Bjorvatn B, Myhr K, et al. Poor sleep in patients with multiple sclerosis. *PLoS One* (2012) **7**(11):e49996. doi:10.371/journal.pone.0049996
27. Manconi M, Rocca MA, Ferini-Strambi L, Tortorella P, Agosta F, Comi G, et al. Restless leg syndrome is a common finding in multiple sclerosis and correlates with cervical cord damage. *Mult Scler* (2008) **14**:86–93. doi:10.1177/1352458507080734
28. Italian REMS Study Group, Manconi M, Ferini-Strambi L, Filippi M, Bonanni E, Iudice A, et al. Multicenter case-control study on restless legs syndrome in multiple sclerosis: the REMS study. *Sleep* (2008) **31**(7):944–52.
29. Merlino G, Fratticci L, Lenchig C, Valente M, Cargnelutti D, Picello M, et al. Prevalence of 'poor sleep' among patients with multiple sclerosis: an independent predictor of mental and physical status. *Sleep Med* (2009) **10**:26–34. doi:10.1016/j.sleep.2007.11.004
30. Moreira NC, Damasceno RS, Medeiros CA, Bruin PF, Teixeira CA, Horta WG, et al. Restless leg syndrome, sleep quality and fatigue in multiple sclerosis patients. *Braz J Med Biol Res* (2008) **41**:932–7. doi:10.1590/S0100-879X2008001000017
31. Pokryszko-Dragan A, Bilinska M, Gruszka E, Biel L, Kaminska K, Konieczna K. Sleep disturbances in patients with multiple sclerosis. *Neurol Sci* (2012) **34**(8):1291–6. doi:10.1007/s10072-012-1229-0
32. Stanton BR, Barnes F, Silber E. Sleep and fatigue in multiple sclerosis. *Mult Scler* (2006) **12**:481–6. doi:10.1191/135248506ms1320oa
33. Braley TJ, Chervin RD, Segal BM. Fatigue, tiredness, lack of energy, and sleepiness in multiple sclerosis patients referred for clinical polysomnography. *Mult Scler Int* (2012) **2012**:1–7. doi:10.1155/2012/673936
34. Fleming WE, Pollak CP. Sleep disorders in multiple sclerosis. *Semin Neurol* (2005) **25**:64–8. doi:10.1055/s-2005-867075
35. Lunde HMB, Bjorvatn B, Myhr KM, Bo L. Clinical assessment and management of sleep disorders in multiple sclerosis: a literature review. *Acta Neurol Scand* (2012) **127**(Suppl 196):24–30. doi:10.1111/ane.12046
36. Clark CM, Fleming JA, Li D, Oger J, Klonoff H, Paty D. Sleep disturbance, depression, and lesion site in patients with multiple sclerosis. *Arch Neurol* (1992) **49**:641–3. doi:10.1001/archneur.1992.00530300077013
37. Brass SD, Duquette P, Prouix-Therrien J, Auerbach S. Sleep disorders in patients with multiple sclerosis. *Sleep Med Rev* (2010) **14**:121–9. doi:10.1016/j.smrv.2009.07.005
38. Strober LB, Arnett PA. Sleep changes in multiple sclerosis (MS): from the individual's perspective. *J Sleep Disord Treat Care* (2013) **2**(4). doi:10.4172/2325-9639.1000122
39. Côté I, Trojan D, Kaminska M, Cardoso M, Benedetti A, Weiss D, et al. Impact of sleep disorder treatment on fatigue in multiple sclerosis. *Mult Scler* (2013) **19**(4):480–9. doi:10.1177/1352458512455958
40. Veauthier CM, Gaede G, Radbruch H, Gottschalk S, Wernecke D, Paul F. Treatment of sleep disorders may improve fatigue in multiple sclerosis. *Clin Neurol Neurosurg* (2013) **115**:1826–30. doi:10.1016/j.clineuro.2013.05.018
41. Veauthier C, Radbruch H, Gaede G, Pfueller CF, Dorr J. Fatigue in multiple sclerosis is closely related to sleep disorders: a polysomnographic cross-sectional study. *Mult Scler* (2011) **17**(5):613–22. doi:10.1177/1352458510393772
42. Ghajarzadeh M, Sahraian MA, Fateh R, Daneshmand A. Fatigue, depression, and sleep disturbances in Iranian patients with multiple sclerosis. *Acta Med Iran* (2012) **50**(4):244–9.
43. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis* (1994) **18**(Suppl1):S79–83. doi:10.1093/clinids/18.Supplement_1.S79
44. Flachenecker P, Kumpfel T, Kallmann B, Gottschalk M, Grauer O, Rieckmann P, et al. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. *Mult Scler* (2002) **8**:523–6. doi:10.1191/1352458502ms839oa
45. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index (PSQI): a new instrument for psychiatric research and practice. *Psychiatry Res* (1989) **28**(2):193–213. doi:10.1016/0165-1781(89)90047-4
46. Nyenhuis DL, Luchetta T, Yamamoto C, Terrien A, Bernardin L, Rao SM, et al. The development, standardization, and initial validation of the Chicago

multiscale depression inventory. *J Pers Assess* (1998) **70**(2):386–401. doi:10.1207/s15327752jpa7002_14
47. Dayapogu N, Tan M. Evaluation of the effect of progressive relaxation exercises on fatigue and sleep quality in patients with multiple sclerosis. *J Altern Complement Med* (2012) **18**(10):983–7. doi:10.1089/acm.2011.0390
48. Krupp LB, LaRocca NG, Muir-Nash G, Steinberg G. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* (1989) **46**:1121–3. doi:10.1001/archneur.1989.00520460115022

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Impact of natalizumab treatment on fatigue, mood, and aspects of cognition in relapsing–remitting multiple sclerosis

Annett Kunkel[1], Martin Fischer[2], Judith Faiss[1], Doreen Dähne[1], Wolfgang Köhler[2] and Jürgen H. Faiss[1]*

[1] *Department of Neurology, Asklepios Fachklinikum Teupitz, Teupitz, Germany,* [2] *Department of Neurology, Fachkrankenhaus Hubertusburg, Wermsdorf, Germany*

Background/objective: Fatigue, cognitive, and affective disorders are relevant symptoms in multiple sclerosis (MS). The treatment with Natalizumab has a positive effect on physical disabilities in patients with relapsing–remitting MS (RRMS). Some studies describe improvements in cognition and fatigue over 1 year of treatment. Only little is known about longer treatment effects especially on fatigue, and also on cognition and mood. Therefore, the present retrospective open label observational study investigates the effect of Natalizumab on fatigue, attention, and depression over a treatment period of 2 years.

Methods: About 51 RRMS patients who were treated with Natalizumab (male = 11, female = 40; mean age: 33. 9 ± 9. 1 years) were included. The neuropsychological assessment consisted of different tests of attention (TAP: alertness, divided attention, flexibility, SDMT, PASAT), fatigue (WEIMuS, FSMC), and depression (CES-D). The assessments occurred immediately before the first administration of Natalizumab, after 1 and 2 years of treatment.

Results: Significant improvements were found in aspects of attention and depression from baseline to follow-up 1 [alertness: reaction time (RT) cued, $p < 0.05$; divided attention: visual RT, $p < 0.05$; SDMT: $p = 0.05$; CES-D: $p < 0.05$] and from baseline to follow-up 2 (divided attention: visual RT: $p < 0.001$; errors: $p < 0.01$, omissions: $p < 0.05$; flexibility: RT, $p < 0.05$; SDMT: $p < 0.01$; CES-D: $p < 0.05$). No significant changes were detected in fatigue, probably because of the small sample size, especially in the second year of treatment (WEIMuS: $N = 16$, FSMC: $N = 8$).

Conclusion: The results show a positive effect of Natalizumab on attention in patients with RRMS, and for the first time, also in depression after 2 years of observation, and support the efficacy of the treatment over 2 years. More research is needed for fatigue.

Keywords: multiple sclerosis, cognition, fatigue, depression, natalizumab

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****Correspondence:***
Annett Kunkel,
Department of Neurology, Asklepios Fachklinikum Teupitz, Neurologische Klinik, Buchholzer Street 21, Teupitz 15755, Germany
a.kunkel@asklepios.com

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system, which causes myelin destruction and axonal loss in the brain and spinal cord, and leads to different visible and invisible symptoms, such as MS-related fatigue, cognitive dysfunctions, and depression (1, 2). Fatigue affects up to 90% of MS patients in all disease stages (3, 4), has significant socioeconomic consequences, and is a relevant factor of diminished quality of life among patients with MS (5). Different biological and psychological models exist regarding the multifactorial etiology of fatigue (6). Inflammation, demyelination, and also behavioral variables such as anxiety, depression, and reduced activity are associated with fatigue (7).

In addition, cognitive dysfunctions are common in MS (8) and can appear in all disease stages (9–11). The association to fatigue is unclear. Whereas some studies describe an association between fatigue and cognitive impairment (12, 13), in other studies no correlation was found (14, 15). The prevalence rates vary between 43 and 70% depending on the research setting, the characteristics of the clinical sample, and the used assessment tools (16). Most impaired cognitive domains in MS are information processing speed and complex attention, verbal and non-verbal memory, and executive functions, as well as visual spatial functions. Intelligence, language, and semantic memory are mostly preserved (15, 17, 18).

Depression in MS has a prevalence rate up to 50% (19, 20), and is associated with fatigue as well as cognitive functions (1, 21). The differentiation between fatigue and depression is often difficult and symptoms of depression can be mistaken as fatigue.

Different studies describe a beneficial effect of immunmodulatory treatments on cognitive functions by containing the development of new cerebral lesions or reducing brain atrophy (22–24). Less clearly are the effects of immunmodulatory therapies on fatigue and depression. Metz et al. (25) report a more beneficial effect of glatirameracetat than β interferon on fatigue after 6 months of treatment. Other studies found no relationship between depression and treatment with interferons (26, 27). One study reported decreased quality of life, worsened fatigue, and depression under treatment with β interferon (28).

Natalizumab (NTZ) is a humanized monoclonal antibody, and is used as monotherapy in relapsing–remitting MS (RRMS) in severe courses. NTZ has positive effects on physical disabilities, in reducing the relapse rate and magnetic resonance imaging (MRI) detectable disease activity (29, 30). Past studies investigated the effect of NTZ on cognition and partially also on depression and fatigue over the observational periods of 6 months to 1 year (31–35). Putzki et al. (36) encompassed fatigue and depressive symptoms at baseline immediately before the treatment with NTZ and 6 months later. About 46% of the 42 treated patients decreased in the Modified Fatigue Impact Scale [MFIS, (37)] and 39% showed improvements in the Fatigue Severity Scale [FSS, (38)]. No changes were detected in the Beck′s Depression Inventory [BDI, (39)] over the observational period. Another multicenter study (34) with 195 RRMS patients found significant improvements in fatigue after 12 months of treatment with NTZ. Fatigue was measured with the Fatigue Scale for Motor and Cognitive Functions [FSMC, (40)]. All of the secondary outcomes improved over time, including quality of life, sleepiness, depression, cognition, and the degree of disability.

Little is known about the treatment effects of NTZ for longer treatment periods and the effect on specific cognitive domains. Iaffaldano et al. (41) found improvements in fatigue and cognition after 1 year of treatment and partially for fatigue also after 2 years of NTZ treatment. Fatigue was measured with the FSS (38) and improved from initially 45% of patients with fatigue to 29% after 1 year of treatment. This effect remained stable in the second year of treatment. Cognitive impairment, measured by Rao's Brief Repeatable Battery (BRB) and Stroop Test (42), improved significantly only in the first year of treatment (29% to 19% decrease); in the second year, the effect was not statistical significant.

Against the background of the results in the literature and in comparison and addition to the hitherto published data, the aim of the present retrospective open label observational study was the investigation of the effect of NTZ on fatigue, different aspects of cognition, and depression over a treatment period of 1 and 2 years.

Materials and Methods

Study Design and Sample

The present retrospective open label observational study was conducted at two departments of neurology (Teupitz, Wermsdorf) in Germany. Both are accredited MS centers from the German Multiple Sclerosis Association (DMSG). All patients were explained in detail prior to the first application of NTZ through competent MS nurses and the attending physicians; and provided their oral and written informed consent for all procedures; the participation and the accompanying required comprehensive clinical assessment. All used data were made anonymous and were transferred without names, addresses, and date of birth in an evaluation file. No study code was used. Consequently, a subsequent assignment from the data to a special patient record is not possible.

Data of 51 (Teupitz: $N = 33$, Wermsdorf, $N = 18$) patients with a relapsing remitting course of MS (43), who were treated monthly with a constant dose of 300 mg NTZ according to the german pharmaceutical indications over the course of 1 year, were included. Thirty one of these patients continued the application with NTZ for a second year of treatment. The remaining 20 cases completed the second treatment year after time of statistical analysis in the course of the ongoing year. The detailed description of the sample is shown in **Table 1**. Before the treatment with NTZ, most patients had applied other treatment options. Twenty seven patients received Interferon-β1a, 24 received Interferon-β1b, 12 patients were treated with Glatiramer acetate, and 4 patients got Mitoxantron.

Clinical and Cognitive Assessments

Prior to the first application of NTZ, every patient received a standardized comprehensive clinical assessment, consisting of MRI, chest X-ray, gynecological, respectively, urologic check-up, inspection of the skin, determination of visual acuity, sonography of the epigastrum, different blood tests, JVC-antibody test, and the neurological examination with assessment of the degree of disability measured by EDSS (44). The treatment with NTZ

TABLE 1 | Description of the sample.

	Baseline	Year 1	Year 2
N	51	51	31
Age	33.9 ± 9.1[a]		
Gender (male/female)	11/40	11/40	7/24
Disease duration (years)	5.3 ± 4.8[a]		
EDSS[b]	4.0 ± 1.6[a]	3.8 ± 1.7	3.9 ± 1.7
Number of prior medications	1.3 ± 0.8		
Time to follow-up (years)		0.9 ± 0.2	2.0 ± 0.4
Depression-index (CES-D)	18.5 ± 10.1 Cut-off $> 22 = 15$	16.6 ± 10.2	16.6 ± 8.9
Fatigue-index (FSMC)	65.2 ± 17.5 Cut-off $\geq 43 = 9$	65.8 ± 20.5	63.4 ± 20.5
Fatigue-index (WEIMuS)	32.7 ± 15.7 cut-off $\geq 32 = 15$	29.6 ± 18.3	29.6 ± 20.2

[a] *Mean ± SD.*
[b] *Expanded Disability Status Scale (44).*
Prior medications: interferon-β1a, interferon-β1b, glatiramer acetate, Mitoxantron.
WEIMuS, Würzburg Fatigue Inventory for MS (45); FSMC, Fatigue Scale for Motor and Cognitive Functions (40); CES-D, Center for Epidemiological Studies-Depression Scale (46, 47).

included yearly follow-up examinations of MRI, blood test, cognitive assessment, JVC-antibody test, and neurological examination (EDSS).

Furthermore, all patients obtained an annually comprehensive cognitive testing for detecting changes in cognition during the treatment of NTZ. The cognitive assessment was performed by trained psychologists according to standard procedures. All cognitive tests were performed immediately before the first infusion of NTZ, after 1 and 2 years of application with a fixed test battery. All examinations at each measurement point start with the assessment of fatigue and depression. For the evaluation of fatigue, the Fatigue Scale for Motor and Cognitive Functions [FSMC; (40)] and the Würzburg Fatigue Inventory for MS [WEIMuS; (45)] were used. The FSMC consists of 20 items and is a five-stage rating scale without time limit for evaluation. The cut-off for fatigue is $\geq$43. On the other hand, the WEIMuS estimates fatigue in the course of the last week. This questionnaire consists of 17 items and has also a 5-stage rating scale with a cut-off for fatigue of $\geq$32. For the assessment of depressive symptoms, the 20 items of the Center for Epidemiological Studies-Depression Scale [CES-D; (46, 47)] were used. The cut-off for a clinical relevant depression is >22. This cut-off achieves a high sensitivity (82–84%) and specificity (47).

In everyday clinical practice, the neuropsychological examination included the computerized Attention Test Battery [TAP, Version 2.2; (48)], with the subtests alertness (responsiveness), divided attention and flexibility, as well as the Symbol Digit Modalities Test [SDMT; (49)], for the assessment of different aspects of attention and information processing speed. Additionally, verbal memory was tested using the Auditory Verbal Learning test (50) and non-verbal memory using the "Diagnosticum fuer Cerebralschaedigung" [DCS; (51)]. Visuospatial abilities were assessed by the Rey–Osterrieth Complex Figure Test (ROCF) using the Taylor Scoring System (52). A Word Fluency Test was used for a screening of executive functions with the subtests animals, S-words, and alternating G- and R-words (53). In addition, a recognition vocabulary test was used to assess premorbid aspects of intelligence [German Vocabulary Scale, WST; (54)]. All cognitive tests were given in a fixed order: SDMT, AVLT (learning, interference), ROCF, three subtests of the TAP, AVLT (recall and recognition), DCS, fluency, WST.

Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA). Only the data concerning fatigue, depression, and attention were analyzed. Tests for memory and executive functions were not analyzed because of the missing control group, against the background of learning effects. Variables were reported by using descriptive statistics. Differences from baseline to follow-up measurement points (year 1, year 2) were evaluated using the *t*-test for paired samples and the Wilcoxon Rank test. The statistical analysis for 2 years is based only on those patients who remained in the study the whole time ($N = 31$), because in the utilized paired sample *t*-test only those cases were included for which data for both time points were available. The *p*-value <0.05 was considered as statistical significant on one-sided testing. Not all tests could be given at all measurement points because of limited physical and cognitive skills. The following 10 test-parameters were used for the statistical analysis:

1. Attention Test Battery
   Alertness:
   median reaction time (AL RT), measured in milliseconds (ms).
   median reaction time cued (AL RT cued) in ms (responsiviness).
   Divided Attention:
   median divided attention reaction time visual (Divid Att RT vis) in ms.
   median divided attention reaction time auditory (Divid Att RT aud) in ms.
   divided attention errors (Divid Att errors).
   divided attention omissions (Divid Att omissions).
   Flexibility:
   median flexibility reaction time (Flex RT) in ms.
   flexibility errors (Flex errors).
   flexibility performance index (Flex perfom index).
2. SDMT
   number of correct answers.

For the assessment of fatigue and depression with the WEIMuS, FSMC, and CES-D, the total values were used for the statistical analysis.

Results

The statistical analysis was subdivided into three parts. In the first part, the data of the total sample were analyzed. The second and third part describes the data of the subsamples of patients with fatigue and depression, respectively.

Total Sample

Fifty-one patients (11 men, 40 women) with an age between 19 and 51 years (Median: 33.9 ± 9.1) were treated with NTZ for 1 year. The mean disease duration was 5.3 ± 4.8 years (minimum: 0.34 years, maximum: 17.65 years). The average number of MS medications prescribed prior to NTZ was 1.3 ± 0.8.

TABLE 2 | Changes in fatigue and depression over the total sample and both years of observation.

	First year of treatment		Second year of treatment	
	Baseline ***N*** **= 51**	**Year 1 (*p**)** ***N*** **= 51**	**Baseline** ***N*** **= 31**	**Year 2 (*p**)** ***N*** **= 31**
WEIMuS	30.75 ± 14.76[a]	29.06 ± 18.67 (0.19)	30.94 ± 14.65	28.88 ± 21.18 (0.27)
FSMC	64.71 ± 21.19[a]	64.29 ± 23.85 (0.47)	69.50 ± 10.66	73.00 ± 12.35 (0.31)
CES-D	18.96 ± 10.07[a]	16.83 ± 10.21 (0.06)	19.16 ± 8.97	16.16 ± 8.95 (0.07)

WEIMuS, Würzburg Fatigue Inventory for MS; FSMC, Fatigue Scale for Motor and Cognitive Functions; CES-D, Center for Epidemiological Studies-Depression Scale (german variant, longform).
[a]Mean ± SD.
**p-value following paired sample t-test.*

The time between baseline and first follow-up assessment after 1 year of treatment was in mean 0.9 ± 0.2 years. About 31 of these patients (7 men, 24 women) were treated for a second year with NTZ (mean time to follow-up from baseline to year 2 was 2.03 ± 0.4 years). No significant changes were found in the degree of disability, measured by EDSS from baseline (EDSS = 3.99 ± 1.55) to year 1 (EDSS = 3.77 ± 1.73; $p = 0.06$) and from baseline (EDSS = 4.13 ± 1.65) to year 2 (EDSS = 3.90 ± 1.68; $p = 0.19$) for the total sample.

At baseline, the mean fatigue scores (WEIMuS, FSMC) were 30.75 ± 14.76 and 64.71 ± 21.19, respectively, as shown in **Table 2**, ranging from 0 to 64 points in the WEIMuS and 31 to 93 points in the FSMC. From baseline to year 1, as well as to year 2, no significant changes were observed (**Table 2**). In the second year of treatment, the WEIMuS ranged between 0 and 66 points and the FSMC ranged between 20 and 91 points.

In depression, measured by the CES-D, only a statistical trend for significant changes over both time points were observed in the total sample (**Table 2)**.

The analysis of cognitive parameters (**Table 3**) showed significant changes after 1 year of treatment in 3 out of 10 parameters, and 5 out of 10 parameters in the second year of treatment. Significant changes were evident in the subtests alertness [responsiveness (alertness): $p < 0.05$], and divided attention of the TAP (median reaction time visual: $p < 0.05$), and the SDMT ($p < 0.05$). After the second year of treatment, the effect in the divided attention was stable for the visual reaction time ($p < 0.001$) and extended for the error rate ($p < 0.01$) and number of omissions ($p = 0.05$). Furthermore, the reaction time, as part of cognitive flexibility, significantly changed from baseline to year 2 ($p = 0.05$). Above that, the number of correct answers in the SDMT was significant better after the second year of treatment in comparison to baseline ($p < 0.01$).

Patients with Fatigue

At baseline, 28 patients (54.90%) of the total sample reported a fatigue syndrome. After the first year of treatment with NTZ, again, 28 patients (54.90%) of the sample complaint about fatigue, and after 2 years of treatment still 19 patients (61.29%) reported a fatigue syndrome. Therefore, no significant changes in fatigue were observed over the three measurement points (**Table 4**).

The subgroup of patients with fatigue did not differ in age, disease duration, EDSS, and cognitive performance from the other patients (results of the independent *t*-tests are not shown, because they are not significant).

Table 4 shows the changes over time in the attention parameters in the subgroup of patients with fatigue. After the first year of treatment, 2 out of 10 cognitive parameters were significantly changed (one trend toward significance in SDMT), and in the second year 3 out of 10 parameters showed significant changes (two trends). From baseline to year 1, patients with fatigue reached significant improvements in the subtests alertness ($p < 0.05$) and flexibility ($p < 0.05$). The SDMT showed a trend toward significance ($p = 0.05$). In year 2, different parameters of divided attention (reaction time visual, $p < 0.05$; omissions, $p < 0.05$) and flexibility (reaction time, $p = 0.05$) significantly improved. The SDMT also showed a trend toward significance.

Furthermore, changes in the value of depression were observed. At baseline, the mean CES-D (22.04 ± 8.24) reached the cut-off for a clinical relevant depression. After 1 year of treatment as well as after 2 years, the CES-D value decreased in mean to 19.19 in year 1 and 17.46 in year 2. Both improvements showed a trend toward significance.

Patients with Depression

In contrast to the total sample, a clear improvement in the CES-D value was evident over the observational period. At baseline, 15 patients (29.41%) reported a CES-D value that suggests a clinically relevant depression, in contrast to 21.56% (11 patients) after 1 year and 22.58% (7 patients) after 2 years of NTZ treatment. The CES-D values decreased significantly from baseline to year 1 [$t = 2.17$ (14), $p < 0.05$] and from baseline to year 2 [$t = 2.81$ (8), $p < 0.05$]. No significant changes were detected between year 1 and year 2 [$t = 1.45$ (8), $p = 0.18$].

Changes in cognitive parameters, as shown in **Table 5** were detected similar to the total sample in the divided attention (baseline to year 1: omissions: $p < 0.05$; baseline to year 2: visual reaction time: $p < 0.05$) and flexibility (baseline to year 2: flexibility reaction time: $p < 0.05$). In the first year, one cognitive parameter improved, and in the second year two parameters.

Concerning fatigue, no significant changes were observed in the observational period. After the first year of NTZ treatment, the WEIMuS-score was almost identical (**Table 5**). In the second year, the score decreased about some points, but without statistical significance.

Discussion

In this retrospective open label observational study, cognitive performance, depression, and fatigue of 51 RRMS patients treated with NTZ over 1 year, and 31 of them treated over 2 years with NTZ were investigated.

Looking at the total sample, the patients cognitively improved in different aspects of attention, namely responsiveness (alertness), information processing speed, and divided attention (visual reaction time) after 1 year of treatment with NTZ. After 2 years of

TABLE 3 | Changes in different aspects of attention over 2 years of treatment with NTZ.

	First year of treatment		Second year of treatment	
	Baseline ***N*** **= 51**	**Year 1 (*p**)** ***N*** **= 51**	**Baseline** ***N*** **= 31**	**Year 2 (*p**)** ***N*** **= 31**
AL RT[a]	279.05 ± 73.11	268.49 ± 54.30(0.13)	294.23 ± 86.15	283.39 ± 65.65 (0.22)
AL RT cued[a]	277.16 ± 84.01	**256.75 ± 37.25 (0.02)**	289.23 ± 102.96	269.35 ± 48.74 (0.11)
Divid Att RT vis[a]	884.24 ± 182.45	**844.22 ± 137.60 (0.02)**	912.29 ± 214.89	**832.66 ± 165.45 (0.00)**
Divid Att RT aud[a]	612.00 ± 91.04	614.04 ± 89.71 (0.42)	626.50 ± 85.56	623.39 ± 91.33 (0.41)
Divid Att errors	2.36 ± 4.06	1.55 ± 2.85 (0.11)	2.75 ± 4.97	**1.14 ± 2.01 (0.01)**
Divid Att omissions	2.06 ± 0.96	1.72 ± 1.49 (0.12)	2.25 ± 1.95	**1.64 ± 1.54 (0.05)**
Flex RT[a]	931.07 ± 778.20	769.97 ± 255.33 (0.07)	1116.31 ± 1040.21	**738.78 ± 260.58 (0.05)**
Flex errors	3.94 ± 6.80	2.24 ± 2.07 (0.25)	4.83 ± 8.71	1.50 ± 1.46 (0.10)
Flex Perform Index	5.09 ± 6.56	4.18 ± 8.56 (0.39)	4.95 ± 5.11	8.36 ± 7.90 (0.07)
SDMT	49.06 ± 10.01	**51.88 ± 7.88 (0.02)**	46.67 ± 9.30	**53.08 ± 7.53 (0.01)**

[a] *In milliseconds (ms).*
All values are presented as means ± SD.
AL RT, alertness, reaction time; AL RT cued, alertness reaction time cued; Divid Att RT vis, divided attention reaction time visual; Divid Att RT aud, divided attention reaction time auditory; Divid Att errors, divided attention errors; Divid Att ommisions, divided attention omission; Flex RT, flexibility reaction time; Flex errors, flexibility errors; Flex Perfom Index, flexibility performance index; SDMT, symbol digit modalities test.
**p-value following paired sample t-test.*
The bold font indicates the statistical significant results.

TABLE 4 | Analysis of cognitive parameters from patients with fatigue at baseline.

Patients with fatigue	First year of treatment		Second year of treatment	
	Baseline ***N*** **= 28**	**Year 1 (*p**)** ***N*** **= 28**	**Baseline** ***N*** **= 16**	**Year 2 (*p**)** ***N*** **= 16**
AL RT[a]	277.39 ± 73.20	271.16 ± 65.55 (0.33)	297.75 ± 87.16	280.00 ± 62.01 (0.14)
AL RT cued[a]	279.61 ± 87.85	**255.36 ± 40.29 (0.04)**	295.25 ± 110.03	266.19 ± 50.43 (0.12)
Divid Att RT vis[a]	856.41 ± 152.23	834.00 ± 135.99 (0.16)	900.47 ± 186.05	**811.20 ± 187.30 (0.03)**
Divid Att RT aud[a]	619.26 ± 93.08	627.22 ± 89.85 (0.31)	630.33 ± 92.93	632.00 ± 82.70 (0.46)
Divid Att errors	2.59 ± 4.19	2.26 ± 3.54 (0.46)	2.80 ± 5.26	1.40 ± 2.44 (0.07)
Divid Att omissions	2.11 ± 2.08	1.81 ± 1.54 (0.22)	2.60 ± 2.13	**1.67 ± 1.76 (0.02)**
Flex RT[a]	763.25 ± 219.31	778.75 ± 232.57 (0.36)	869.57 ± 269.18	**744.00 ± 294.57 (0.04)**
Flex errors	2.00 ± 3.26	2.69 ± 2.44 (0.17)	2.43 ± 4.72	1.00 ± 0.82 (0.34)
Flex Perform Index	6.97 ± 6.45	**2.17 ± 10.13 (0.03)**	6.22 ± 6.52	8.06 ± 9.47 (0.14)
SDMT	48.91 ± 9.85	51.45 ± 7.85 (0.05)	47.00 ± 9.62	52.75 ± 9.16 (0.05)
WEIMuS[b]	42.19 ± 7.90	41.31 ± 13.18 (0.37)	43.50 ± 8.14	39.50 ± 18.22 (0.19)
FSMC[b]	70.17 ± 17.01	64.67 ± 26.10 (0.14)	69.50 ± 10.66	73.00 ± 12.35 (0.31)
CES-D	22.04 ± 8.24	19.19 ± 6.63 (0.06)	22.15 ± 8.52	17.46 ± 7.11 (0.06)

[a] *In milliseconds (ms).*
All values are presented as means ± SD.
[b] *WEIMuS and FSMC: first year: N = 16, second year: N = 8.*
AL RT, alertness, reaction time; AL RT cued, alertness reaction time cued; Divid Att RT vis, divided attention reaction time visual; Divid Att RT aud, divided attention reaction time auditory; Divid Att errors, divided attention errors; Divid Att ommisions, divided attention omission; Flex RT, flexibility reaction time; Flex errors, flexibility errors; Flex Perfom Index, flexibility performance index; SDMT, symbol digit modalities test; WEIMuS, Würzburg Fatigue Inventory for MS; FSMC, fatigue Scale for Motor and Cognitive Functions; CES-D, Center for Epidemiological Studies-Depression Scale.
**p-value following paired sample t-test.*
The bold font indicates the statistical significant results.

treatment, additional effects were evident in errors and omissions in divided attention and the flexibility reaction time.

About 55% of the patients suffered from fatigue at baseline. This value even increased to 61% in the second treatment year. Although the fatigue itself was not affected by the treatment, patients suffering from fatigue showed improvements in responsiveness, divided attention, information processing speed, and flexibility after the first and the second year of treatment.

The data suggests that NTZ may have a positive effect on depression in patients with RRMS. The CES-D values of the 29% patients with a baseline depression decreased so that after the first and second year of treatment, only 22% suffered from depression.

The present results are partially comparable to the hitherto published data. The main differences are the lack of improvement in fatigue in the present sample in comparison to the data in the

TABLE 5 | Analysis of cognitive parameters from patients with depression at baseline.

Patients with depression	First year of treatment		Second year of treatment	
	Baseline ***N*** **= 15**	**Year 1 (*p**)** ***N*** **= 15**	**Baseline** ***N*** **= 9**	**Year 2 (*p**)** ***N*** **= 9**
AL RT[a]	265.17 ± 41.55	284.80 ± 63.93 (0.07)	275.39 ± 42.51	282.78 ± 47.98 (0.32)
AL RT cued[a]	266.47 ± 55.03	268.27 ± 33.95 (0.45)	270.67 ± 63.34	272.89 ± 35.06 (0.45)
Divid Att RT vis[a]	859.43 ± 161.07	827.73 ± 95.46 (0.15)	900.06 ± 194.25	**833.67 ± 140.78 (0.02)**
Divid Att RT aud[a]	604.93 ± 77.83	614.20 ± 80.100 (0.32)	613.00 ± 55.94	611.67 ± 58.51 (0.48)
Divid Att errors	1.40 ± 1.88	1.00 ± 1.06 (0.14)	1.44 ± 2.35	0.78 ± 1.64 (0.07)
Divid Att omissions	2.07 ± 1.98	**1.13 ± 1.12 (0.03)**	2.89 ± 2.03	1.44 ± 1.94 (0.04)
Flex RT[a]	867.81 ± 255.95	820.04 ± 227.88 (0.17)	964.50 ± 305.81	**762.14 ± 260.07 (0.03)**
Flex errors	2.85 ± 3.51	2.69 ± 2.52 (0.48)	3.14 ± 4.67	1.00 ± 0.82 (0.11)
Flex Perform Index	2.75 ± 4.38	−0.31 ± 9.11 (0.12)	4.48 ± 5.35	5.42 ± 6.37 (0.21)
SDMT	51.00 ± 4.24	52.50 ± 2.12 (0.25)		
WEIMuS	40.73 ± 8.75	39.18 ± 15.13 (0.35)	43.20 ± 10.37	35.40 ± 19.34 (0.27)
CES-D	**30.13 ± 6.26**	**24.00 ± 11.77 (0.02)**	**28.67 ± 4.35**	**18.44 ± 9.98 (0.01)**

[a] *In milliseconds (ms).*

All values are presented as means ± SD.

AL RT, alertness, reaction time; AL RT cued, alertness reaction time cued; Divid Att RT vis, divided attention reaction time visual; Divid Att RT aud, divided attention reaction time auditory; divid Att errors, divided attention errors; Divid Att ommisions, divided attention omission; Flex RT, flexibility reaction time; Flex errors, flexibility errors; Flex Perfom Index, flexibility performance index; SDMT, symbol digit modalities test; WEIMuS, Würzburg Fatigue Inventory for MS.

**p-value following paired sample t-test.*

The bold font indicates the statistical significant results.

literature and the improved depression. Three published studies have longitudinally assessed the effect of NTZ especially on fatigue as primary outcome variable (34, 36, 41).

Putzki et al. (36) described a contrary effect in comparison to the present data. In their study, an improvement in fatigue but not in depression was detected, however, over a shorter observational period of 6 months. In addition, other assessment tools (MFIS, FSS, BDI) were used, so that the results are not completely comparable to the present data. Especially, the BDI encompasses other aspects of depression as the CES-D. For patients with MS, the CES-D seems to be more appropriate. Furthermore, the different treatment periods with NTZ can be a reason for the different results. Against the background of learning effects, longer time periods for retesting are recommended.

Svenningson et al. (34) found in a considerably greater sample (195 patients), an improvement in fatigue over an observational period of 1 year. In this study comparable to the present study, the FSMC was used for assessing fatigue and the CES-D for evaluation of depression. Patients with a higher fatigue score and a lower depression score at baseline showed a stronger improvement after 12 months of treatment. Fatigue reduced from severe to moderate, according to the FSMC, a well reviewed fatigue scale in MS (55). Secondly and comparable to the present data, an improvement in depression was observed. The CES-D score improved from initially 18.3 before treatment to 14.2 after 12 months of treatment. Such a trend was also observed in the present study (decrease from 18.96 at baseline to 16.83 year 1).

In the study from Iffaldano et al. (41), 100 patients with RRMS were treated with NTZ over 2 years. As mentioned above, cognitive parameters were assessed by the BRB and Stroop paradigma, fatigue was measured with the FSS. Fatigue reduced from initially 45 (FSS = 4.01 ± 1.63) to 29% (FSS = 3.61 ± 1.56) after 1 year of treatment and from 52.8 [28 (53) patients] to 34% [18 (53) patients] in the second year. Regarding the cognition at baseline, 29% of patients were classified as cognitive impaired and failed at least in three tests of the BRB and Stroop test. After 1 year of treatment, the number of cognitive impaired patients decreased to 19%, and in the subgroup of patients with 2 years of treatment from initially 22.6 to 17%, which was statistical significant. In contrast to the present data, no effect was found in depression, measured again with the BDI.

Changes in fatigue as well as in cognition during 12 weeks of treatment were described also by Wilken et al. (35). They used three different fatigue assessment tools (MFIS, FSS, visual analog scale). The observed effect improved or remained stable up to 48 weeks after initiation of NTZ treatment.

The reason for the different fatigue results between the present data and previously published data can be the small sample sizes, especially in the second year of treatment in the present study as well as the different assessment periods of the used questionnaires. The WEIMuS evaluates the behavior only of the last week, whereas the FSMC use an overall assessment without time limit. However, in the literature, predominantly other assessment tools were used (FSS, MFIS) with again other assessment periods. The MFIS focuses on the last 4 weeks, the FSS asks for fatigue in general. Furthermore, there are differences in the content of the questionnaires. Whereas, the FSS focus on fatigue in general, the MFIS and FSMC ask for fatigue more specific, and may evaluate cognitive and physical fatigue separately. Therefore, the comparability of the published results is limited. Recently, the FSMC is the recommended questionnaire for assessment of fatigue in MS (55).

Other studies with different observational periods describe comparable to the present data, mostly a positive effect of NTZ on different aspects of cognition. Lang et al. (32) found significant improvements in cognition after 6 months of treatment with NTZ in a sample of 29 patients with RRMS. Mainly improvements

were detected in verbal and non-verbal memory, alertness, quality of life, depression, and fatigue. A total of 15 (30) assessed parameters improved over time, 15 remained equal. These results are comparable with another sample of 40 patients with RRMS (31), treated with NTZ over 6 months. Cognitive improvements were demonstrated by using a comprehensive cognitive battery. About 52.5% of all treated patients improved in cognition, 30% have shown no change, and 17.5% decreased in cognition. The authors mentioned a strong effect in cognition because of the small cohort. Therefore, they recommend the use of a comprehensive neuropsychological test battery to assess cognitive functions in MS, relating to the MACFIMS (56). Mattioli et al. (57) found improvements in memory and speed processing tasks after 2 years of treatment. In contrast, an addition to the data in the literature, the present study focused only on different aspect of attention but confirm presented results until now.

However, some limiting factors of the present study must be acknowledged. At first, the sample size in both observational periods is still small. Limiting factor of all described results from the literature, as well as from the present results, is the lack of control groups. From ethical point of view, there are many barriers for controlled observational studies to assess the effect of immunomodulatory treatments in patients with MS. To use a placebo or other drug, in comparison to a treatment group, have to be exactly examined ethically.

Furthermore, the comparison between NTZ and other immunomodulatory treatments is very difficult because of the different activity spectrum. Also, practice effects cannot be excluded. In the present study, the time difference between the measurement points is relatively long. Before each attention assessment, several practice trials were conducted to minimize practice effects. A recommendation for controlling the practice effect is an optimal test selection and timing of testing with a repetitive cognitive testing after a longer time periods, e.g., 6 and 12 months (58). A repetitive testing in healthy adults with the subtests alertness and flexibility (TAP) after 6 and 12 months was not significantly improved (58). Therefore, the present data can be evaluated as improvement. The results on the depressed subgroup may be affected by the regression to the mean phenomenon.

In summary, the results of this retrospective open label observational study show a positive effect of NTZ on different aspects of attention and depression in patients with highly active RRMS after 1 year of treatment. The effects were stable also in a subgroup of patients after 2 years of treatment. No effect was detected in fatigue most likely because of the small sample size or the different assessment tools. Despite, fatigue patients improved in information processing speed, divided attention, and cognitive flexibility as well as in the degree of depression. Treatment with NTZ over longer periods may stabilize or improve different aspects of cognition and mood. The observed changes were clinically relevant. Patients reflected more balance, a better mood, lower sadness, a more restful sleep and more power for daily activities, and hobbies. They were more efficient in daily life, showed a better participation in social life, and were able to work again in their profession or a mini-job. The presented results confirm and expand previous published data especially for longer treatment periods. For the clinical practice, a regularly assessment of cognition, mood, and fatigue during the treatment period with NTZ is recommended for detecting improvement as well as regarding the PML risk. For a better comparison between study results, a uniform assessment procedure for the cognitive testing, while treatment with NTZ, and the evaluation of fatigue and depression are needed. Until now for the evaluation of fatigue, the FSMC is recommended (55).

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References

1. Kinsinger SW, Lattie E, Mohr DC. Relationship between depression, fatigue, subjective cognitive impairment, and objective neuropsychological functioning in patints with multiple sclerosis. *Neuropsychology* (2010) **24**(5):573–80. doi:10.1037/a0019222
2. Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. *Mult Scler* (2003) **9**(3):219–27. doi:10.1191/1352458503ms904oa
3. Krupp L. Fatigue is intrinsic to multiple sclerosis (MS) and is the most commonly reported symptom of the disease. *Mult Scler* (2006) **12**:367–8. doi:10.1191/135248506ms1373ed
4. Lerdal A, Celius EG, Krupp L, Dahl AA. A prospective study of patterns of fatigue in multiple sclerosis. *Eur J Neurol* (2007) **14**:1338–48. doi:10.1111/j.1468-1331.2007.01974.x
5. Janardha V, Bakshi R. Quality of life in patients with multiple sclerosis: the impact of fatigue and depression. *J Neurol Sci* (2002) **205**:51–8. doi:10.1016/S0022-510X(02)00312-X
6. Braley TJ, Chervin RD. Fatigue in multiple sclerosis: mechanisms, evaluation and treatment. *Sleep* (2010) **33**(8):1061–7.
7. van Kessel K, Moss-Morris R. Understanding multiple sclerosis fatigue: a synthesis of biological and psychological factors. *J Psychosom Res* (2006) **61**:5583–5. doi:10.1016/j.jpsychores.2006.03.006
8. Langdon DW. Cognition in multiple sclerosis. *Curr Opin Neurol* (2011) **24**:244–9. doi:10.1097/WCO.0b013e328346a43b
9. Potagas C, Giogkaraki E, Koutsis G, Mandellos D, Tsirempolou E, Sfagos C, et al. Cognitive impairment in different MS subtypes and clinically isolated syndromes. *J Neurol Sci* (2008) **267**:100–6. doi:10.1016/j.jns.2007.10.002
10. Glanz BI, Healy BC, Hviid LE, Chitnis T, Weiner HL. Cognitive deterioration in patients with early multiple sclerosis. *J Neurol Neurosurg Psychiatry* (2012) **83**:38–43. doi:10.1136/jnnp.2010.237834
11. Faiss JH, Dähne D, Baum K, Deppe R, Hoffmann F, Köhler W, et al. Reduced magnetisation transfer ratio in cognitively impaired patients at the very early stage of multiple sclerosis: a prospective, multicenter, cross-sectional study. *BMJ Open* (2014) **4**:e004409. doi:10.1136/bmjopen-2013-004409
12. Cameron MH, Peterson V, Boudreau E, Downs A, Lovera J, Kim E, et al. Fatigue is associated with poor sleep in people with multiple sclerosis and cognitive impairment. *Mult Scler Int* (2014) **2014**:872732. doi:10.1155/2014/872732
13. Andreasen AK, Spliid PE, Andersen H, Jakobsen J. Fatigue and processing speed are related in multiple sclerosis. *Eur J Neurol* (2010) **17**:212–8. doi:10.1111/j.1468-1331.2009.02776.x
14. Jougleux-Vie C, Duhin E, Deken V, Outteryck O, Vermersch P, Zéphir H. Does fatigue complaint reflect memory impairment in multiple sclerosis? *Mult Scler Int* (2014) **2014**:692468. doi:10.1155/2014/692468
15. Amato MP, Zipoli V, Portaccio E. Cognitive changes in multiple sclerosis. *Expert Rev Neurother* (2008) **8**:1585–96. doi:10.1586/14737175.8.10.1585
16. Fischer M, Kunkel A, Bublak P, Faiss JH, Hoffmann F, Sailer M. How reliable is he classification of cognitive impairment across different criteria in early and

late stages of multiple sclerosis? *J Neurol Sci* (2014) **343**:91–9. doi:10.1016/j.jns.2014.05.042
17. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol* (2008) **7**:1139–51. doi:10.1016/S1474-4422(08)70259-X
18. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. frequency, patterns, and prediction. *Neurology* (1991) **41**:685–91. doi:10.1212/WNL.41.5.685
19. Feinstein A. Mood disorders in multiple sclerosis and the effects on cognition. *J Neurol Sci* (2006) **245**:63–6. doi:10.1016/j.jns.2005.08.020
20. Feinstein A. Multiple sclerosis and depression. *Mult Scler* (2011) **17**:1276–81. doi:10.1177/1352458511417835
21. Patrick E, Christodoulou C, Krupp LB. Longitudinal correlates of fatigue in multiple sclerosis. *Mult Scler* (2009) **15**:258–61. doi:10.1177/1352458508097466
22. Amato MP, Langdon D, Montalban X, Benedict RHB, DeLuca J, Krupp LB, et al. Treatment of cognitive impairment in multiple sclerosis: position paper. *J Neurol* (2013) **260**:1452–68. doi:10.1007/s00415-012-6678-0
23. Comi G. Effects of disease modifying treatments on cognitive dysfunction in multiple sclerosis. *Neurol Sci* (2010) **31**(Suppl 2):261–4. doi:10.1007/s10072-010-0436-9
24. Patti F, Leone C, D'Amico E. Treatment options of cognitive impairment in multiple sclerosis. *Neurol Sci* (2010) **31**(Suppl 2):265–9. doi:10.1007/s10072-010-0438-7
25. Metz LM, Patten SB, Archibald CJ, Bakker JI, Harris CJ, Patry DG, et al. The effect of immunmodulatory treatment on multiple sclerosis fatigue. *J Neurol Neurosurg Psychiatry* (2004) **75**:1045–7. doi:10.1136/jnnp.2002.007724
26. Kim S, Foley FW, Picone MA, Halper J, Zemon V. Depression levels and interferon treatment in people with multiple sclerosis. *Int J MS Care* (2012) **14**:10–6. doi:10.7224/1537-2073-14.1.10
27. Galeazzi GM, Ferrari S, Giaroli G, Mackinnon A, Merelli E, Motti L, et al. Psychiatric disorders and depression in multiple sclerosis outpatients: impact of disability and interferon beta therapy. *Neurol Sci* (2005) **26**:255–62. doi:10.1007/s10072-005-0468-8
28. Simone IL, Ceccarelli A, Tororella C, Bellacosa A, Pellegrini F, Plasmati I, et al. Influence of interferon beta treatment on quality of life in multiple sclerosis patients. *Health Qual Life Outcomes* (2006) **4**:96. doi:10.1186/1477-7525-4-96
29. Polman CH, O'Connor PW, Havdrova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* (2006) **354**:899–910. doi:10.1056/NEJMoa044397
30. Havdrova E, Galetta S, Hutchinson M, Stefoski D, Bates D, Polman CH, et al. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the natalizumab safety and efficiacy in relapsing-remitting multiple sclerosis (AFFIRM) study. *Lancet Neurol* (2009) **8**:254–60. doi:10.1016/S1474-4422(09)70021-3
31. Edwards KR, Goodman WA, Ma CY. Improvement of neuropsychological function in cognitively impaired multiple sclerosis patients treated with natalizumab. *Int J MS Care* (2012) **14**:100–4. doi:10.7224/1537-2073-14.2.100
32. Lang C, Reiss C, Mäurer M. Natalizumab may improve cognition and mood in multiple sclerosis. *Eur Neurol* (2012) **67**:162–6. doi:10.1159/000334722
33. Mattioli F, Stampatori C, Capra R. The effect of natalizumab on cognitive function in patients with relapsing-remitting multiple sclerosis: preliminary results of a 1-year follow-up study. *Neurol Sci* (2011) **32**:83–8. doi:10.1007/s10072-010-0412-4
34. Svenningsson A, Falk E, Celuis EG, Fuchs S, Schreiber K, Berkö S. Natalizumab treatment reduces fatigue in multiple sclerosis. Results from the TYNERGY trial; a study in the real life setting. *Plos One* (2013) **8**(3):e58643. doi:10.1371/journal.pone.0058643
35. Wilken J, Kane RL, Sullivan CL, Gudesblatt M, Lucas S, Falli R, et al. Changes in fatigue and cognition in patients with relapsing forms of multiple sclerosis treated with natalizumab. *Int J MS Care* (2013) **15**:120–8. doi:10.7224/1537-2073.2012-043
36. Putzki N, Yaldizli Ö, Tettenborn B, Diener HC. Multiple sclerosis associated fatigue during natalizumab treatment. *J Neurol Sci* (2009) **285**:109–13. doi:10.1016/j.jns.2009.06.004
37. Beramaschi R, Romai A, Versino M, Poil R, Cosi V. Clinical aspects of fatigue in multiple sclerosis. *Funct Neurol* (1997) **12**:247–51.
38. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with mutiple sclerosis and systemic lupus erythematosus. *Arch Neurol* (1989) **46**:1121–3. doi:10.1001/archneur.1989.00520460115022
39. Beck AT, Ward CH, Medelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* (1961) **4**:561–71. doi:10.1001/archpsyc.1961.01710120031004
40. Penner IK, Raselli C, Stocklin M, Opwis K, Kappos L, Calabrese P. The fatigue scale for motor and cognitve functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult Scler* (2009) **15**:1509–17. doi:10.1177/1352458509348519
41. Iffaldano P, Viterbo RG, Paolicelli D, Lucchese G, Portaccio E, Goretti B, et al. Impact of natalizumab on cognitive performances and fatigue in relapsing multiple sclerosis. A prospective, open-label, two years observational study. *PLoS One* (2012) **7**(4):e35843. doi:10.1371/journal.pone.0035843
42. Amato MP, Portaccio E, Goretti B, Zipoli V, Ricchiuti L, deCaro MF, et al. The Rao's brief repeatable battery and stroop test: normative values with age, education and gender correction in an Italian population. *Mult Scler* (2006) **12**:787–93. doi:10.1177/1352458506070933
43. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* (2011) **69**:292–302. doi:10.1002/ana.22366
44. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* (1983) **33**:1444–52. doi:10.1212/WNL.33.11.1444
45. Flachenecker P, Müller G, König H, Meissner H, Toyka KV, Rieckmann P. Fatigue "in multiple sclerosis. Development and validation of the" Würzburger fatigue inventory for MS. *Nervenarzt* (2006) **77**:165–74. doi:10.1007/s00115-005-1990-x
46. Radloff L. The CES-D sclae. A self-report depression scale for research in the general population. *Appl Psychol Meas* (1977) **1**:385–401. doi:10.1177/014662167700100306
47. Hautzinger M, Bailer M, Hofmeister D, Keller F. *ADS Allgemeine Depressionsskala*. Göttingen: Hogrefe (2012).
48. Zimmermann P, Fimm B. *Testbatterie zur Aufmerksamkeitsprüfung, Version 2.2*. Herzogenrath: Psychologische Testsysteme Vera Fimm (2009).
49. Smith A. *Symbol Digit Modalities Test*. Los Angeles: Western Psychological Services (2000).
50. Helmstaedter C, Lendt M, Lux S. *Verbaler Lern- und Merkfähigkeitstest: VLMT, Manual*. Weinheim: Beltz-Test (2001).
51. Wolfram H, Neumann J, Wieczorek V. *Psychologische Leistungstests der Neurologie und Psychiatrie*. 2nd ed. Leipzig: Thieme (1989). p. 89–102.
52. Strauss E, Sherman EMS, Spreen O. *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. 3rd ed. Oxford: Oxford University Press (2006).
53. Aschenbrenner S, Tucha O, Lange KW. *Regensburger Wortflüssigkeits-Test, Handanweisung*. Göttingen: Hogrefe (2000).
54. Schmidt KH, Metzler P. *Wortschatztest*. Weinheim: Beltz Test (1992).
55. Elbers RG, Rietberg BM, van Wegen EEH, Verhoef J, Kramer SF, Terwee CB. Self-report fatigue questionnaires in multiple sclerosis, Parkinson's disease and stroke: a systematic review of measurement properties. *Qual Life Res* (2012) **21**:925–44. doi:10.1007/s11136-011-0009-2
56. Benedict RH, Fischer JS, Archibald CJ, Arnett PA, Beatty WW, Bobholz J, et al. Minimal neuropsychological assessment of MS patients. a consensus approach. *Clin Neuropsychol* (2002) **16**:381–97. doi:10.1076/clin.16.3.381.13859
57. Mattioli F, Stampatori C, Bemmomi F, Capra R. Natalizumab efficiacy on cognitive impairment in MS. *Neurol Sci* (2001) **31**(Suppl 3):S321–3. doi:10.1007/s10072-010-0351-0
58. Bartels C, Wegrzyn M, Wiedl A, Ackermann V, Ehrenreich H. Practise effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing. *BMC Neurosci* (2010) **11**:118. doi:10.1186/1471-2202-11-118

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Improvement in fatigue during natalizumab treatment is linked to improvement in depression and day-time sleepiness

Iris-Katharina Penner[1]*, Eva Catharina Sivertsdotter[2], Elisabeth G. Celius[3], Siegrid Fuchs[4], Karen Schreiber[5], Sara Berkö[6] and Anders Svenningsson[7], for the TYNERGY trial investigators[†]

[1] *Department of Cognitive Psychology and Methodology, University of Basel, Basel, Switzerland*
[2] *BiogenIdec Sweden AB, Upplands Väsby, Sweden (formerly employed)*
[3] *Department of Neurology, Oslo University Hospital, Ullevål, Norway*
[4] *Department of Neurology, Medical University of Graz, Graz, Austria*
[5] *Department of Neurology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark*
[6] *BiogenIdec Sweden AB, Upplands Väsby, Sweden*
[7] *Department of Pharmacology and Clinical Neuroscience, University Hospital of Northern Sweden, Umeå University, Umeå, Sweden*

Edited by:
Christian Dettmers, Kliniken Schmieder Konstanz, Germany

Reviewed by:
Timo Partonen, National Institute for Health and Welfare, Finland
Herbert Schreiber, Neuro Trans Data (NTD) Study Group on Multiple Sclerosis, Germany

****Correspondence:***
Iris-Katharina Penner, University of Basel, Missionsstrasse 60/62, Basel 4055, Switzerland
e-mail: ik.penner@unibas.ch

[†]Trial investigators are listed in Acknowledgments at the end of the paper.

Background: Fatigue is a frequent symptom in multiple sclerosis (MS) and often interrelated with depression and sleep disorders making symptomatic treatment decisions difficult. In the single-arm, observational phase IV TYNERGY study, relapsing–remitting MS patients showed a clinically meaningful decrease in fatigue over 1 year of treatment with natalizumab.

Objective: To evaluate whether fatigue improvement might be directly linked to improved depression and day-time sleepiness.

Methods: Patients were assessed regarding fatigue, depression, and day-time sleepiness. The relation between changes of the two latter symptoms and changes in fatigue was analyzed.

Results: After 1 year of natalizumab treatment, the majority of patients (>92%) remained stable or improved in total, motor, and cognitive fatigue. Proportion of patients without depression increased by 17% while proportions of mildly depressed patients or patients with potential major depression decreased by 5 and 12%, respectively. Proportion of patients classified as not being sleepy increased by 13% while proportions of sleepy and very sleepy patients decreased by 11 and 2%, respectively. Most importantly, improved depression and sleepiness were significantly related to improved fatigue.

Conclusion: Our findings highlight the importance of patient-reported outcomes in identifying potential benefits of drug treatment beyond its well-established effects on disease activity and disability progression.

Keywords: fatigue, multiple sclerosis, treatment response, depression, sleepiness

INTRODUCTION

Fatigue is defined as an extreme form of exhaustion with obvious negative effects on quality of life. With a prevalence ranging between 53 and 95% (1, 2), it is the most frequent "hidden symptom" in multiple sclerosis (MS). Often, fatigue symptoms force individuals to substantially reduce their workload or to even quit their occupation completely. There is evidence that MS-fatigue is strongly related to depression and sleep disorders (3, 4) although the underlying pathophysiological processes are still not completely understood. From the patient's perspective, these factors are of particular importance in the context of the overall burden of the disease. However, effective symptomatic treatment specifically for fatigue is still missing, leaving the patient with feelings of helplessness, and the physician unsatisfied.

Patients suffering from obvious fatigue symptoms are often treated with antidepressants, most likely efficacious, partly due to the strong association between depression and fatigue. Further, modafinil, amantadine, and aminopyridine are known as treatment options although the therapeutic efficacy is still a matter of debate.

In terms of MS disease-modifying drugs (DMTs), there are no conclusive data available regarding their efficacy on fatigue symptoms. Studies using first generation DMTs, e.g., interferon (IFN) and glatiramer acetate (GA) have yielded divergent results (5–8) while two recent publications on the impact of natalizumab on fatigue (9, 10) showed significant improvement of symptoms after a 1- and 2-year follow-up period, respectively.

In the prospective, multicentre, open-label, observational phase IV TYNERGY study, patients with relapsing-remitting MS

(RRMS) who were naïve to natalizumab treatment at baseline experienced improvement in MS-related fatigue (primary efficacy endpoint) over 1 year of treatment (10). The present data analysis was focused especially on the question whether the amount of fatigue improvement was directly linked to improvements in depression and day-time sleepiness.

MATERIALS AND METHODS

PARTICIPANTS

Eligible patients were prescribed natalizumab according to national guidelines, were 18–65 years old (inclusive) at screening, and presented with at least mild fatigue {as determined by the Fatigue Scale for Motor and Cognitive Functions [FSMC (11)] sum score of ≥43; see **Table 1**}. Patients who had no symptoms of fatigue (i.e., had an FSMC total score <43 at baseline), had an Expanded Disability Status Scale (EDSS) score ≥6.0, were receiving amphetamine medication, or had major depression (assessed by clinical interview of the patient and review of the medical records) were excluded from the study.

The intent-to-treat population (ITT) included all enrolled patients ($N = 195$). A total of 31 withdrawals occurred over the trial period, leaving 164 patients who completed the trial. More than two-thirds of the 195 patients were female (71.3%) (**Table 2**). At baseline, the average age was 39.7 years, and the average duration of MS was 8.8 years. The median EDSS score at baseline was 3.0, and two-thirds of the patients experienced a relapse within 6 months prior to the baseline visit. Most patients (86%) had previously received disease-modifying therapy; a third of the patients (31%) had received interferon (IFN) beta in the month prior to inclusion in TYNERGY.

The study was conducted in compliance with Good Clinical Practices (GCP) and the Declaration of Helsinki, and was approved by the institutional ethical review board at the University Hospital of Northern Sweden, Umeå. Consecutive patients prescribed natalizumab at the participating centers gave their written, informed consent to enter the study after the therapy decision was made.

STUDY DESIGN

The TYNERGY study used a one-armed trial design to primarily evaluate the change in fatigue after 1 year of natalizumab treatment with a well-defined and validated instrument, the FSMC, designed for use in MS patients. Cut-off values for the clinical categories mild, moderate, and severe MS-related fatigue are shown in **Table 1**.

Besides fatigue, other important aspects that may have an important effect on functioning and well being of MS patients were assessed at baseline, at month 6, and at month 12. They were: work capacity (assessed by the Capacity for Work Questionnaire – CWQ), health related quality of life (HRQoL), sleepiness, depression, cognitive impairment (assessed by the Symbol Digit Modalities Test – SDMT, and the Paced Auditory Serial Addition Test – PASAT), walking speed, MS disease disability, and overall activity using a step counter that was worn for 7 days the week before the study visit.

The DMTs used prior to initialization of natalizumab were documented. All concomitant medications taken during the trial were recorded and special attention was paid to change in symptomatic fatigue therapy, e.g., modafinil and amantadine. Information on relapses, adverse events (AEs), and serious adverse events (SAEs) were collected.

The first patient's first visit was on March 23, 2009 and the last patient's last visit on June 30, 2011. EudraCT number for the Swedish protocol: 2008-008065-35. Clinical Trials.gov identifier: NCT00884481. The study was considered observational in Austria, Norway, and Denmark.

The study was performed at 27 centers: 12 in Sweden, 7 in Norway, 5 in Austria, and 3 in Denmark. Patients were scheduled for five assessment visits (baseline and at months 3, 6, 9, and 12) over a period of 12 months.

Results have been described in detail elsewhere (10).

ASSESSMENT INSTRUMENTS

Fatigue was assessed by the FSMC, a validated 20-item questionnaire specifically developed for MS patients. The FSMC allows separate evaluation of motor and cognitive fatigue and clinical grading of fatigue severity.

Depression was measured by the Center for Epidemiologic Studies Depression Scale (CES-D). The CES-D is a short

Table 1 | FSMC cut-off values.

Score/subscore	Cut-off value	Grading of fatigue
FSMC sum (total) score	≥43	Mild fatigue
	≥53	Moderate fatigue
	≥63	Severe fatigue
FSMC cognitive score	≥22	Mild cognitive fatigue
	≥28	Moderate cognitive fatigue
	≥34	Severe cognitive fatigue
FSMC motor score	≥22	Mild motor fatigue
	≥27	Moderate motor fatigue
	≥32	Severe motor fatigue

Table 2 | Demographics and baseline characteristics.

Variable	Total ITT population ($N = 195$)
Gender, female, *n* (%)	139 (71.3)
Race, white, *n* (%)	188 (96.4)
Age (years)	
Mean (SD)	39.7 (9.2)
Median	39.9
Min, Max	18.3, 63.8
EDSS score, median (range)	3.0 (0.0–7.0)
Received IFN beta therapy in month prior to TYNERGY, *n* (%)	61 (31.3)
Duration of MS (years)	
Mean (SD)	8.8 (7.0)
Median	6.7
Min, Max	0.2, 30.5

SD, standard deviation.

self-report scale designed to measure depressive symptomatology in the general population. It consists of 20 questions and scores ranging from 0 to 60: a score <15, no depression; A score 15–21, mild-to-moderate depression; A score >21, possibility of major depression.

Day-time sleepiness was assessed by the Epworth Sleepiness Scale (ESS) for day-time sleepiness. The ESS is a short, eight-item questionnaire designed to determine the level of day-time sleepiness. Scores range from 0 to 24: a score in the 0–9 range is considered normal. A score in the 10–24 range indicates that expert medical advice should be sought. A score of ≥10 is considered sleepy. A score of ≥18 is considered very sleepy.

STATISTICAL ANALYSES

Statistical analyses were based on pooled datasets from all participating countries. All statistical tests were two-sided with a 5% level of significance unless otherwise stated. Fatigue was classified as mild, moderate, or severe, according to the FSMC score cut-off values listed in **Table 1**. On the basis of FSMC scores at 1 year, patients were categorized into three groups:

- Worsened fatigue (a shift to higher fatigue classifications, e.g., moderate to severe);
- Stable fatigue (no change in fatigue classification);
- Improved fatigue (a shift to lower fatigue classifications, e.g., moderate to mild).

Correlations between changes in FSMC motor and cognitive sub-scores and changes in CES-D and ESS scores were evaluated using Pearson correlation coefficients. Associations between FSMC status (worsened, stable, or improved) and changes in CES-D and ESS at 1 year were assessed by analysis of covariance, with adjustment for baseline scores and antidepressant use.

All statistical analysis and programing were done using SAS v9.2.

RESULTS

CHANGES IN FATIGUE

After 1 year of natalizumab treatment, the majority of patients remained stable or improved in FSMC total (96%), motor (97%), and cognitive (92%) scores (10) (see **Figure 1**).

CHANGES IN DEPRESSION AND ASSOCIATION WITH CHANGES IN FATIGUE SCORES

The proportion of patients with no depression increased by 17%, while proportions of patients mildly to moderately depressed or with potential major depression decreased by 5 and 12%, respectively (**Figure 2**). CES-D score changes differed among worsened, stable, and improved FSMC total/subscale subgroups ($P < 0.01$), with greatest improvements in patients with improved FSMC scores (**Figure 3**). Improved FSMC total, motor, and cognitive scores were associated with improved mood (correlation coefficients = 0.45, 0.39, 0.47, respectively, $P < 0.01$).

CHANGES IN SLEEPINESS AND ASSOCIATION WITH CHANGES IN FATIGUE SCORES

The proportion of patients classified as not sleepy on ESS increased by 13%. Proportions of patients classified as sleepy or very sleepy decreased by 11 and 2%, respectively (**Figure 4**).

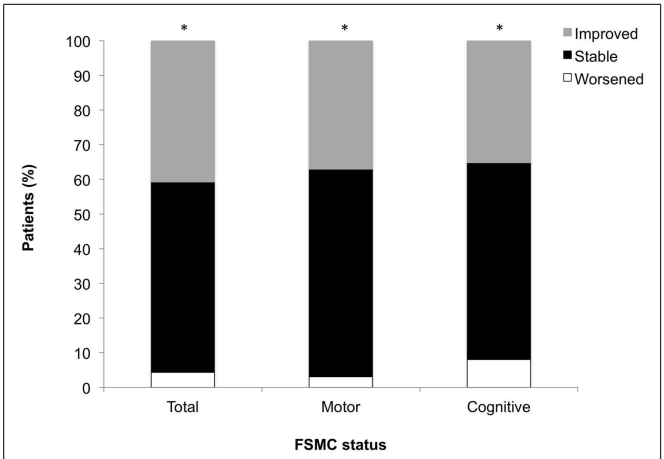

FIGURE 1 | Changes from baseline in total, motor, and cognitive FSMC scores. *$P < 0.001$ across status groups (worsened, stable, improved). Worsened = shift to higher fatigue classification; stable = no change in fatigue classification; improved = shift to lower fatigue classification.

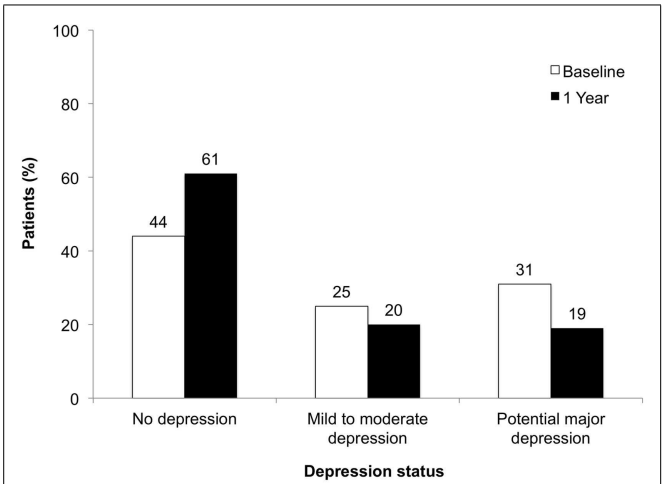

FIGURE 2 | Depression status at baseline and at 1 year of follow-up.

Improvement in FSMC total, motor, and cognitive scores was associated with improved ESS scores (correlation coefficients = 0.44, 0.37, 0.46, respectively, $P < 0.01$). ESS-score changes differed among worsened, stable, and improved total/subscale FSMC subgroups ($P < 0.01$), with greatest improvements in patients with improved FSMC scores (**Figure 5**).

DISCUSSION

The present data analysis was focused on the association between already reported clinically meaningful changes in MS-fatigue under natalizumab treatment (10) and strongly associated factors such as depression and day-time sleepiness.

Our results clearly demonstrate that natalizumab-treated MS patients in TYNERGY exhibited not only improvements in fatigue but also in depression, and day-time sleepiness from baseline to year 1. Measures of total, motor, and cognitive fatigue were stable

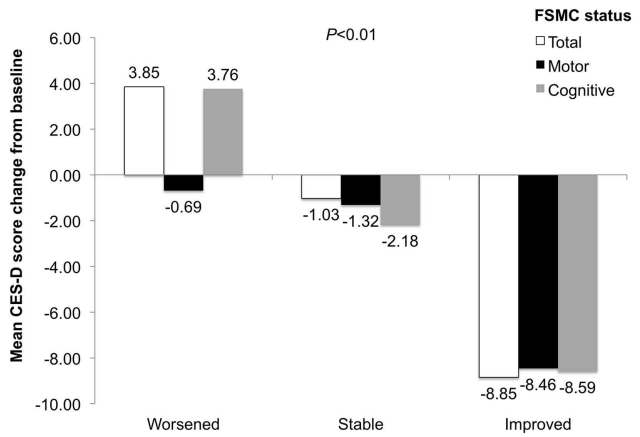

FIGURE 3 | CES-D score change in patients with worsened, stable, and improved FSMC total, motor, and cognitive scores. *P* value is for comparison across subgroups of worsened, stable, and improved.

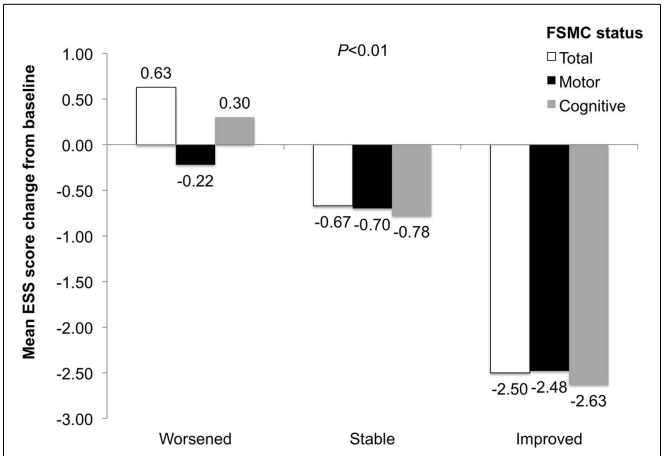

FIGURE 5 | ESS-score change in patients with worsened, stable, and improved FSMC total, motor, and cognitive scores. *P* value is for comparison across subgroups of worsened, stable, and improved.

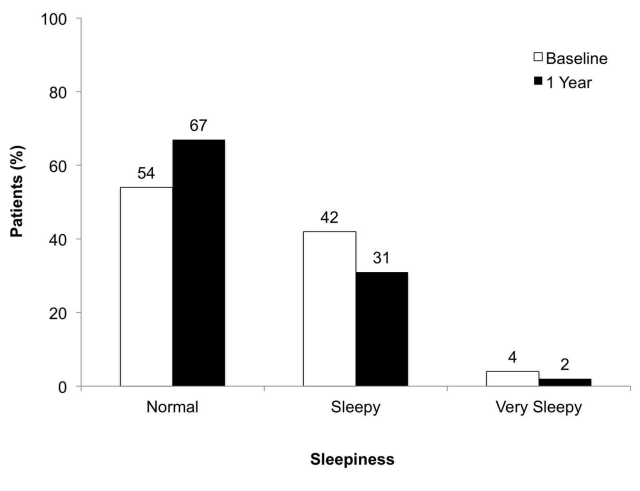

FIGURE 4 | Degree of sleepiness at baseline and at 1 year of follow-up.

or improved in more than 90% of patients, all of whom had at least mild fatigue at baseline. This large beneficial effect on fatigue symptoms is most likely referable to the high anti-inflammatory efficacy of the drug and the lack of specific side-effects, which are discussed to increase fatigue.

Although patients with major depressive disorder were excluded from the study, 56% of patients had some degree of depression at baseline. After 1 year of natalizumab treatment, the proportion of patients categorized as depressed had decreased to 39%. Mean CES-D scores decreased (improved) by as much as 8.85 points from baseline. This absolute change is greater than the six-point difference between the pre-specified categories of mild-to-moderate depression and possible major depression, suggesting that the absolute score changes observed were clinically meaningful.

The proportion of patients with some degree of sleepiness decreased from 46% at baseline to 33% at year 1. In contrast to the change in depressive symptoms, the absolute changes in ESS scores were smaller than the change of at least eight points that would be needed to shift between categories of sleepiness. The reason for this discrepancy remains unclear. One might assume that the mechanisms underlying sleepiness are more specific than those causing depression. For depression and fatigue, some pathophysiological similarities such as disturbed serotonergic neurotransmission have been reported [e.g., Hanley and Van de Kar (12)]. For Fatigue and sleep disorders, we have evidence of an interrelation (13). The underlying processes, however, are still unknown.

We are aware that an observational trial always runs the risk of influence by a placebo effect, when starting a new and more efficient treatment. However, since all scales displayed highly significant improvements with an additional increase over time, this argument is not likely to be major in explaining our results.

Besides these promising results, we are aware of limitations that need to be addressed. First, the TYNERGY trial lacks of a control group showing that the reported effects are purely driven by the drug. At the time of study start, there was no other second-line treatment available and it was regarded as unethical to include a control arm since all patients had high disease activity. Second, we were not able to study a causal relation among fatigue, depression, and sleepiness but only relations or associations. Nonetheless, it is of clinical importance to realize that improved fatigue symptoms are associated with an increase of patients' well being in terms of decreased levels of depression and sleepiness. Third, our study was primarily focused on patient-reported outcomes since these tools offer insight into patients' view and feelings. We did not control for important confounders such as cytokine influence, which is known to be modulated by natalizumab (14) nor did we control for concomitant medication influence. Finally, the fact that more than 30% of our patients received IFNs prior to study inclusion might have driven in part the effects documented under natalizumab treatment. However, when controlling for different previous treatments, the effect of natalizumab on fatigue remained stable speaking in favor of a therapeutic effect.

CONCLUSION

Improvement in fatigue, as measured by decreasing total, motor, and cognitive FSMC scores, was associated with improvement of depression status measured by CES-D and improvement of sleepiness status measured by ESS.

While additional research is needed to elucidate a causal relationship among fatigue, depression, and sleepiness in MS, these findings from TYNERGY highlight the important role of patient-reported outcomes in identifying potential benefits of natalizumab treatment beyond its well-established effects on disease activity and disability progression.

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REFERENCES

1. Amato MP, Portaccio E. Management options in multiple sclerosis-associated fatigue. *Expert Opin Pharmacother* (2012) **13**(2):207–16. doi:10.1517/14656566.2012.647767
2. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. *Can J Neurol Sci* (1994) **21**:9–14.
3. Bakshi R, Shaikh ZA, Miletich R, Czarnecki D, Dmochowski J, Henschel K, et al. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. *Mult Scler* (2000) **6**:181–5. doi:10.1191/135245800701566052
4. Veauthier C, Radbruch H, Gaede G, Pfueller CF, Dörr J, Bellmann-Strobl J, et al. Fatigue in multiple sclerosis is closely related to sleep disorders: a polysomnographic cross-sectional study. *Mult Scler* (2011) **17**(5):613–22. doi:10.1177/1352458510393772
5. Melanson M, Grossberndt A, Klowak M, Leong C, Frost EE, Prout M, et al. Fatigue and cognition in patients with relapsing multiple sclerosis treated with interferon beta. *Int J Neurosci* (2010) **120**(10):631–40. doi:10.3109/00207454.2010.511732
6. Metz LM, Patten SB, Archibald CJ, Bakker JI, Harris CJ, Patry DG, et al. The effect of immunomodulatory treatment on multiple sclerosis fatigue. *J Neurol Neurosurg Psychiatry* (2004) **75**(7):1045–7. doi:10.1136/jnnp.2002.007724
7. Patti F, Amato MP, Trojano M, Bastianello S, Tola MR, Picconi O, et al. Quality of life, depression and fatigue in mildly disabled patients with relapsing-remitting multiple sclerosis receiving subcutaneous interferon beta-1a: 3-year results from the COGIMUS (COGnitive Impairment in MUltiple Sclerosis) study. *Mult Scler* (2011) **17**(8):991–1001. doi:10.1177/1352458511401943
8. Ziemssen T, Hoffman J, Apfel R, Kern S. Effects of glatiramer acetate on fatigue and days of absence from work in first-time treated relapsing-remitting multiple sclerosis. *Health Qual Life Outcomes* (2008) **6**:67. doi:10.1186/1477-7525-6-67
9. Iaffaldano P, Viterbo RG, Paolicelli D, Lucchese G, Portaccio E, Goretti B, et al. Impact of natalizumab on cognitive performances and fatigue in relapsing multiple sclerosis: a prospective, open-label, two years observational study. *PLoS One* (2012) **7**(4):e35843. doi:10.1371/journal.pone.0035843
10. Svenningsson A, Falk E, Celius EG, Fuchs S, Schreiber K, Berkö S, et al. Natalizumab treatment reduces fatigue in multiple sclerosis. Results from the TYNERGY trial; a study in the real life setting. *PLoS One* (2013) **8**(3):e58643. doi:10.1371/journal.pone.0058643
11. Penner IK, Raselli C, Stöcklin M, Opwis K, Kappos L, Calabrese P. The fatigue scale for motor and cognitive functions (FSMC) – validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult Scler* (2009) **15**(12):1509–17. doi:10.1177/1352458509348519
12. Hanley NR, Van de Kar LD. Serotonin and the neuroendocrine regulation of the hypothalamic – pituitary-adrenal axis in health and disease. *Vitam Horm* (2003) **66**:189–255. doi:10.1016/S0083-6729(03)01006-9
13. Veauthier C, Paul F. Sleep disorders in multiple sclerosis and their relationship to fatigue. *Sleep Med* (2014) **15**(1):5–14. doi:10.1016/j.sleep.2013.08.791
14. Mellergard J, Edström M, Vrethem M, Ernerudh J, Dahle C. Natalizumab treatment in multiple sclerosis: marked decline of chemokines and cytokines in cerebrospinal fluid. *Mult Scler* (2010) **16**(2):208–17. doi:10.1177/1352458509355068

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Management of fatigue in persons with multiple sclerosis

Fary Khan[1,2,3]*, Bhasker Amatya[1] and Mary Galea[1,2]

[1] *Department of Rehabilitation Medicine, Royal Melbourne Hospital, Melbourne, VIC, Australia*
[2] *The University of Melbourne, Melbourne, VIC, Australia*
[3] *School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia*

Edited by:
Christian Dettmers, Kliniken Schmieder Konstanz, Germany

Reviewed by:
Thomas Henze, Reha Zentrum Nittenau, Germany
Claude Vaney, Berner Klinik Montana, Switzerland

****Correspondence:***
Fary Khan, Department of Rehabilitation Medicine, Royal Melbourne Hospital, Poplar Road, Parkville, Melbourne, VIC 3052, Australia
e-mail: fary.khan@mh.org.au

Fatigue is one of the most common symptoms of multiple sclerosis. Despite advances in pharmacological and non-pharmacological treatment, fatigue continues to be the disabling symptom in persons with MS (pwMS), affecting almost 80% of pwMS. In current practice, both pharmacological and non-pharmacological interventions are used in combination, encompassing a multi-disciplinary approach. The body of research investigating the effect of these interventions is growing. This review systematically evaluated the existing evidence on the effectiveness and safety of different interventions currently applied for the management of fatigue in person with multiple sclerosis in improving patient outcomes, to guide treating clinicians.

Keywords: multiple sclerosis, fatigue, disability, rehabilitation outcomes, symptomatic treatment

BACKGROUND

Multiple sclerosis (MS), a chronic progressive demyelinating disease of the central nervous system (CNS), is the commonest cause of chronic neurological disability in young adults (1, 2). It affects approximately 2.5 million persons worldwide and the prevalence of MS in Australia is estimated to be over 20,000 (95.2 per 100,000) persons (2, 3). MS is complex and the exact pathogenesis is unclear. Fatigue is one of the most common symptoms of MS, affecting almost 80% of persons with MS (pwMS) (2), with 55% of pwMS describing it as one of the worst symptoms they experience (1). Fatigue is defined as "*a subjective lack of physical or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities*" (4). The definitive cause of fatigue in MS is currently unknown, however, it is postulated that MS-related fatigue may result from centrally mediated processes characterized by MS itself, such as demyelination and axonal loss in the CNS or immune actions (*Primary fatigue*) or from MS-related complications (trigeminal neuralgia, spasms, psychological issues, etc.), musculoskeletal problems (pain, posture, gait anomalies, etc.), sleep problems, and medications (*Secondary fatigue*) (5, 6). Experimental studies have shown that fatigue results from reduced voluntary activation of muscles by means of central mechanisms (5). In general, fatigue is a poorly defined construct and hence difficult to measure (7). The MS International Federation recognized two types of fatigue in pwMS, namely: *physical or motor fatigue* (muscle weakness, slurred speech, unable to perform daily tasks, etc.) and *cognitive fatigue* (deterioration of cognitive function such as, reduced reaction time response, alertness during the day, difficulty in thinking, concentration, memory, recall, word finding, etc.) (7, 8). Further, fatigue can be acute (newly occurring in the past 6 weeks) or chronic (lasting longer than 6 weeks) (4). Brañas et al. classifies fatigue experienced by pwMS into: "fatigability" (increased weakness with exercise or as the day progresses) and "lassitude" (abnormal constant and persistent sense of tiredness) (9). In contrast to fatigue in normal people, MS-related fatigue has distinctive characteristics, including: occurs on a daily basis; worse as day progresses; aggravated by heat and humidity; comes on more easily and suddenly; more severe than normal fatigue; and more likely to interfere with role performance and physical functioning (2, 9). Clinically, fatigue may manifest as exhaustion, lack of energy, increased somnolence, or worsening of MS symptoms and activity, and heat typically can exacerbate symptoms (6). The mechanism for fatigue in MS is not known and several different factors are believed to contribute to fatigue (**Box 1**).

Fatigue is prevalent in the MS population and a significant health problem, adversely impacting on activities of daily living, ability to work, social life, and quality of life (QoL) (4). Fatigue has been associated with increased cognitive impairment and on a person's participatory roles (such as relationships and social integration, etc.) (11). There is strong consensus in literature that many psychosocial factors influence adjustment to fatigue, including the family's response, coping behaviors, psychological distress, and fatigue-related disability (1, 5). Fatigue is also associated with poorer general health, increased disability, and higher rates of health care utilization (12, 13). In a descriptive study of MS-related disability ($n = 101$), 81% reported fatigue, with those in higher fatigue grades reporting more disability and health care visits, and lower QoL (14). In another study ($n = 656$ patients), 22% reported limitation in level of physical activity, 14% stated it required them to have more frequent rest breaks, and 10% had to discontinue work due to fatigue (15).

Multiple sclerosis can have a fluctuating and often progressive course, making symptomatic management more challenging. The key to symptomatic management of pwMS, including fatigue, is achievement of individualized, patient-centered goals that are set collaboratively with patients, their carers, and the rehabilitation team in a functional context, and should be based on the medical and functional status of each patient (16–18). The quality and

Box 1 | Primary and secondary factors in Multiple Sclerosis fatigue.

Primary Factors

- Immune dysregulation – changes in neuroendocrine function.
- Central nervous system mechanisms – neuronal dysfunction due to immune injury, demyelination and inflammation, impaired innervation, and activation of muscle groups leading to compensatory increase in central motor drive exertion and more energy depletion.
- Endocrine factors – abnormalities in hypothalamic/pituitary/adrenal axis.
- Neurotransmitter dysregulation – dopaminergic, histaminergic, and serotonergic pathways may contribute to fatigue.

Secondary Factors

- Physical deconditioning from failure to get adequate exercise.
- Sleep dysfunction – may also be due to nocturnal spasms, pain, incontinence, and depression.
- Pain – sensory disturbances, neuralgia, dysesthesia, and spasms.
- Psychological factors – lack of self-efficacy may increase feelings of fatigue.
- Depression – closely related to poor sleep, pain, and fatigue.
- Medications – can worsen fatigue [antispasticity agents, e.g., Baclofen].

Adapted from MacAllister and Krupp and Kos et al. (5, 10).

quantity of fatigue, and its impact on function is obtained in the patient assessment and history. All contributing factors to fatigue should be identified, and other non-MS causes should be excluded and/or treated appropriately (4). A number of instruments exist in MS literature for the assessment of fatigue and can be subjective (self-reported by patients) and objective (quantified by clinicians through various parameters) (10). Subjective or patient-reported instruments are specifically designed to incorporate a patient's viewpoint and are more practical for use in clinical settings (10, 19). A list of commonly used subjective measures of MS-related fatigue is provided in **Table 1**.

The published National Institute for Clinical Excellence (NICE) clinical practice guidelines on the management of MS (26) highlights the significance of diagnosing and treating fatigue as part of the management plan. A clinical decision-making flowchart for managing fatigue in MS (10) is shown in **Figure 1**. Both pharmacological and non-pharmacological interventions individually or in combination are recommended for the management of fatigue in pwMS. Evidence supporting the efficacy of these interventions in MS-related fatigue is still ambiguous and insufficient (5, 9). The published guidelines acknowledge that the recommendations were mostly driven by the expert opinions rather than by high-quality research-derived evidence (26). Further, interventions for fatigue management in pwMS are still not prescribed in a systematic way (9).

The most commonly used agents for pharmacological treatment for fatigue in pwMS include amantadine, modafinil, and pemoline (9). The NICE guidelines (26) concluded that the efficacy of any pharmacological agents specifically to treat neurological fatigue is yet to be established. Many argue that non-pharmacologic approaches used in isolation and/or in combination with pharmacological agents are the mainstay in the management of fatigue in pwMS (9, 10). Non-pharmacological interventions may include education (e.g., avoid heat, use air conditioners, and cooling gel vests); address lifestyle factors (e.g., diet and exercise; avoid physical activity at midafternoon); pacing (regular rest breaks between activities); energy conservation and work simplification strategies (e.g., use of assistive devices, adaptive equipment, gait aids), and improve aerobic capacity and endurance (e.g., structured exercise programs).

Despite advances in pharmacological and non-pharmacological treatment, MS-related fatigue continues to be the common disabling symptom in pwMS. In current practice, both pharmacological and non-pharmacological interventions are used in combination, encompassing a multi-disciplinary approach. The body of research investigating the effect of these interventions on management of fatigue in MS is growing. The benefit and harms associated with most of these interventions in pwMS needs to be established comprehensively to guide treating clinicians. Therefore, the aim of this review is to systematically evaluate the existing evidence to investigate the effectiveness and safety of interventions for the management of fatigue in pwMS in improving patient outcomes.

METHODS

An integrated approach was used, which included a comprehensive review of literature (peer review and gray literature) documenting interventions currently used in management of fatigue in MS. A comprehensive search of the literature published was undertaken till 6th June 2014 using Medline, Embase, PubMed, and Cochrane Library databases. The search strategy included interventional studies investigating management of fatigue in pwMS, using combinations of multiple search terms for three themes: MS, interventions (pharmacological and non-pharmacological), and fatigue. Medical subject heading (MeSH) search terms were used for all databases and a keyword search was used if the MeSH term was not available. The bibliographies of identified articles were scrutinized for additional references and a manual search of relevant journals was undertaken. A gray literature search using different internet search engines and websites such as: system for Information on Gray Literature in Europe; New York Academy of Medicine Gray Literature Collection, and Google Scholar, was also undertaken. Additional searches of the websites of prominent national and international organizations associated with MS management were conducted to identify relevant reports, health technology assessments, or other related materials.

Table 1 | Commonly used subjective measures of MS-related fatigue.

Name of scale	Reference	Population	Specified fatigue subscales	No. of items	Scoring
Modified fatigue impact scale	Paralyzed Veterans of America, 1998 (4)	MS	Physical, cognitive, and psychosocial	21	1–7 (Likert scale)
Rochester fatigue diary	Schwid et al. (20)	MS	Lassitude [reduced energy]	12	0–100 (mm) visual analog scale
Fatigue descriptive scale	Iriarte et al. (21)	MS	Spontaneous mention of fatigue, antecedent conditions, frequency, impact on life	5	0–3 (Likert scale)
Fatigue impact scale	Fisk et al. (22)	MS	Physical, cognitive, psychosocial	40	0–4 (Likert scale)
Fatigue assessment instrument	Schwartz et al. (23)	MS, chronic fatigue syndrome, lupus, dysthymia, healthy	Fatigue severity, situation specificity, consequences of fatigue, responds to rest/sleep	29	1–7 (Likert scale)
Single item visual analog scale of fatigue	Krupp et al. (24)	MS, lupus, healthy	Depends on the question	1	0–100 (mm) visual analog scale
Fatigue severity scale	Krupp et al. (24)	MS, lupus, healthy	None	9	1–7 (Likert scale)
Fatigue scale for motor and cognitive functions (FSMC)	Penner et al. (25)	MS	Motor and cognition	20	1–5 (Likert scale)

Adapted from MacAllister and Krupp (10) and Kos et al. (5).

INCLUSION CRITERIA

Studies that compared various interventions in management of fatigue in pwMS with routinely available local services or lower levels of intervention or placebo, or studies that compared such interventions in different settings or at different levels of intensity, were included. All systematic reviews, meta-analyses, randomized clinical trials (RCTs), and controlled clinical trials (CCTs), quasi-randomized and quasi-experimental designs with comparative controls, and controlled before-and-after studies were included. Whenever RCTs/CCTs were lacking, a search for relevant observational studies was conducted. Studies involving other medical conditions, where data were specifically provided for MS-related fatigue, were also included. Descriptive studies and narrative reviews were explored to identify policies, protocols, and gaps in service provision. Where high-quality systematic reviews or meta-analyses were identified, articles published prior to the date of that review's search strategy were excluded.

EXCLUSION CRITERIA

Limits placed included English-language publication and inclusion of adults aged 18 years and above. Theses, narrative reviews, editorials, case reports, economic evaluation, conference proceedings, and studies evaluating surgical intervention or diagnostic procedures for MS-related fatigue were excluded.

STUDY SELECTION

Two authors (Bhasker Amatya and Mary Galea) independently screened and shortlisted all abstracts and titles of studies identified by the search strategy for inclusion and appropriateness based on the selection criteria. Each study was evaluated independently by authors. If necessary, the full text of the article was obtained for further assessment to determine whether the article met the inclusion/exclusion criteria. If no consensus was reached regarding the possible inclusion/exclusion of any individual study, a final consensus decision was made by the third author (Fary Khan). Further information about the complete description of the interventions from the trialists was obtained, where necessary.

DATA EXTRACTION

Data extraction was conducted by two authors independently, using a standard *pro forma*. The information obtained from all included studies was: publication date and country, study location, study design, intervention, outcome measures used, and fatigue-related outcomes. Any discrepancies were resolved by all authors re-reviewing the study.

Evidence for all included studies was categorized according to study design using a hierarchy of evidence in descending order and priority were given to the most recently published high-quality systematic reviews or meta-analysis and RCT. Formal levels of evidence were assigned using a standard format defined by National Health and Medical Research Council (NHMRC) pilot program 2005–2006 for intervention studies (**Table 2**) (27).

RESULTS

The electronic database search retrieved 1673 published articles on fatigue in MS; 428 articles met title inclusion criteria of which 55 articles met the abstract inclusion criteria and went on to full-text review. Four articles that met the abstract inclusion criteria were identified from the bibliographies of relevant articles. Overall, 27 studies (12 systematic reviews/meta-analyses, 12 RCTs, 2 CCT, and 1 comparative studies) fulfilled the inclusion criteria for this review. The study selection process is summarized in the PRISMA flow diagram shown in **Figure 2**.

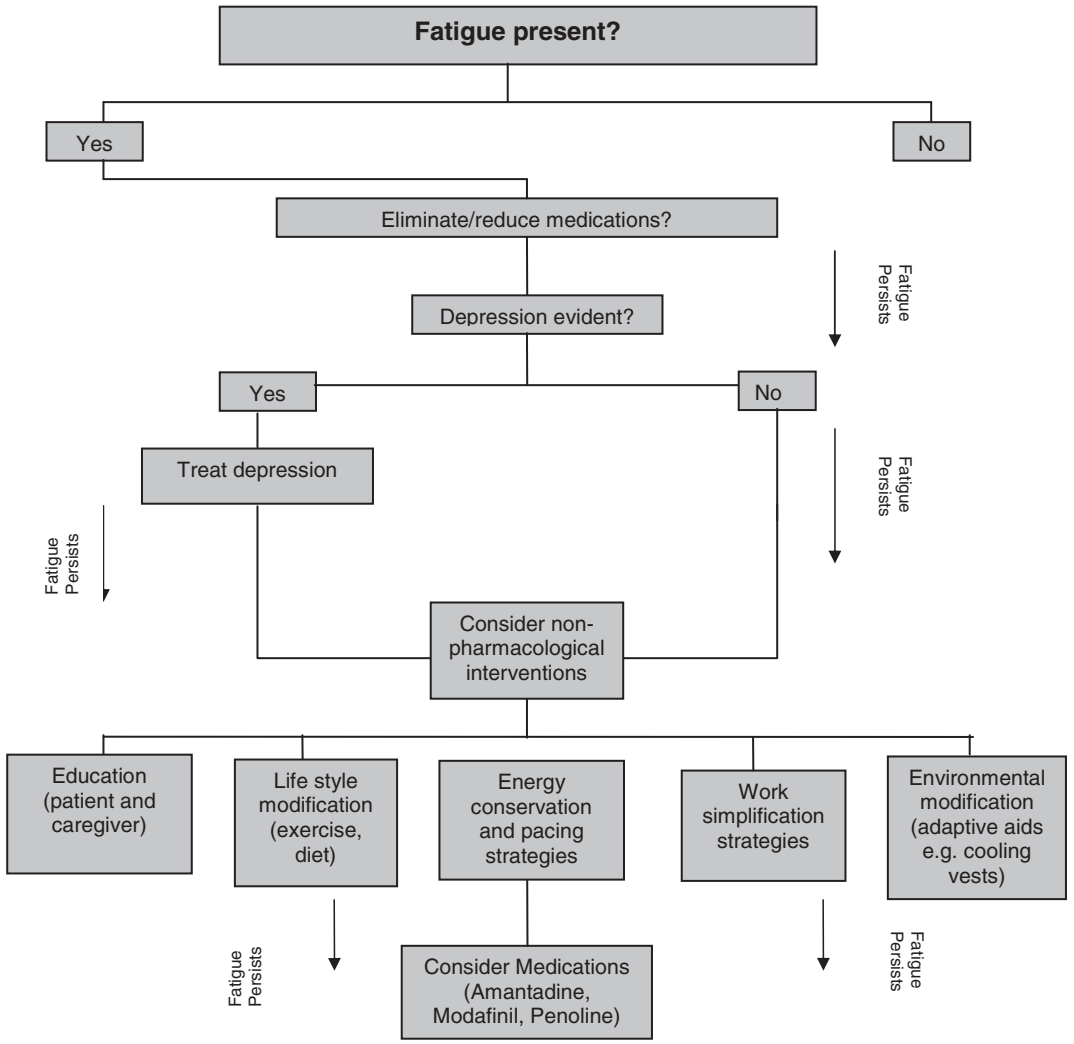

FIGURE 1 | Clinical decision-making flow chart for treating fatigue in MS. Adapted from MacAllister and Krupp (10).

EVIDENCE FOR PHARMACOLOGICAL INTERVENTIONS FOR FATIGUE IN PERSONS WITH MS

Currently, different pharmacological agents are used for treatment for fatigue in pwMS, which include amantadine, modafinil, and pemoline (9, 11). Modafinil, a "wake promoting" agent that selectively works in the hypothalamic pathways used in narcolepsy, has been reported to improve fatigue in progressive MS (5, 9). The efficacy of pemoline, a CNS stimulant, is still unclear (9, 28, 29). Amino pyridines (potassium channel blockers) and amantadine (*N*-methyl D-aspartate receptor antagonist) have been trialed; however, systematic reviews failed to find evidence for efficacy or safety for their use (30). There is empirical support for use of antidepressants in MS-related fatigue, as depression is considered to be one of the major contributing factors (31, 32).

A recently published comprehensive meta-analysis of different interventions (pharmacological and non-pharmacological) included seven RCTs evaluating different medications used for the management of fatigue in pwMS. The authors found weak and inconclusive beneficial effects of pharmacological intervention for MS-related fatigue, with small and non-significant pooled effect sizes (ESs) with a relatively narrow 95% CI (ES = 0.07, 95% CI: −0.22 to −0.37, $p = 0.63$) (11). The pharmacological agents in this review were restricted to Amantadine and Modafinil. Similar inconclusive and insufficient research-derived evidence to support the various pharmacological treatments was reported in another comprehensive systematic review of pharmacological interventions for MS-fatigue published previously (9). The authors systematically reviewed studies investigating only two pharmacological agents: amantadine and pemoline. The studies evaluating the effectiveness of amantadine (four RCTs) showed a pattern in favor of amantadine compared with placebo; however, there was considerable uncertainty about the validity and clinical significance of this finding. Studies investigating efficacy of pemoline (n = two RCTs) demonstrated no overall tendency in favor of pemoline over placebo (9). In addition, an excess of reports of adverse effects was noted for pemoline.

Table 2 | Designations of "levels of evidence" according to type of research question (27) (intervention studies only).[a]

Level	Intervention
I	A systematic review of level II studies
II	A randomized controlled trial
III-1	A pseudo-randomized controlled trial (i.e., alternate allocation or some other method)
III-2	A comparative study with concurrent controls • Non-randomized experimental trial • Cohort study • Case–control study • Interrupted time-series with a control group
III-3	A comparative study without concurrent controls • Historical control study • Two or more single arm study • Interrupted time-series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

[a] *Note that our selection criteria exclude studies at level III-3 and IV.*

One comprehensive systematic review exploring efficacy of different pharmacological treatments on non-specific fatigue in palliative care included 10 studies investigating amantadine ($n = 6$), pemoline, and modafinil in pwMS (33). The authors reported mixed results with weak and inconclusive data. Amantadine (total $n = 6$) was found to demonstrate some improvement in fatigue in pwMS (meta-analysis of three-studies; standard mean difference compared to placebo 1.68). Both pemoline ($n = 3$) and modafinil ($n = 2$) failed to demonstrate a significant effect for management of fatigue in pwMS (33).

Commonly used pharmacological agents for fatigue and MS are summarized in **Table 3**, along with indications, doses, and side effects.

Summary

Different pharmacological agents used for treatment of fatigue in pwMS include Amantadine, Modafinil, and Pemoline. There is however, insufficient research-derived evidence to support these pharmacological agents for management of MS related fatigue.

EVIDENCE FOR NON-PHARMACOLOGICAL INTERVENTIONS FOR FATIGUE IN PERSONS WITH MS

There is widespread agreement in the literature that, due to the complex, multidimensional, and highly subjective nature of MS-related fatigue, comprehensive goal orientated management programs that incorporate multi-disciplinary (MD) expertise are required, and patients need to be evaluated regularly through appropriate clinical outcome measures (17, 18). The characteristics of the all included studies evaluating non-pharmacological interventions for fatigue in pwMS are summarized in **Table 4**.

MULTI-DISCIPLINARY REHABILITATION (LEVEL I EVIDENCE)

Existing clinical practice guidelines for MS recommend comprehensive, co-ordinated MD care, including symptomatic management, and appropriate follow up, education, and support for patients and carers (26). MD rehabilitation, a co-ordinated delivery of patient-centered, time-based, functionally oriented intervention/s by two or more disciplines (such as physiotherapy, occupational therapy, social work, psychology, and other allied health, nursing), under medical supervision (17), should be the best approach in symptomatic management in MS, including fatigue (5, 34). A systematic review of MD rehabilitation in MS (17), found a "strong evidence" to support MD rehabilitation in producing short-term gains at the levels of activity (disability) and participation in patients with MS. Of the 10 included trials, fatigue was considered in only two studies evaluating outpatient and home-based rehabilitation programs. A CCT (35) evaluating the influence of an extended MD outpatient rehabilitation found that fatigue symptoms were significantly reduced in the treatment group compared to the control group at 1-year follow-up ($p = 0.004$). Similar result was reported in another RCT evaluating impact of outpatient MD rehabilitation. The authors reported that a 12-week rehabilitation program significantly reduced fatigue and improved social functioning and depression ($p < 0.001$) (36). There was no convincing evidence regarding the effectiveness of inpatient MD rehabilitation programs for management of fatigue (17). An RCT investigating MD inpatient rehabilitation did not find any significant benefits of such a program on disability level or perceived fatigue (37).

SPECIFIC REHABILITATION INTERVENTIONS

The cause and effect of fatigue are considered to be multidimensional and its impact extends from general everyday activity to overall QoL of pwMS (11, 38). Improving or restoring physical and psychosocial abilities and education have been proposed to counteract many MS-fatigue-related consequences. A rehabilitation approach to fatigue management in pwMS includes a spectrum of interventions, which have been examined in several published reviews. However, many of these interventions have not yet been included routinely in comprehensive MD rehabilitation programs, and few studies show their implementation. The existing evidence for various specific rehabilitation interventions for fatigue management in pwMS is summarized below.

PHYSICAL THERAPEUTIC MODALITIES

Physical therapeutic modalities are considered to be one of the most efficient strategies in rehabilitation of MS patients in improving or restoring physical abilities. However, its role in MS-related fatigue management has been controversial. In past years, pwMS were advised not to participate in physical activities because it was believed to lead to worsening of symptoms or fatigue (15, 39, 40). However, recent studies on exercise therapy in MS have demonstrated that it results in substantial long-term reduction in functional limitations and enhanced QoL, and have the potential to reduce fatigue in pwMS (39).

EXERCISE (LEVEL I)

Exercise therapy is a core rehabilitative measure, which aims to improve motor functions (such as co-ordination, fine-movements), balance, gait, and reduction of MS-related symptoms. Compared with the other interventions, exercise has been

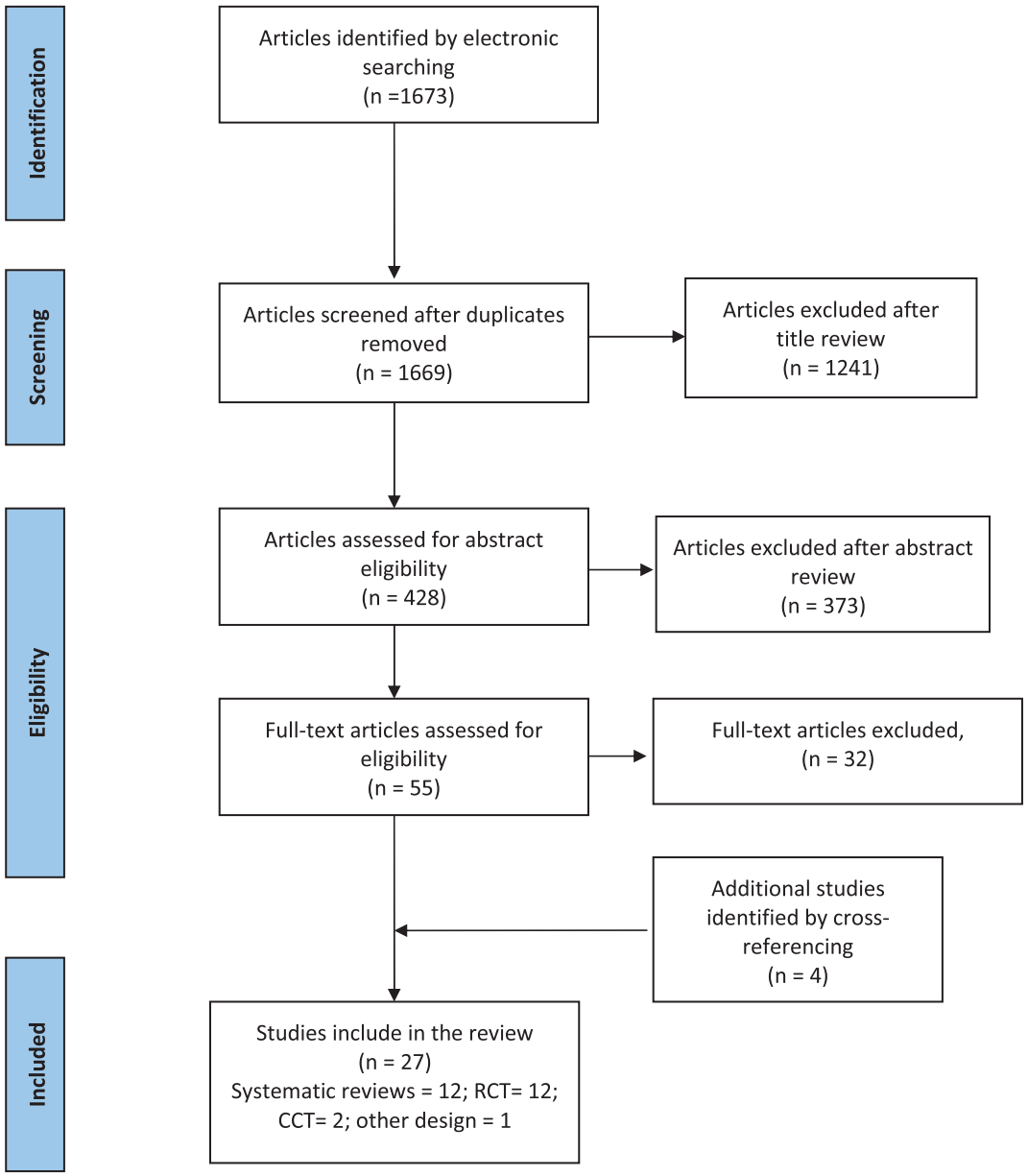

FIGURE 2 | PRISMA flow diagram showing selection of article review.

more frequently investigated for MS-related fatigue, which has resulted in several systematic reviews/meta-analyses evaluating various exercise modalities for the management of fatigue (11, 41–45). A wide range of exercise interventions were investigated, which included resistance training, endurance training, aquatic exercises, leisure activities, and a combination of two or more exercise modalities. In a recently published systematic review, Asano and Finlayson reported strong evidence for exercise-based rehabilitation in terms of reducing severity of patient-reported fatigue (11). Although there was heterogeneity among the included trials ($n = 10$ studies; $p = 0.003$), exercise interventions were still found to have a significant beneficial effect in managing fatigue in pwMS (pooled ES was 0.57; 95% CI: 0.10–1.04, $p = 0.02$). The authors stated that the extent of the intervention effects varied considerably and only a certain group of patients (younger, with stable MS) appear to experience benefit. For other MS subgroups, such as older adults or those with progressive MS and/or severe disability, there was no evidence of benefit. Further, it was not possible to identify which types or components or intensity of exercise achieved benefits for fatigue management. Another meta-analysis ($n = 17$ RCTs), demonstrated a similar positive effect of exercise interventions for MS-related fatigue (45). The authors showed that exercise training was associated with a significant reduction in fatigue among pwMS (weighted

Table 3 | Commonly used pharmacologic treatments for MS-related fatigue.

Drug	Brand name	FDA indications	Dosage	Common side effects
Amantadine	Symmetrel®	Influenza; Parkinson's Disease	100 mg BID	• Livedo reticularis • Orthostatic hypotension • Peripheral edema • Headache • Dizziness • Nausea • Insomnia
Modafinil	Provigil®	Narcolepsy; shift-work sleep disorder; excessive daytime sleepiness from OSA not relieved by CPAP	Start 200 mg every morning or at start of shift, may escalate to 400 mg	• Anxiety • Headache • Dizziness • Nausea • Hypertension • Palpitations • Insomnia
Armodafinil	Nuvigil®	See Modafinil	Start at 150 mg every morning or at start of shift, may escalate to 250 mg	• See Modafinil
Pemoline	Cylert®	Attention deficit hyperactivity disorder (ADHD)	Starting at 37.5 mg/day and gradually increased by 18.75 mg at 1 week intervals. The maximum recommended daily dose is 112.5 mg	• Hepatic dysfunction • Insomnia • Convulsive seizures • Hallucinations • Dyskinetic movements of the tongue, lips, face and extremities • Abnormal oculomotor function • Dizziness • Increased irritability; headache; and drowsiness • Anorexia and weight loss • Nausea and stomach ache

Adapted from Braley and Chervin (6) and Branas et al. (9).

mean ES = 0.45; 95% CI = 0.22–0.68, $p \leq 0.001$) (45). A systematic review by Andreasen et al. assessed the beneficial effect of different exercise categories separately; these included endurance training, resistance training, combined, or "other" training modalities (39). The authors, consistent with other reviews, found marked heterogeneity among the trials, as only a few studies evaluated MS fatigue as the primary outcome and many studies included non-fatigued MS patients. Overall, all type of exercise interventions were shown to have the potential to reduce MS fatigue (39). The authors concluded that, compared to other exercise modalities, endurance training was studied more frequently ($n = 11$ studies) and showed more consistent positive effects (39).

Several reviews evaluated exercise therapy for MS in general (42, 44, 46) and reported strong evidence in favor of exercise therapy compared to no exercise therapy, in terms of muscle power, exercise tolerance, and mobility-related activities. Conversely, subgroup analysis of results on fatigue showed mixed results. One study found that neurophysiologically based physiotherapy or a combined training program (physiotherapy plus aerobic training) were associated with significant improvement in impairment and fatigue (47).

Summary

Overall, the evidence regarding exercise modalities for MS-related fatigue was inconsistent and data for an optimal type or intensity of exercise intervention are still insufficient. Some types of exercise interventions which include endurance and a resistance-training component may have potential beneficial effects on fatigue reduction in pwMS.

AQUATIC THERAPY (LEVEL II)

Few studies have evaluated aquatic therapy, which aims to reduce resistance of movements and gravity by exercising in water (pool therapy, hydrotherapy, balneotherapy), for management of fatigue in pwMS (48–52). There is evidence from two RCTs showing beneficial effects of an aquatic exercise program for MS-related fatigue. One RCT examined the effectiveness of a supervised 8-week aquatic exercise training program (60 min session, three times a week) on fatigue and health-related QoL in women ($n = 32$) with MS (50). The participants in the aquatic exercise group showed significant improvements in fatigue and QoL after 4 and 8 weeks compared with the control group (50). Another RCT ($n = 73$) suggested that a structured aquatic exercise (Ai Chi) program for 20 weeks (40 sessions) improved fatigue, pain,

Table 4 | Non-pharmacological interventions for fatigue in MS.

Study, year country	Study design	Potential intervention	Outcome measures for fatigue	Main findings	Level of evidence[a]
MULTI-DISCIPLINARY (MD) REHABILITATION					
Khan et al. 2011 (17, 31), Australia	Systematic review, $n = 10$ trials (nine RCTs and one CCT)	Extended MD outpatient rehabilitation Inpatient MD rehabilitation	Fatigue, frequency, FIS; MS-related symptom checklist composite score MSIS29, VAS	• Fatigue symptoms significantly • Improved social functioning and depression • No significant benefits on perceived fatigue or disability level	I
PHYSICAL MODALITIES					
Exercise					
Asano and Finlayson 2014 (11), Canada	Meta-analysis, $n = 10$ RCTs	Various types of exercises (progressive resistance, aerobic, inspiratory exercises, aquatic exercises, vestibular rehabilitation, and leisure exercises)	FSS, MFIS, FIS	• Significant beneficial effect in managing fatigue [pooled effect size (ES) was 0.57; 95% CI: 0.10–1.04, $p = 0.02$] • ES for the exercise interventions range: −0.24 (95% CI: −1.15 to 0.64) to 2.05 (95% CI: 1.00–3.11)	I
Latimer-Cheung et al. 2013 (42), Canada	Systematic review, $n = 54$ trials (30 evaluating fatigue outcomes: 15 RCTs and 15 other design)	Aerobic fitness; muscle strength (resistance training) and combined	FSS, FIS, MFIS, SF-36 (vitality subscale), PMS (energy and fatigue subscales), MSQL-54 (energy subscale)	• Aerobic exercise: significant improvements in some general fatigue symptoms but not specific symptoms after 2–6 months of light to moderate cycling for 40–60 min three times/week; decreases in general, physical, and psychological fatigue symptoms after 8 weeks of moderate-intensity aerobic activities two times/week • Traditional resistance training: improvements in general symptomatic fatigue after a 12-week, two times/week resistance training program (8–15 RM); decreased fatigue overall or specifically physical and psychological fatigue after 8 weeks of moderate-intensity resistance training two times/week (6–15 RM) • Combined training programs: significant increase in vitality or decrease in fatigue severity after 5–8 weeks of supervised aerobic and resistance training performed at moderate to high intensity; significant improvements in fatigue symptoms or severity after 8–10 weeks of two to three times/week combined training • Other types of exercise (sport, yoga, body weight support treadmill training, aquatic exercise, cycling, and Pilates): a significant decrease on at least one indicator of fatigue (general or specific) symptoms	III-1
Andreasen et al. 2011 (39), Denmark	Systematic review, $n = 21$ trials (11 RCTs, 1 CCT, 9 other design)	Endurance training, resistance, training, combined training, or "other" training modalities	FSS, MFI, MFIS, FCMC	• Exercise therapy on MS fatigue show heterogeneous results and only few studies have evaluated MS fatigue as the primary outcome • All type of exercise modalities have potential to reduce MS fatigue • Not clear whether any exercise modalities are superior to others	III-1

(Continued)

Table 4 | Continued

Study, year country	Study design	Potential intervention	Outcome measures for fatigue	Main findings	Level of evidence[a]
Neill et al. 2006 (43), Australia	Systematic review, $n = 11$ trials [combined for MS, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE); various study design]	Aerobic exercise, resistance training	FIS, FSS, SF-36, POMS, VAS,	• Aerobic exercise (home-based or supervised classes) is effective in managing fatigue for some people with MS, RA and SLE • Six studies reported statistically significant reductions in fatigue from aerobic exercise interventions • Low-impact aerobics, walking, cycling, and jogging were effective interventions	III-1
Aquatic therapy					
Kargarfard et al. 2012 (50), Iran	RCT, $n = 32$ women with MS	Aquatic exercise: joint mobility, flexor and extensor muscle strength, balance movements (60 min session three times/week), control group: usual care	MFIS, MSQL-54	• Patients in the aquatic exercise group showed significant improvements in fatigue and QoL after 4 and 8 weeks ($p = 0.002$ and <0.001, respectively)	II
Castro-Sánchez et al. 2012 (48), Spain	RCT, $n = 73$ pwMS	Treatment group: aquatic Tai-Chi (40 sessions) ($n = 36$); control group: relaxation ($n = 37$)	FSS, MFIS	• Treatment group showed a significant score reduction in fatigue at week 20 ($p < 0.032$) that was maintained at week 24 ($p < 0.038$) • An improvement was shown by 48% of the treatment group • Significant improvement in pain, spasms, disability, fatigue, and depression was also reported in treatment group	II
Bayraktar et al. 2013 (53), Turkey	CCT, $n = 23$ pwMS	Treatment group: aquatic Tai-Chi ($n = 15$); control group: exercise at home ($n = 8$)	FSS	• Significant in reduction in fatigue in the treatment group ($p < 0.05$) • Improvement in balance, functional mobility, upper and lower extremity muscle strength was also noted in treatment group ($p < 0.05$)	III-1
Tai chi					
Castro-Sánchez et al. 2012 (48), Spain	RCT, $n = 73$ pwMS	Treatment group: aquatic Tai-Chi (40 sessions) ($n = 36$); control group: relaxation ($n = 37$)	FSS, MFIS	See "Aquatic Therapy" section above	II
Bayraktar et al. 2013 (53), Turkey	CCT, $n = 23$ pwMS	Treatment group: aquatic Tai-Chi ($n = 15$); control group: exercise at home ($n = 8$)	FSS	See "Aquatic Therapy" section above	III-1
Mills et al. 2000 (56), UK	Comparative study, $n = 8$ pwMS	Tai Chi/QiGong along with the teaching QiGong self-massage. TuiNa and daily home practice for 30 min	POMS, 21-Item symptom checklist	• Significant improvements in fatigue post intervention	III-2
Cooling devices					
Beenakker et al. 2001 (57), Netherlands	RCT, $n = 10$	Wearing cooling garment for 60 min at 7°C (active cooling); control group: 26°C (sham cooling).	MFIS	• Beneficial effect of cooling therapy in reducing fatigue, improving postural stability and muscle strength in pwMS	II

(Continued)

Table 4 | Continued

Study, year country	Study design	Potential intervention	Outcome measures for fatigue	Main findings	Level of evidence[a]
White et al. 2000 (58), USA	RCT, $n = 6$ pwMS	Immersing participants' lower body regions in water baths at 16–17°C for 30 min before training	FIS	• Reduced fatigability during training sessions ($p < 0.05$) • Fewer heat-induced symptoms such as ataxia, blurred vision, and foot drop during exercise preceded by cooling	II
Pulsed electro-magnetic devices					
Lappin et al. 2003 (60), USA	RCT, $n = 117$ pwMS	"Enermed" – active low-level, pulsed electro-magnetic field device worn up to 24 h daily on one or more acupressure points for up to 4–8 weeks	MSQLI	• Statistically significant decreases in fatigue for the intervention groups (0.05) • Overall QoL significantly greater on the active device group • No treatment effects for bladder control and a disability composite, and mixed results for spasticity	II
Richards et al. 1997 (61), USA	RCT, $n = 33$ pwMS	"Enermed" – see above	Patient-reported performance scales	• Significant improvement in the performance scale (PS) combined rating for bladder control, cognitive function, fatigue level, mobility, spasticity, and vision (active group -3.83 ± 1.08, $p < 0.005$; placebo group -0.17 ± 1.07, change in PS scale)	II
BEHAVIORAL AND EDUCATIONAL INTERVENTIONS					
Asano and Finlayson 2014 (11), Canada	Meta-analysis, $n = 8$ RCTs	Various types of psychological/educational interventions (fatigue management program, energy conservation course, CBT, mindfulness intervention)	FSS, MFIS, FIS	• Significant beneficial effect in managing fatigue [pooled effect size (ES) was 0.54; 95% CI: 0.30–0.77, $p < 0.001$] • ES for the educational interventions range: from -0.16 (95% CI: -0.72 to 0.38) to 1.11 (95% CI: 0.43 to 1.78)	I
Neill J et al. 2006 (43), Australia	Systematic review, $n = 15$ trials (combined for MS, RA and SLE; various study design design)	Education programs, energy conservation, self-management, fatigue management program, CBT	FIS, FSS, SF-36, POMS, VAS,	• Behavioral interventions appeared effective in reducing fatigue • Education alone or with exercise reduced fatigue and increased vitality in pwMS • Rehabilitation program and counseling were effective in reducing fatigue	III-2
Fatigue management programs					
Thomas et al. 2013 (70), UK	RCT, $n = 164$ pwMS	Group-based interactive program for managing MS-fatigue [fatigue: applying cognitive behavioral and energy effectiveness techniques to lifestyle (FACETS] (90-min sessions weekly for 6 weeks facilitated by two health professionals ($n = 84$); control group ($n = 80$) usual care)	FAI, MSFS	• At 1-month post intervention: significant differences favoring the intervention group on fatigue self-efficacy (mean difference = 9; 95% CI 4–14; ES = 0.54, $p = 0.001$). • At 4 months follow-up: positive effects of the program still remained significant with moderated effect size (ES = 0.36; $p = 0.05$; mean difference = 6; 95% CI 0–12); significant improvement in fatigue severity was also found in intervention group ($p = 0.01$)	II
Thomas et al. 2014 (64), UK	RCT, $n = 164$ pwMS	Same as above	Same as above	• At 1-year follow-up: benefits of the FACETS program for fatigue severity and self-efficacy mostly sustained (ES = -0.29, $p = 0.06$ and 0.34, $p = 0.09$, respectively); additional significant improvements in QoL ($p = 0.046$)	II

(Continued)

Table 4 | Continued

Study, year country	Study design	Potential intervention	Outcome measures for fatigue	Main findings	Level of evidence[a]
Kos et al. 2007 (34), Belgium	RCT, $n = 51$ pwMS	Multi-disciplinary fatigue management program: interactive educational sessions about possible strategies to manage fatigue and reduced energy levels (four 2 h sessions/week) ($n = 28$); control group: placebo	MFIS	• No efficacy in reducing the impact of fatigue compared to a placebo intervention program (ES = −0.16)	II
Energy conservation interventions					
Blikman et al. 2013 (65), Netherlands	Systematic review, $n = 6$ trials (four RCTs and two CCTs)	Energy conservation interventions: education about balancing, modifying and prioritizing activities, rest, self-care, effective communication, biomechanics, ergonomics, and environmental modification	FIS	• Energy conservation interventions were more effective than no treatment in improving subscale scores of FIS: cognitive mean difference (MD = −2.91; 95% CI, −4.32 to −1.50), physical (MD = −2.99; 95% CI, −4.47 to −1.52), and psychosocial (MD = −6.05; 95% CI, −8.72 to −3.37) • QoL scores on physical, social function and mental health (also improved significantly in treatment group • None of the studies reported long-term results	I
Mindfulness-based interventions					
Simpson et al. 2014 (66), UK	Systematic review, $n = 3$ trials (two RCTs and one CCT)	Mindfulness-based interventions: mindful breath awareness, mindful movement, and body awareness or "scanning"	MFIS, POM	• Significantly beneficial effect on fatigue scores • One RCT found significant post-intervention reduction in fatigue in both overall population and in subgroup analyses of those with pre-intervention impairment ($p < 0.001$ for both). • Beneficial effect maintained at 6 months	I
Cognitive and psychological interventions					
Moss-Morris et al. 2012 (68), UK	RCT$n = 40$ pwMS	Intervention group ($n = 23$): internet-based cognitive behavior therapy (CBT) – "MS Invigor8" (eight tailored, interactive sessions with a clinical psychologist over 8–10 weeks)Control group ($n = 17$): standard care	MFIS	• Significant greater improvements in fatigue severity and impact; and also in anxiety, depression and quality-adjusted life years in treatment group	II
van Kessel et al. 2008 (69), New Zealand	RCT$n = 72$	Treatment group ($n = 35$): CBT (eight weekly sessions)Control group ($n = 37$): relaxation therapy	CFS, MFIS	• Both groups showed clinically significant decreases in fatigue • Significantly greater improvements in fatigue in treatment group ($p < 0.02$) compared to relaxation therapy group: ES = 3.03 (95% CI 2.22–3.68) for the CBT group across 8 months compared with the relaxation therapy group (ES 1.83; 95% CI 1.26–2.34)	II

[a] *Levels of evidence' categorized according to National Health and Medical Research Council (NHMRC) pilot program 2005–2006 for intervention studies (23).*
CBT, cognitive behavioral therapy; CCT, clinical controlled trial; CFS, Chalder fatigue scale; ES, effect size; 95% CI, 95% confidence interval; FAI, fatigue assessment instrument; FSMC, fatigue scale for motor and cognitive functions; FSS, fatigue severity scale; FIS, fatigue impact scale; MFIS, modified fatigue impact scale; MSFS, multiple sclerosis-fatigue self-efficacy; MSIS, multiple sclerosis impairment scale; MSIS29, multiple sclerosis impact scale; MSQL-54, multiple sclerosis quality of life-54 MFI, multidimensional fatigue inventory; POMS, profile of mood states; QoL, quality of life; RCT, randomized controlled trial; SF-36, short-form health survey-36, VAS, visual analog scales.

spasms, disability, and depression in pwMS (48). Bayraktar et al. investigated the effects of a similar aquatic exercise program (Ai Chi) in a CCT ($n = 23$) on balance, functional mobility, strength, and fatigue in ambulatory pwMS (53). The authors reported significant improvements in fatigue, static standing balance, functional mobility, and upper and lower extremity muscle strength in the treatment group ($p < 0.05$) (53).

Summary

Aquatic exercise training can improve fatigue and other MS-related symptoms, function and quality of life of pwMS and could be considered for inclusion in management programs.

TAI CHI (LEVEL II)

Tai Chi is gaining momentum in rehabilitation settings and can improve balance, posture, muscle strength, psychological issues (stress reduction, and decreased anxiety, depression and mood disturbance) and general well-being in people with various medical conditions (54, 55). The effects of Tai Chi on fatigue in pwMS have been evaluated in only a few studies. Two trials (one RCT and one CCT) (also reported under aquatic exercise) investigated the effectiveness of Tai Chi aquatic exercise program in reducing symptoms, including fatigue and improving physical function in pwMS (48, 53). There was a significant reduction in fatigue in individuals with MS participating in the Tai Chi classes as compared to the control group (see above in section "Aquatic Therapy"). Another comparative study found that practicing Tai Chi for 2 months daily was associated with some improvements in fatigue and significant improvements in balance and depressive symptoms in pwMS (56).

Summary

There is limited evidence suggesting the effectiveness of Tai chi in improving fatigue symptoms in pwMS. Further studies with a larger sample size are needed to confirm the potential effectiveness of Tai chi in fatigue management in pwMS.

COOLING THERAPY (LEVEL II)

Physiological approaches such as cooling techniques using different cooling temperatures and durations have been tested for symptomatic management in heat-sensitive pwMS. Beenakker et al. conducted a RCT showing a beneficial effect of cooling therapy in reducing fatigue, improving postural stability, and muscle strength in pwMS when wearing a cold vest with active cooling (7°C, 60 min) (57). Another study investigating the effects of immersing participants' lower body regions in water baths at 16–17°C for 30 min before training, found that fatigability significantly reduced in these patients during training sessions (58). These effects of cooling on functional improvements are most probably due to temperature-induced changes (Uhthoff phenomenon) in central motor conduction in demyelinated fibers (59).

Summary

Pre-cooling or cooling during and after therapy may decrease fatigue and increase the effect of active physical training in thermo sensitive pwMS. However, the evidence is limited and unclear. Further research is required to identify who will benefit from these techniques.

PULSED ELECTRO-MAGNETIC DEVICES (LEVEL II)

Low-level pulsed electro-magnetic field devices have been investigated in a few trials and have shown positive effects in reducing for MS-related fatigue (60–62). A multi-center RCT ($n = 117$) found that wearing an active low-level, pulsed electro-magnetic field device on one or more acupressure points daily for up to 4–8 weeks, significantly decreased fatigue (60). Similar positive results were reported in another RCT ($n = 33$) conducted earlier using the similar device (61). The clinical effects in these trials were small and long-term follow-up data were lacking.

Summary

Exposure to pulsing, weak electromagnetic fields can alleviate fatigue symptoms in pwMS, however, additional research is needed into the feasibility and long-term use of these devices, due to limited access and cost of devices.

BEHAVIORAL AND EDUCATIONAL INTERVENTIONS

Several published reviews and studies have examined the effectiveness of various types of behavioral and/or educational interventions for management of fatigue in pwMS, which included group fatigue management programs, energy conservation programs, and psychotherapies [e.g., cognitive behavioral therapy (CBT) and mindfulness-based intervention]. A meta-analysis investigated overall effectiveness of different types of educational programs on reducing the impact or severity of self-reported fatigue in pwMS (11). The authors included eight RCTs, involving 662 pwMS. Educational interventions included a fatigue management program, energy conservation programs, mindfulness interventions, and CBT. The authors found significant global improvement with a large pooled treatment ES for the educational interventions of 0.54 (95% CI: 0.30–0.77 $p < 0.001$; range: −0.16 to 1.11) (11).

FATIGUE MANAGEMENT PROGRAMS (LEVEL II)

A number of structured fatigue management programs have been explored in pwMS and most appeared effective in reducing fatigue. A multi-centered parallel arm RCT ($n = 164$) evaluated the effectiveness of a group-based program for managing MS-fatigue [fatigue: applying cognitive behavioral and energy effectiveness techniques to lifestyle (FACETS)], which was based upon a conceptual framework integrating elements from cognitive behavioral, social-cognitive, energy effectiveness, self-management, and self-efficacy theories (62). The program consisted of interactive group sessions and activities (90-min sessions weekly for 6 weeks) and was facilitated by two health professionals (such as occupational therapists, nurses, or physiotherapists). The authors found significant differences favoring the intervention group on fatigue self-efficacy at 1 month follow-up (mean difference = 9; 95% CI 4–14) with a large ES (ES = 0.54, $p = 0.001$). At 4 months follow-up, the positive effects of the program still remained significant with a moderate ES (ES = 0.36; $p = 0.05$; mean difference = 6; 95% CI 0–12). In addition, significant improvement in fatigue severity was also found in the intervention group ($p = 0.01$) at 4 months follow-up (62). In a 1-year follow-up study by the same authors, the findings showed that the benefits of the FACETS program for fatigue severity and self-efficacy were mostly sustained, with a slight reduction in standardized ESs (ES = −0.29, $p = 0.06$ and

0.34, $p = 0.09$, respectively) with additional significant improvements in QoL ($p = 0.046$) (63). Another RCT ($n = 51$) evaluating the efficacy of a MD fatigue management program in pwMS, however, showed no efficacy in reducing the impact of fatigue compared to a placebo intervention program (34). The MD fatigue management program comprised interactive educational sessions about possible strategies to manage fatigue and reduced energy levels (2 h sessions weekly for 4 weeks).

Summary

A structured fatigue management program based on psychological approaches delivered by health professionals can be effective in reducing fatigue severity and increasing fatigue self-efficacy for pwMS. It can be clinically beneficial and can be readily incorporated into existing services.

ENERGY CONSERVATION INTERVENTIONS (LEVEL I)

A systematic review evaluated the effectiveness of energy conservation treatment for fatigue and QoL in pwMS (64). The authors included six trials (four RCTs and two CCTs) involving 494 participants, which evaluated different energy conservation interventions based on evidence-based protocols, which included education about balancing, modifying and prioritizing activities, rest, self-care, effective communication, biomechanics, ergonomics, and environmental modification. The results were mixed due to heterogeneity among the included studies. Meta-analysis of two high-quality studies showed that energy conservation interventions treatment was significantly more effective than no treatment (waiting controls) in reducing the impact of fatigue and in improving QoL in the short-term. This was further supported by the qualitative best-evidence synthesis of the other studies showing moderate to strong evidence (64). There was no evidence that MD fatigue management programs were more effective than placebo for any fatigue-related outcome.

Summary

Energy conservation interventions can be effective in reducing the impact of fatigue and improving QoL in pwMS in the short-term. More high-quality RCTs are still needed to investigate the usefulness of these treatments in the longer-term.

MINDFULNESS-BASED INTERVENTIONS (LEVEL I)

Mindfulness-based interventions have become increasingly popular in various areas of chronic disease management such as depression, stroke, chronic pain, etc. (65). Mindfulness-based interventions include a wide range of interventions, such as meditation, relaxation, and breathing techniques, yoga, Tai Chi, hypnosis, visual imagery, and spirituality (55). There are few studies evaluating the effects of the mindfulness-based approach in alleviating fatigue in pwMS. A recently published systematic review of mindfulness-based interventions found only three trials (two RCTs and one CCT) involving 183 participants (65). All trials emphasized on mindful breath awareness, mindful movement, and body awareness or "scanning." All three studies measured the effect of intervention on fatigue and found a significantly beneficial effect of intervention on fatigue scores. One included RCT found a significant post-intervention reduction in fatigue in both the overall population and in subgroup analyses of those with pre-intervention impairment. This beneficial effect was maintained at 6 months (65).

Summary

Mindfulness-based interventions can be beneficial for fatigue management in pwMS and are conceptually appealing. These interventions could be considered in a patient management plan.

COGNITIVE AND PSYCHOLOGICAL INTERVENTIONS (LEVEL II)

Several studies have investigated cognitive training in pwMS aiming mainly to improve attentional deficits, communication, and memory (66). Overall evidence for beneficial effects of psychological interventions in management of fatigue in pwMS is scarce. A systematic review reported that cognitive behavioral approaches were beneficial in the treatment of depression and in helping people adjust to, and cope with having MS (66). However, the authors did not find any studies focusing on psychological approaches to managing fatigue in pwMS. Findings from a few studies evaluating fatigue as a secondary outcome showed inconclusive and/or non-significant improvements in fatigue management (66).

A recent RCT ($n = 40$) showed that an internet-based cognitive behavior therapy (CBT) program – "MS Invigor8" was an effective treatment for MS-related fatigue (67). The CBT included eight tailored, interactive sessions with a clinical psychologist over 8–10 weeks. The treatment group reported significantly greater improvements in fatigue severity and impact as well as in anxiety, depression and quality-adjusted life years (67). Another RCT ($n = 72$) showed significantly greater improvements in fatigue in pwMS after eight weekly sessions of CBT ($p < 0.02$) compared to relaxation therapy (68). However, both groups showed clinically significant decreases in fatigue. ESs for reduction in fatigue from baseline to the end of treatment were 3.03 (95% CI 2.22–3.68) for the CBT group across the 8 months compared with the relaxation therapy group (ES 1.83; 95% CI 1.26–2.34) (68).

Summary

Psychological interventions, particularly CBT, can be a clinically and cost-effective treatment for MS fatigue. There has been a growing interest in these interventions as a means of empowering patients, improving symptoms and overall quality of life. Additional studies are warranted, particularly those that include larger numbers of people and longer term follow-up.

SUMMARY

Fatigue, a multidimensional, complex, and highly subjective symptom, is one of the most frequent symptoms of MS patients. It is associated with several factors or mechanisms. There is a continuing need for a comprehensive, multi-disciplinary long-term management, which includes both pharmacological and non-pharmacological interventions. This systematic review provides an evidence-based overview of the effectiveness of different interventions (pharmacological and non-pharmacological) currently used to alleviate fatigue in pwMS. It highlights the lack of, methodologically robust trials to evaluate effectiveness of MS fatigue management interventions.

Despite many interventions (both pharmacological and non-pharmacological) used for the management of fatigue in pwMS, effects of these vary considerably and any beneficial effect was at

best modest and/or is yet to be established. Non-pharmacological interventions (both exercise and psychological/educational interventions) appear to have a stronger and more significant favorable effect on reducing the impact or severity of fatigue compared to commonly prescribed pharmacological agents.

In conclusion, there is increasing awareness of the role of both pharmacological and non-pharmacological interventions in early and long-term management of fatigue in pwMS. Although this review highlights the lack of high-quality studies evaluating fatigue management strategies in pwMS (types, settings, components, modalities, and duration of therapy), it adds to the existing evidence by providing structured pre-defined "level of evidence" to support different interventions for the management of fatigue in this population. The findings from this review suggest that non-pharmacological approaches used in isolation and/or in combination with pharmacological agents should be the mainstay of management of fatigue in pwMS. Further studies across the broad range of interventions for the management of fatigue in MS are warranted, using high-quality research approaches.

REFERENCES

1. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. *Can J Neurol Sci* (1994) **21**(1):9–14.
2. MS Society Australia. *MS Practice – for Health Professionals.* (2014). Available from: www.msaustralia.org.au
3. Multiple Sclerosis Research Australia (MSRA). *Economic Impact of Multiple Sclerosis in 2010: Australian MS Longitudinal Study*. Multiple Sclerosis Research Australia: Chatswood, NSW (2010).
4. Multiple Sclerosis Council for Clinical Practice Guidelines. *Fatigue and Multiple Sclerosis: Evidence-Based Management Strategies for Fatigue in Multiple Sclerosis.* Washington DC: Paralyzed Veterans of America (1998).
5. Kos D, Kerckhofs E, Nagels G, D'Hooghe MB, Ilsbroukx S. Origin of fatigue in multiple sclerosis: review of the literature. *Neurorehabil Neural Repair* (2008) **22**(1):91–100. doi:10.1177/1545968306298934
6. Braley TJ, Chervin RD. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. *Sleep* (2010) **33**(8):1061–7.
7. Neumann M, Sterr A, Claros-Salinas D, Gütler R, Ulrich R, Dettmers C. Modulation of alertness by sustained cognitive demand in MS as surrogate measure of fatigue and fatigability. *J Neurol Sci* (2014) **340**(1–2):178–82. doi:10.1016/j.jns.2014.03.024
8. Multiple Sclerosis International Federation (MSIF). *Fatigue and MS, in MS in Focus.* London: Multiple Sclerosis International Federation (2011).
9. Brañas P, Jordan R, Fry-Smith A, Burls A, Hyde C. Treatments for fatigue in multiple sclerosis: a rapid and systematic review. *Health Technol Assess* (2000) **4**(27):1–61.
10. MacAllister WS, Krupp LB. Multiple sclerosis-related fatigue. *Phys Med Rehabil Clin N Am* (2005) **16**(2):483–502. doi:10.1016/j.pmr.2005.01.014
11. Asano M, Finlayson M. Meta-analysis of three different types of fatigue management interventions for people with Multiple Sclerosis: exercise, education, and medication. *Mult Scler Int* (2014) **2014**:798285. doi:10.1155/2014/798285
12. Janardhan V, Bakshi R. Quality of life in patients with multiple sclerosis: the impact of fatigue and depression. *J Neurol Sci* (2002) **205**(1):51–8. doi:10.1016/S0022-510X(02)00312-X
13. Krause I, Kern S, Horntrich A, Ziemssen T. Employment status in multiple sclerosis: impact of disease-specific and non-disease-specific factors. *Mult Scler* (2013) **19**(13):1792–9. doi:10.1177/1352458513485655
14. Khan F, Pallant JF, Brand C, Kilpatrick TJ. Effectiveness of rehabilitation intervention in persons with multiple sclerosis: a randomised controlled trial. *J Neurol Neurosurg Psychiatry* (2008) **79**(11):1230–5. doi:10.1136/jnnp.2007.133777
15. Sutherland G, Andersen MB. Exercise and multiple sclerosis: physiological, psychological, and quality of life issues. *J Sports Med Phys Fitness* (2001) **41**(4):421–32.
16. Kaires P. Fatigue in MS: cross-sectional correlation with brain MRI. *Neurology* (2000) **54**(8):1709–10. doi:10.1212/WNL.54.8.1709-a
17. Khan F, Turner-Stokes L, Ng L, Kilpatrick T. Multidisciplinary rehabilitation for adults with multiple sclerosis. *Cochrane Database Syst Rev* (2011) **2**:CD006036. doi:10.1002/14651858.CD006036.pub2
18. Thompson AJ. Symptomatic treatment in multiple sclerosis. *Curr Opin Neurol* (1998) **11**(4):305–9. doi:10.1097/00019052-199808000-00005
19. Khan F, Amatya B, Ytterberg C, Johansson S, Kesselring J. Content comparison of multidimensional, patient-reported outcome measures in multiple sclerosis rehabilitation and the International Classification of Functioning, Disability and Health (ICF): a systematic review. *Neurodegen Dis Manag* (2013) **3**(6):549–64. doi:10.2217/nmt.13.57
20. Schwid SR, Covington M, Segal BM, Goodman AD. Fatigue in multiple sclerosis: current understanding and future directions. *J Rehabil Res Dev* (2002) **39**(2):211–24.
21. Iriarte J, Katsamakis G, de Castro P. The fatigue descriptive scale (FDS): a useful tool to evaluate fatigue in multiple sclerosis. *Mult Scler* (1999) **5**(1):10–6. doi:10.1177/135245859900500103
22. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis* (1994) **18**(Suppl 1):S79–83. doi:10.1093/clinids/18.Supplement_1.S79
23. Schwartz JE, Jandorf L, Krupp LB. The measurement of fatigue: a new instrument. *J Psychosom Res* (1993) **37**(7):753–62. doi:10.1016/0022-3999(93)90104-N
24. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* (1989) **46**(10):1121–3. doi:10.1001/archneur.1989.00520460115022
25. Penner IK, Raselli C, Stöcklin M, Opwis K, Kappos L, Calabrese P. The fatigue scale for motor and cognitive functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult Scler* (2009) **15**(12):1509–17. doi:10.1177/1352458509348519
26. National Institute for Clinical Excellence (NICE). *Management of Multiple Sclerosis in Primary and Secondary Care. Clinical Guidelines 8.* London: National Institute for Clinical Excellence (2003).
27. National Health and Medical Research Council (NHMRC). *NHMRC Additional Levels of Evidence and Grades for Recommendations for Developers of Guidelines.* (2009). Available from: https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf
28. Krupp LB, Coyle PK, Doscher C, Miller A, Cross AH, Jandorf L, et al. Fatigue therapy in multiple sclerosis: results of a double-blind, randomized, parallel trial of amantadine, pemoline, and placebo. *Neurology* (1995) **45**(11):1956–61. doi:10.1212/WNL.45.11.1956
29. Weinshenker BG, Penman M, Bass B, Ebers GC, Rice GP. A double-blind, randomized, crossover trial of pemoline in fatigue associated with multiple sclerosis. *Neurology* (1992) **42**(8):1468–71. doi:10.1212/WNL.42.8.1468
30. Solari A, Uitdehaag B, Giuliani G, Pucci E, Taus C. Aminopyridines for symptomatic treatment in multiple sclerosis. *Cochrane Database Syst Rev* (2002) **4**:CD001330. doi:10.1002/14651858.CD001330
31. Khan F, Amatya B, Turner-Stokes L. Symptomatic therapy and rehabilitation in primary progressive multiple sclerosis. *Neurol Res Int* (2011) **740505**:22. doi:10.1155/2011/740505
32. Mohr DC, Hart SL, Goldberg A. Effects of treatment for depression on fatigue in multiple sclerosis. *Psychosom Med* (2003) **65**(4):542–7. doi:10.1097/01.PSY.0000074757.11682.96
33. Peuckmann V, Elsner F, Krumm N, Trottenberg P, Radbruch L. Pharmacological treatments for fatigue associated with palliative care. *Cochrane Database Syst Rev* (2010) **11**:CD006788. doi:10.1002/14651858.CD006788.pub2
34. Kos D, Duportail M, D'Hooghe M, Nagels G, Kerckhofs E. Multidisciplinary fatigue management programme in multiple sclerosis: a randomized clinical trial. *Mult Scler* (2007) **13**(8):996–1003. doi:10.1177/1352458507078392
35. Di Fabio RP, Soderberg J, Choi T, Hansen CR, Schapiro RT. Extended outpatient rehabilitation: its influence on symptom frequency, fatigue, and functional status for persons with progressive multiple sclerosis. *Arch Phys Med Rehabil* (1998) **79**(2):141–6. doi:10.1016/S0003-9993(98)90290-8
36. Patti F, Ciancio MR, Reggio E, Lopes R, Palermo F, Cacopardo M, et al. The impact of outpatient rehabilitation on quality of life in multiple sclerosis. *J Neurol* (2002) **249**(8):1027–33. doi:10.1007/s00415-002-0778-1
37. Storr LK, Sorensen PS, Ravnborg M. The efficacy of multidisciplinary rehabilitation in stable multiple sclerosis patients. *Mult Scler* (2006) **12**(2):235–42. doi:10.1191/135248506ms1250oa

38. Motl RW, McAuley E. Symptom cluster as a predictor of physical activity in multiple sclerosis: preliminary evidence. *J Pain Symptom Manage* (2009) **38**(2):270–80. doi:10.1016/j.jpainsymman.2008.08.004
39. Andreasen AK, Stenager E, Dalgas U. The effect of exercise therapy on fatigue in multiple sclerosis. *Mult Scler* (2011) **17**(9):1041–54. doi:10.1177/1352458511401120
40. Sabapathy NM, Minahan CL, Turner GT, Broadley SA. Comparing endurance- and resistance-exercise training in people with multiple sclerosis: a randomized pilot study. *Clin Rehabil* (2011) **25**(1):14–24. doi:10.1177/0269215510375908
41. Kjolhede T, Vissing K, Dalgas U. Multiple sclerosis and progressive resistance training: a systematic review. *Mult Scler* (2012) **18**(9):1215–28. doi:10.1177/1352458512437418
42. Latimer-Cheung AE, Pilutti LA, Hicks AL, Martin Ginis KA, Fenuta AM, MacKibbon KA, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. *Arch Phys Med Rehabil* (2013) **94**(9):1800e–28e. doi:10.1016/j.apmr.2013.04.020
43. Neill J, Belan I, Ried K. Effectiveness of non-pharmacological interventions for fatigue in adults with multiple sclerosis, rheumatoid arthritis, or systemic lupus erythematosus: a systematic review. *J Adv Nurs* (2006) **56**(6):617–35. doi:10.1111/j.1365-2648.2006.04054.x
44. Motl RW, Gosney JL. Effect of exercise training on quality of life in multiple sclerosis: a meta-analysis. *Mult Scler* (2008) **14**(1):129–35. doi:10.1177/1352458507080464
45. Pilutti LA, Greenlee TA, Motl RW, Nickrent MS, Petruzzello SJ. Effects of exercise training on fatigue in multiple sclerosis: a meta-analysis. *Psychosom Med* (2013) **75**(6):575–80. doi:10.1097/PSY.0b013e31829b4525
46. Rietberg MB, Brooks D, Uitdehaag BM, Kwakkel G. Exercise therapy for multiple sclerosis. *Cochrane Database Syst Rev* (2005) **1**:CD003980. doi:10.1002/14651858.CD003980.pub2
47. Rasova K, Havrdova E, Brandejsky P, Zálisová M, Foubikova B, Martinkova P. Comparison of the influence of different rehabilitation programmes on clinical, spirometric and spiroergometric parameters in patients with multiple sclerosis. *Mult Scler* (2006) **12**(2):227–34. doi:10.1191/135248506ms1248oa
48. Castro-Sánchez AM, Matarán-Peñarrocha GA, Lara-Palomo I, Saavedra-Hernández M, Arroyo-Morales M, Moreno-Lorenzo C. Hydrotherapy for the treatment of pain in people with multiple sclerosis: a randomized controlled trial. *Evid Based Complement Alternat Med* (2012) **2012**:473963. doi:10.1155/2012/473963
49. Gehlsen GM, Grigsby SA, Winant DM. Effects of an aquatic fitness program on the muscular strength and endurance of patients with multiple sclerosis. *Phys Ther* (1984) **64**(5):653–7.
50. Kargarfard M, Etemadifar M, Baker P, Mehrabi M, Hayatbakhsh R. Effect of aquatic exercise training on fatigue and health-related quality of life in patients with multiple sclerosis. *Arch Phys Med Rehabil* (2012) **93**(10):1701–8. doi:10.1016/j.apmr.2012.05.006
51. Pariser G, Madras D, Weiss E. Outcomes of an aquatic exercise program including aerobic capacity, lactate threshold, and fatigue in two individuals with multiple sclerosis. *J Neurol Phys Ther* (2006) **30**(2):82–90. doi:10.1097/01.NPT.0000282572.63297.3d
52. Salem Y, Scott AH, Karpatkin H, Concert G, Haller L, Kaminsky E, et al. Community-based group aquatic programme for individuals with multiple sclerosis: a pilot study. *Disabil Rehabil* (2011) **33**(9):720–8. doi:10.3109/09638288.2010.507855
53. Bayraktar D, Guclu-Gunduz A, Yazici G, Lambeck J, Batur-Caglayan HZ, Irkec C, et al. Effects of Ai-Chi on balance, functional mobility, strength and fatigue in patients with multiple sclerosis: a pilot study. *NeuroRehabilitation* (2013) **33**(3):431–7. doi:10.3233/NRE-130974
54. Bowling AC. Complementary and alternative medicine in multiple sclerosis. *Continuum (Minneap Minn)* (2010) **16**(5):78–89. doi:10.1212/01.CON.0000389935.84660.a5
55. Mehendale K, Aruin AS. Exercise approaches to ameliorate fatigue in people with Multiple Sclerosis. *J Nov Physiother* (2013) **3**:179. doi:10.4172/2165-7025.1000179
56. Mills N, Allen J, Carey-Morgan S. Does Tai Chi/Qi Gong help patients with Multiple Sclerosis? *J Bodywork Move Ther* (2000) **4**:39–48. doi:10.1054/jbmt.1999.0139
57. Beenakker EA, Oparina TI, Hartgring A, Teelken A, Arutjunyan AV, De Keyser J. Cooling garment treatment in MS: clinical improvement and decrease in leukocyte NO production. *Neurology* (2001) **57**(5):892–4. doi:10.1212/WNL.57.5.892
58. White AT, Wilson TE, Davis SL, Petajan JH. Effect of precooling on physical performance in multiple sclerosis. *Mult Scler* (2000) **6**(3):176–80. doi:10.1191/135245800701566043
59. Humm AM, Beer S, Kool J, Magistris MR, Kesselring J, Rösler KM. Quantification of Uhthoff's phenomenon in multiple sclerosis: a magnetic stimulation study. *Clin Neurophysiol* (2004) **115**(11):2493–501. doi:10.1016/j.clinph.2004.06.010
60. Lappin MS, Lawrie FW, Richards TL, Kramer ED. Effects of a pulsed electromagnetic therapy on multiple sclerosis fatigue and quality of life: a double-blind, placebo controlled trial. *Altern Ther Health Med* (2003) **9**(4):38–48.
61. Richards TL, Lappin MS, Acosta-Urquidi J, Kraft GH, Heide AC, Lawrie FW, et al. Double-blind study of pulsing magnetic field effects on multiple sclerosis. *J Altern Complement Med* (1997) **3**(1):21–9. doi:10.1089/acm.1997.3.21
62. Sandyk R. Treatment with weak electromagnetic fields improves fatigue associated with multiple sclerosis. *Int J Neurosci* (1996) **84**(1–4):177–86. doi:10.3109/00207459608987261
63. Thomas PW, Thomas S, Kersten P, Jones R, Nock A, Slingsby V, et al. Multicentre parallel arm randomised controlled trial to assess the effectiveness and cost-effectiveness of a group-based cognitive behavioural approach to managing fatigue in people with multiple sclerosis. *BMC Neurol* (2010) **10**:43. doi:10.1186/1471-2377-10-43
64. Thomas PW, Thomas S, Kersten P, Jones R, Slingsby V, Nock A, et al. One year follow-up of a pragmatic multi-centre randomised controlled trial of a group-based fatigue management programme (FACETS) for people with multiple sclerosis. *BMC Neurol* (2014) **14**(1):109. doi:10.1186/1471-2377-14-109
65. Blikman LJ, Huisstede BM, Kooijmans H, Stam HJ, Bussmann JB, van Meeteren J. Effectiveness of energy conservation treatment in reducing fatigue in multiple sclerosis: a systematic review and meta-analysis. *Arch Phys Med Rehabil* (2013) **94**(7):1360–76. doi:10.1016/j.apmr.2013.01.025
66. Simpson R, Booth J, Lawrence M, Byrne S, Mair F, Mercer S. Mindfulness based interventions in multiple sclerosis - a systematic review. *BMC Neurol* (2014) **14**:15. doi:10.1186/1471-2377-14-15
67. Thomas PW, Thomas S, Hillier C, Galvin K, Baker R. Psychological interventions for multiple sclerosis. *Cochrane Database Syst Rev* (2006) **1**:CD004431.
68. Moss-Morris R, McCrone P, Yardley L, van Kessel K, Wills G, Dennison L. A pilot randomised controlled trial of an Internet-based cognitive behavioural therapy self-management programme (MS Invigor8) for multiple sclerosis fatigue. *Behav Res Ther* (2012) **50**(6):415–21. doi:10.1016/j.brat.2012.03.001
69. van Kessel K, Moss-Morris R, Willoughby E, Chalder T, Johnson MH, Robinson E. A randomized controlled trial of cognitive behavior therapy for multiple sclerosis fatigue. *Psychosom Med* (2008) **70**(2):205–13. doi:10.1097/PSY.0b013e3181643065
70. Thomas S, Thomas PW, Kersten P, Jones R, Green C, Nock A, et al. A pragmatic parallel arm multi-centre randomised controlled trial to assess the effectiveness and cost-effectiveness of a group-based fatigue management programme (FACETS) for people with multiple sclerosis. *J Neurol Neurosurg Psychiatry*. (2013) **84**(10):1092–9. doi:10.1136/jnnp-2012-303816

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