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Review article

A qualitative review of the neurophysiological underpinnings of fatigue in multiple sclerosis

Afiqah Yusuf [a,*], Lisa Koski [b,c]

[a] Integrated Program in Neuroscience, McGill University, Montreal, QC H3A 1A1, Canada
[b] The Research Institute of the McGill University Health Centre, Canada
[c] Department of Neurology and Neurosurgery, McGill University, Montreal, QC H3A 1A1, Canada

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ABSTRACT

Fatigue is debilitating in multiple sclerosis (MS) and may have multiple causes. Recent investigations into objectively measurable correlates of fatigue have used transcranial magnetic stimulation (TMS) to examine a range of neurophysiological measures of neural excitability that may be altered in patients with MS. This qualitative review was conducted to test the hypothesis that changes in neural excitability are a contributing factor in MS-related fatigue. A search of the English language literature led to the compilation and synthesis of original research papers in which various aspects of neural excitability and neural transmission were measured using TMS in patients with MS. The resulting papers were classified into three categories of study relevant to fatigue: abnormalities in excitability and their correlation with self-reported fatigue; effects of exercise-induced fatigue on neural excitability; and effects of fatigue medications on neural excitability. Evidence of an association between fatigue and intracortical inhibition is both limited and conflicting, and no evidence suggests associations of fatigue with corticomotor excitability or neuronal conduction. Pharmacologically-induced changes in fatigue were found to correlate with changes in intracortical excitability. No conclusions could be drawn regarding neural excitability and exercise-induced fatigue, due to variability in study populations, outcome measures, and exercise protocols across different studies. Suggestions for future studies in this area are proposed with a view to identifying potentially modifiable factors contributing to fatigue in MS.

Contents

1. Introduction

Fatigue, defined as a "subjective lack of physical and/or mental energy, perceived by the individual or caregiver to interfere with usual and desired activities" [1], is a debilitating symptom reported by as

* Corresponding author at: McGill University, Royal Victoria Hospital, 687 Pine Avenue West R4.75, Montreal, QC H3A1A1, Canada. Tel.: +1 514 934 1934 x34420.
E-mail address: afiqah.yusuf@mail.mcgill.ca (A. Yusuf).

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many as 75% of people with multiple sclerosis (MS) [2]. Self-report questionnaires such as the Fatigue Severity Scale (FSS) [3] and Fatigue Impact Scale [4] were developed to measure the severity of fatigue and its impact on daily life. Unfortunately, the multifactorial nature of fatigue has hampered efforts to develop treatments targeting its underlying cause. Fatigue has been associated with a range of MS-associated variables, including sleep disorders, depression, anxiety, level of neurologic disability and disease course [5].

A growing number of studies seek to understand fatigue by examining differences in structural and functional measures of neural activity in patients with MS. The hypothesis tested in such research is that abnormalities in excitatory and/or inhibitory neural activity may contribute to the subjective experience of fatigue in people with MS. MS patients reporting fatigue show reduced glucose metabolism in frontal and premotor regions [6], and abnormally high increases in blood-oxygen-level-dependent signal during voluntary movement [7]. Abnormalities in neurophysiological measures of cortical excitability and neurotransmission have also been considered as possible contributors to fatigue. Dozens of studies have now examined abnormalities in corticospinal excitability, intracortical facilitation and/or intracortical inhibition in patients with MS using transcranial magnetic stimulation (TMS), although relatively few have investigated the relationship between such measures and self-reported fatigue.

Another approach to understanding the mechanisms underlying fatigue involves comparing the depth or rate of decline in performance on a motor task (motor fatigability) in MS patients with or without self-reported fatigue. While motor fatigability is driven largely by peripheral muscle fatigue in healthy subjects, changes within the corticospinal motor pathways such as decreased motoneuron firing rates, may also contribute to performance declines in patients with MS. These changes representing declines in "central activation" are known as *central fatigability* [8].

Finally, an association between clinical response to medications aimed at reducing fatigue, and changes in TMS measures of neural excitability would also provide support for the hypothesis that abnormalities in central activation are contributors to fatigue.

The time is right for a critical review of such studies with the aim of guiding future research in this area. This qualitative review focuses exclusively on studies in which TMS measures of neural excitability were examined in MS patients. These studies fall along three distinct lines of inquiry: 1) associations between neural excitability and self-reported fatigue, 2) central and peripheral correlates of muscular fatigue, and 3) effects of fatigue-alleviating medications on neural excitability.

2. Methods

On November 1st, 2011, the search terms "multiple sclerosis transcranial magnetic stimulation" were entered in PubMed to identify relevant research studies published in the English language: 131 results were retrieved from the search. The first author read the abstracts and excluded any papers that did not study patients with MS, or did not include a measure of neural excitability, or did not report on original research findings, e.g. review papers. Out of the 131 papers, 40 eligible papers were then examined in full and assigned for review under one or more of the three lines of inquiry listed above. Thirty-five of the 40 papers investigated whether components of neural excitability in MS patients were abnormal and thus, were categorized under inquiry 1. Nine of the 40 papers examined changes after muscular fatigue in patients with MS and were classified under inquiry 2. Five papers 40 papers were placed under inquiry 3; of these, two were also included in inquiry 1, and one was included in inquiry 2. The first author also checked the reference lists of the 40 articles, but no additional relevant papers were identified. Details on the methods and results of these studies were extracted and summarized in tabular form.

3. Part I: neural excitability and fatigue in MS

Each of the following sections begins with a brief explanation of the neurophysiological measures subsumed under each construct, i.e., corticospinal excitability, intracortical inhibition or facilitation, and transcallosal inhibition, before reviewing the data obtained on these measures from patients with MS.

3.1. Corticospinal excitability

The lowest stimulus intensity of TMS that can elicit a muscle response, i.e., the motor threshold reflects physiological as well as anatomical features of the corticospinal system [9]. Increased motor thresholds may indicate reduced neuronal membrane excitability, decreased number of corticomotor neurons and/or a diminished strength of corticospinal projection. The size of the motor evoked potential (MEP) in response to a single suprathreshold pulse can also reflect the excitability of and projections within the corticospinal tract [9]. Absent MEPs or decreased MEP amplitudes may indicate reduced cortical excitability, "temporal dispersion of the descending volley, conduction block" [10], or a loss of neurons or axons altogether [9]. Central motor conduction time (CMCT) is the conduction time between the motor cortex and spinal motor neurons, calculated by subtracting the spinal motor neuron to muscle latency from the cortex to muscle latency [11]. Prolonged CMCT may indicate reduced cortical excitability, "demyelination of central motor pathways, loss of large fibers, or slow summation of descending excitatory potentials in the corticospinal tract evoked by TMS i.e. temporal dispersion" [10].

Thirty-five studies examined differences in motor thresholds, MEP amplitude, and CMCT between MS patients and healthy controls. Compared with healthy controls, patients with MS were observed to have elevated thresholds in 10 out of 20 studies, smaller MEPs in 17 out of 25 studies, and prolonged CMCTs in 22 out of 26 studies. Only three studies attempted to understand the underlying neurophysiology of fatigue by examining its association with corticospinal excitability [12–14] (Table 1). All three studies grouped MS patients with the relapsing–remitting MS course according to their scores on the FSS: patients "with fatigue" scored more than 4 on the scale, while the remaining patients were "without fatigue". Two of the studies excluded patients with motor symptoms in the upper extremities [12,14], while the third [13] had no exclusion criteria related to upper extremities. None of the three studies found evidence of an association between self-reported fatigue and motor thresholds, MEP amplitudes, or central motor conduction time [12–14].

3.2. Intracortical excitability: inhibition and facilitation

TMS techniques may also provide information on the interplay between excitatory and inhibitory mechanisms acting on corticospinal neurons. The paired pulse method involves delivering two stimuli to the same cortical region; the two pulses interact and result in either a larger or smaller MEP amplitude than delivering one pulse alone, depending on the intensities of the stimuli and the time between them, i.e., interstimulus interval.

3.2.1. Short-interval intracortical inhibition (SICI)

SICI refers to the suppression of MEP amplitude, reflecting GABA-ergic intracortical inhibitory mechanisms, which is observed when a suprathreshold TMS pulse is preceded 1–6 ms earlier by a subthreshold conditioning pulse [15]. Three [12,16,17] out of four studies provided evidence for reduced short-interval intracortical inhibition in MS patients compared to healthy controls, while the remaining study [13] showed no difference in intracortical inhibition. Two of these studies compared short-interval intracortical inhibition between patients reporting high vs. low fatigue: Liepert et al. found reduced short-interval intracortical inhibition in patients reporting