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Research report

Multiple measures of corticospinal excitability are associated with clinical features of multiple sclerosis

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HIGHLIGHTS

- Corticospinal excitability and inhibition are altered in individuals with MS.
- Cortical and interhemispheric excitability accounts for unique variance in EDSS.
- Measures of corticospinal excitability may be used as biomarkers of MS disability.

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ABSTRACT

In individuals with multiple sclerosis (MS), transcranial magnetic stimulation (TMS) may be employed to assess the integrity of corticospinal system and provides a potential surrogate biomarker of disability. The purpose of this study was to provide a comprehensive examination of the relationship between multiple measures corticospinal excitability and clinical disability in MS (expanded disability status scale (EDSS)). Bilateral corticospinal excitability was assessed using motor evoked potential (MEP) input–output (IO) curves, cortical silent period (CSP), short-interval intracortical inhibition (SICI), intracortical facilitation (ICF) and transcallosal inhibition (TCI) in 26 individuals with MS and 11 healthy controls. Measures of corticospinal excitability were compared between individuals with MS and controls. We evaluated the relationship(s) between age and clinical demographics such as age at MS onset (AO), disease duration (DD) and clinical disability (EDSS) with measures of corticospinal excitability. Corticospinal excitability thresholds were higher, MEP latency and CSP onset delayed and MEP durations prolonged in individuals with MS compared to controls. Age, DD and EDSS correlated with corticospinal excitability thresholds. Also, TCI duration and the linear slope of the MEP amplitude IO curve correlated with EDSS. Hierarchical regression modeling demonstrated that combining multiple TMS-based measures of corticospinal excitability accounted for unique variance in clinical disability (EDSS) beyond that of clinical demographics (AO, DD). Our results indicate that multiple TMS-based measures of corticospinal and interhemispheric excitability provide insights into the potential neural mechanisms associated with clinical disability in MS. These findings may aid in the clinical evaluation, disease monitoring and prediction of disability in MS.

1. Introduction

Multiple sclerosis (MS) is an idiopathic inflammatory disorder of the central nervous system [1], characterized by the demyelination of white matter throughout the brain and spinal cord [2], which can be observed even early in the disease [1]. There is substantial individual variability in disease progression in MS, with

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the majority of individuals beginning in a relapsing stage of the disease (relapsing-remitting MS (RRMS)) which can transition to a secondary progressive stage (SPMS) in later years leading to more permanent disability [3,4].

Magnetic resonance imaging (MRI) is one tool that has been used as a measure of disease state, which plays a major role in MS diagnosis and in the monitoring of disease progression. However, the evidence for a consistent relationship between neuroimaging findings and disability remains incomplete [5]. Peripherally and centrally evoked potentials may also play an important supportive role in the clinical evaluation of MS, providing functional information not available with conventional MRI [3,6].

Motor evoked potentials (MEPs) elicited using transcranial magnetic stimulation (TMS) over the primary motor cortex (M1) are a useful way to assess corticospinal excitability as conducted from the central to peripheral nervous system. In individuals with MS, TMS elicited MEPs may be employed to assess the integrity of corticospinal system; multiple studies indicate that MEPs may provide a potential surrogate biomarker of disease state and progression [1,2,6–10]. Several TMS-based neurophysiological measures demonstrate abnormalities in corticospinal excitability in individuals with MS, including altered central motor conduction time (CMCT), longer cortical silent periods (CSP) [2], delayed MEP latency [1,2,11,12], decreased MEP amplitudes [1,2,8,11], lower short-interval intracortical inhibition (SICI) [8], abnormal motor thresholds [8,10,13,14], and altered interhemispheric interactions [2,8], with considerable variability between individuals. These abnormalities in TMS measures have been suggested to be a result of abnormal propagation of neural signals throughout the corticospinal system, possibly due to partial demyelination of corticospinal tracts and/or by lesions in the motor cortices [2,6,13]. Typically, previous research in MS has assessed corticospinal excitability of MEP amplitudes at a single suprathreshold intensity [1,2,6]. Importantly, studies of corticospinal excitability in MS have not utilized the MEP input–output (IO) curve which assesses corticospinal excitability using a range of stimulator intensities to provide information about neurons that are intrinsically less excitable or spatially further from the central representation of the target muscle. As such, IO curves offer a more comprehensive evaluation of overall corticospinal excitability as compared to motor thresholds, MEP amplitude or latency [15–19].

The most common clinical outcome measure of disability in individuals with MS is the expanded disability status scale (EDSS) [20]. The EDSS assesses levels of motor, sensory and cognitive disability and is informative as a measure of neurological impairment; however, it is limited by poor inter–rater reliability, low sensitivity to clinical change, the nature of an ordinal scale, and dependency on clinician interaction with the patient [21–23]. These limitations highlight the need for more reliable and sensitive neurobiological markers of disease state in order to confirm and complement clinical measures and assessments.

Importantly, some studies show that TMS-based assessments of corticospinal excitability correlate with clinical measures of disability in individuals with MS. Specifically, abnormal transcallosal inhibition (TCI) and CMCT is observed in certain individuals with MS [10,24–26]. Correlations between TCI and EDSS scores has been observed [10], yet this finding has not been consistently demonstrated in individuals who show a RRMS pattern of disease [27]. Further, relationships have been demonstrated between EDSS scores and MEP amplitudes [1], MEP latencies, motor thresholds, and short interval intracortical facilitation (SICF) [6,13,14]. These TMS-based measures may relate to dysfunction in the corticospinal neurons as well as clinical impairment in motor function [28–32]. However, past studies have largely considered measures in isolation rather than comprehensively assessing multiple indices of neurophysiological function in a group of individuals with MS. Further, no studies investigated the relationship between MEP IO curves and clinical measures of disability. Thus, there is a critical need for a full examination of the relationship between multiple measures of neurophysiology and disability to better understand which measures are most beneficial to characterize disease state in MS [33]. It is possible that employing a battery of corticospinal excitability measures may provide additional insights into the neural substrates underlying MS-related disability as compared to single measures collected in isolation.

Therefore, the aims of this study were to investigate: (1) whether multiple bilateral single and paired-pulse TMS measures of intracortical and interhemispheric excitability differ between individuals with MS and healthy controls, (2) consider if these measures are associated with commonly used clinical demographics and clinical disability, and (3) determine whether combining multiple measures of intracortical and interhemispheric corticospinal excitability predicts clinical disability (EDSS) beyond that of commonly used clinical demographics (e.g. AO, DD) in individuals with MS. We hypothesized that there would be significant differences between individuals with MS and healthy controls in: (1) corticospinal excitability thresholds, (2) interhemispheric and intracortical inhibitory circuitry and (3) MEP IO amplitude curve and duration as well as MEP latency. We expected that: (1) increased corticospinal excitability thresholds, decreased magnitude and prolonged duration of TCI, decreased linear slope of the MEP IO amplitude curve and MEP latency would be related to clinical demographics (age of MS onset, disease duration) and clinical disability (EDSS), and (2) multiple measures of corticospinal excitability would predict a significant amount of variance in MS-related disability.

2. Methods

2.1. Participants

Twenty-six individuals (mean age 41.4 years, range: 28–55 years, 5 male) diagnosed with RRMS and 11 healthy controls (mean age 45.6 years, range: 32–58 years, 3 male), were included in the study. Individuals with MS had an EDSS median score of 2.0 (range of 0.0–6.0), mean age at onset of MS (AO) of 40.2 years (range 27–53) and mean disease duration (DD) of 7.6 years (range 0.5–28). All individuals with MS were voluntarily on glatiramer acetate (GA, Copaxone®) treatment at the time of testing, and had previously been using GA treatment for 0–54 (mean 14.5) months. GA was administered as per standard and approved dose and regimen indicated in the Copaxone® product monograph. Additionally, no one from the MS group experienced a relapse in the 3 months prior to participation in this study. The University of British Columbia research ethics board approved all aspects of the study protocol and informed consent was obtained from each participant in accordance with the Declaration of Helsinki. Measures of TMS-elicited corticospinal excitability occurred on one occasion in a session lasting ~2 h and clinical assessments were conducted on a separate day by a licensed physical therapist.

2.2. Electromyographic (EMG) recording

TMS-elicited MEPs were recorded using surface electromyography (EMG). EMG was recorded bilaterally from participants' extensor carpi radialis (ECR) muscle with 3 cm diameter circular surface recording electrodes (Covidien, Mansfield, MA). EMG data were collected using LabChart software (LabChart 7.0). EMG signals were sampled at 40,000 Hz, pre-amplified (1000×) and band-pass filtered at 10–1000 Hz using a Powerlab data acquisition system and two bioamplifiers (AD instruments, Colorado Springs, CO). Data