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

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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

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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.

Keywords

Multiple sclerosis; Transcranial magnetic stimulation; Corticospinal excitability; Expanded disability status scale (EDSS); Human; Brain

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 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 were recorded in a 450 ms sweep from 100 ms before to 350 ms after TMS delivery.

2.3. Transcranial magnetic stimulation (TMS) assessment

During TMS, participants were seated comfortably in an adjustable chair. Single pulse and paired pulse TMS was delivered using a figure-of-eight shaped coil (Magstim 70 mm P/N 9790, Magstim Co., UK) connected to a Magstim 200^2 stimulator (Magstim Co., UK). Each individual participant's MRI scan was used for TMS targeting and position monitoring using Brainsight™ neuronavigation software package (Rogue Research Inc., Montreal, QC, Canada). The 'hotspot' for eliciting MEPs in the contralateral ECR was found by positioning the coil over the scalp region overlying the hand/forearm M1 representation [34]. Standard procedures for determining resting motor threshold (RMT) [64] and active motor threshold (AMT) [35] were performed. TMS pulses were delivered at a random rate between 0.15 and 0.2 Hz throughout the experiment.

2.4. Data collection procedure

MEP IO curves, SICI, intracortical facilitation (ICF), CSP and TCI were recorded from the ECR bilaterally. For MEP IO curves, single TMS pulses were applied over the left and right M1 from 105 to 155% of AMT in increments of 10% (6 per intensity for a total of 36 pulses over each hemisphere) while participants maintained 20% of a maximum voluntary

contraction (MVC) in the contralateral ECR. Participants were asked to squeeze a handgrip dynamometer (AD Instruments, Colorado Springs, CO) to produce an active isometric contraction in the arm contralateral to the identified ECR hotspot. The force signal was digitized and presented on a computer screen in front of the participant for real-time performance feedback in order to maintain a constant level of force production during the assessment. The linear slope of the IO curves were determined from a plot of MEP peak to peak amplitude and duration versus stimulator intensity.

The paired-pulse paradigms, SICI and ICF, were performed as previously described [36], where a subthreshold conditioning stimulus (CS) was followed by a suprathreshold test stimulus (TS) over the M1 hotspot for ECR. The interstimulus interval (ISI) for SICI and ICF was 2 and 12 ms to measure intracortical inhibitory and facilitatory circuits respectively [36,37]. To measure SICI and ICF, a block of TMS pulses consisting of 20 stimuli each of the TS alone, and paired TMS pulses with ISI of 2 ms (SICI) and ISI of 12 ms (ICF) (60 total trials) were collected in a randomized order. The CS was set at 90% of AMT for SICI and ICF, and was kept consistent throughout the experiment. The maximum stimulator output of the TS intensity was adjusted to consistently evoke MEPs in the contralateral ECR of ~1 mV. SICI and ICF were expressed and analyzed as a ratio of CS over TS MEP amplitude (mV), where smaller values represent greater inhibition and greater values represent enhanced facilitation, respectively.

CSP duration [38] was tested with participants maintaining a contraction of the contralateral ECR of 20% MVC and 10 single pulses of TMS were applied over the left and right M1 at an intensity of 150% AMT. The duration (in ms) of the CSP was determined to be from the MEP offset to the re-onset of muscle activity within the ECR muscle [39,40]. For TCI assessment, participants were asked to produce an active isometric contraction of 50% maximum grip force output in the arm ipsilateral to the identified ECR hotspot while 20 single TMS pulses were delivered at 150% RMT. TCI was quantified by the ipsilateral silent period (iSP), defined as the transient reduction in volitional EMG activity elicited by TMS applied over M1 ipsilateral to the active muscle [41–43]. To calculate the CSP and iSP, data for each hemisphere were full-wave rectified and averaged for each hemisphere for each participant. Mean pre-stimulus EMG amplitude (100 ms prior to TMS delivery) was defined as baseline muscle activity. The onset of the CSP was defined as the end of the MEP determined manually. The onset of the iSP was defined as the post-stimulus time point where the rectified EMG signal fell below pre-stimulus mean EMG and continued to decrease to less than 2 standard deviations below this level. The CSP and iSP offset was defined as the point at which the EMG signal resumed the level of the pre-stimulus mean activity consistently for a minimum of 2 ms [42]. The CSP and iSP duration comprised all data points between the onset and offset. The magnitude of iSP was defined as the average EMG level during the iSP (iSP_{mean}) [44]. The iSP_{mean} was then expressed as a ratio of the mean pre-stimulus EMG ($iSP_{mean}/prestim_{mean}$), where a lower value indicates more inhibition. Custom MATLAB scripts (Mathworks, Natick, MA) were used to identify the MEP IO curves (peak to peak amplitude, latency and duration of MEPs), SICI/ICF, and CSP and iSP duration and onset for each participant.

2.5. Statistical analysis

Following visual inspection of the data and objective testing using the Shapiro–Wilk test, all data were found to be normally distributed ($W \geq 0.858$, $p \geq 0.073$), except for AMT ($W = 0.837$, $p = 0.040$), EDSS ($W = 0.883$, $p = 0.008$) and DD ($W = 0.868$, $p = 0.004$). Mixed two-way analysis of variance (ANOVA) was performed to evaluate hemispheric differences (within-subjects factor: left and right hemisphere) and differences between MS and controls (between-subjects factor: MS and Control groups) for RMT, log-transformed AMT, linear slope of the MEP IO amplitude and duration curve, MEP latency, CSP onset and duration, SICI/ICF and iSP magnitude and duration (measures of TCI). Post hoc testing was performed using Tukey's HSD. Statistical significance was set to $p < 0.05$.

If significant hemispheric differences in measures of cortical excitability were not determined with initial two-way ANOVAs, data were averaged across hemispheres. Subsequently, these data were used in exploratory bivariate correlation analyses with clinical measures of bilateral impairment of individuals with MS. The results of the correlation analyses were used to inform the dependent measures that were entered into a hierarchical multiple linear regression designed to explain the variance in clinical outcome that may be predicted by neurophysiological measures. Bivariate correlational analyses (Pearson's r_p for normally distributed data or Spearman's r_s for non-normally distributed data) were conducted to characterize the strength in relationships between RMT, AMT, MEP amplitude and duration IO curve, MEP latency, SICI/ICF, CSP and iSP onset and duration with age, AO, DD and EDSS. As the correlation analyses were run to determine which dependent measures to use in the regression analysis statistical significance was set to $p < 0.05$. Additionally, Fischer's Z-test was performed to directly determine the strength of correlation coefficients between MS and controls for age versus neurophysiological measures.

Finally, a hierarchical multiple linear regression analysis was performed to assess the amount of variance in clinical assessment of disability (EDSS) that was explained by measures of iSP, linear slope of the MEP amplitude IO curve and other clinical demographics (AO and DD). AO and DD were the first predictors entered into the model to account for age of diagnosis and duration of MS and since these are commonly used measures of clinical demographics in MS. The iSP duration was the next predictor entered into the model, followed by the linear slope of the MEP amplitude IO curve. The order of entry was based on correlation results, indicating these measures were most strongly related to clinical disability.

Zero-order, part, and partial correlations were produced for each model. Acceptable collinearity between multiple predictors was determined using the variance inflation factor (below 10) and tolerance levels (above 0.1) [45]. Residual statistics and plots were produced to ensure normality and homoscedasticity of data. Durbin–Watson diagnostics were provided to ensure independence of the residuals [45]. For each statistical test, the significance level was set at $p < 0.05$. All statistical procedures were conducted using SPSS software (SPSS 22.0).

3. Results

During data processing, some participants with MS did not display quantifiable CSP ($n = 3$) or MEP input–output (IO) curves ($n = 4$). MEPs at 155% AMT could not be collected in eight participants with MS due to the required TMS stimulus output being greater than 100% maximum stimulator output (MSO). In these cases, the linear slope of the MEP IO curve was calculated from 105 to 145% AMT. Also, CSP and MEPs at 155% AMT could not be collected in one control participant since the required TMS stimulus output was greater than 100% MSO. Therefore, participants that did not display quantifiable CSP were not included in the statistical analysis for CSP, however the other neurophysiological data collected for these individuals was retained. For MEP latency, no difference was found between stimulation intensities ($F_{(5,135)} = 1.012$, $p = .413$) and therefore the data was collapsed to give an average latency (across TMS stimulation intensities) for the MS and control groups for each hemisphere.

3.1. Comparisons between hemispheres and individuals with MS and controls

Two-way ANOVA revealed significant differences between groups (MS and controls) for linear slope of MEP duration ($F_{(1,32)} = 15.086$, $p < .001$), RMT ($F_{(1,33)} = 5.775$, $p = .022$), log-transformed AMT ($F_{(1,32)} = 7.025$, $p = .012$) and CSP onset ($F_{(1,31)} = 7.344$, $p = .011$), with no significant differences between hemispheres and no interaction between hemisphere and group (MS and controls). Additionally, two-way ANOVA revealed a difference between groups (MS and controls) for MEP latency ($F_{(1,32)} = 10.889$, $p = .002$) and a difference between hemispheres ($F_{(1,32)} = 4.471$, $p = .042$). Post hoc testing using Tukey's HSD revealed that individuals with MS had greater MEP latency in the left hemisphere ($p = 0.015$) whereas controls showed no hemispheric difference ($p = 0.986$). Individuals with MS displayed prolonged MEP duration, higher RMT and AMT, delayed CSP onset and greater MEP latency compared to healthy controls (Fig. 1).

3.2. Correlations between measures of cortical excitability and clinical measures

Statistically significant correlations were revealed between measures of corticospinal excitability, age, clinical demographics and disability in MS (DD and EDSS). Age correlated with RMT ($r_p = 0.623$, $p = 0.001$) and AMT ($r_s = 0.543$, $p = 0.006$) for individuals with MS but not for healthy controls. However, Fischer's Z-test revealed no significant difference between the bivariate correlation coefficients between MS and controls for RMT with age ($Z = -1.2$, $p = 0.2301$) and AMT with age ($Z = -0.84$, $p = 0.401$). DD correlated with RMT ($r_s = 0.503$, $p = 0.012$) and age ($r_s = 0.488$, $p = 0.013$) (Fig. 2A and B). EDSS correlated with the linear slope of the MEP amplitude IO curve ($r_s = -0.595$, $p = 0.003$) and iSP duration ($r_s = 0.392$, $p = 0.05$) (Fig. 2C and D). Finally, confirming previous work, EDSS correlated with RMT ($r_s = 0.408$, $p = 0.048$) and age ($r_s = 0.468$, $p = 0.018$).

3.3. Associations between EDSS, TCI and slope of the MEP amplitude IO curve

Results of the regression analysis are summarized in Table 1. The initial model (AO and DD) did not explain a significant amount of variance in clinical disability (EDSS). The relationship between AO and DD with EDSS is illustrated in Fig. 3A and B. In the second model, the addition of iSP duration explained a unique amount of variance in EDSS ($\Delta R^2 =$

0.201, $p = 0.023$) and the overall model was significant ($R^2 = 0.376$; $F_{(3,19)} = 3.824$; $p = 0.027$). The relationship between iSP duration and EDSS is illustrated in Fig. 3C. Further, the addition of slope of the MEP amplitude IO curve to the model explained an additional amount of unique variance in EDSS ($\Delta R^2 = 0.258$, $p = 0.002$) yielding an overall model that explained the greatest amount of unique variance in clinical disability (EDSS) ($R^2 = 0.635$; $F_{(4,18)} = 7.822$; $p = 0.001$). The relationship between the slope of the MEP amplitude IO curve and EDSS is illustrated in Fig. 3D. Individuals with greater EDSS scores indicating more clinical disability also displayed prolonged iSP duration and lower overall levels of M1 corticospinal excitability with increasing TMS intensity (Fig. 3).

4. Discussion

In this investigation, multiple TMS measures were used to characterize differences in bilateral corticospinal excitability between individuals with MS and healthy controls. We evaluated relationships between multiple measures of bilateral corticospinal excitability and measures of clinical demographics and disability to better understand which measures are most beneficial to characterize disease state in individuals with MS. We provide the first report of a difference in delayed onset of local corticospinal inhibition (CSP onset) between individuals with MS and controls. In addition to confirming previous reports that increased cortical motor thresholds are correlated with increased EDSS [6], the present study showed that elevated cortical thresholds were related to increasing age and DD. Critically, both prolonged iSP duration and decreased slope of the MEP amplitude IO curve accounted for unique variance in clinical disability (EDSS) beyond that of clinical demographics (AO and DD). Additionally, our data confirms previous work demonstrating consistently elevated resting and active motor cortical thresholds, prolonged MEP duration and delayed MEP latency in individuals with MS [8,10,13,14]. The findings of the present study both support and extend previous literature suggesting differences in interhemispheric and corticospinal excitability between MS and healthy controls. Further we show that abnormal corticospinal excitability in individuals with MS affects multiple levels of neurophysiological function in the cortex. These data provide further insights into the potential neural dysfunction associated with clinical disability in MS.

4.1. Corticospinal and interhemispheric excitability and the relationship to clinical measures

Along with confirming previous reports of higher motor thresholds in individuals with MS compared to controls [10,13,14], and the association of increased thresholds with clinical measures such as EDSS [6], the current work also shows that lower MEP IO curve slope was associated with greater disability (EDSS). MEP amplitude IO curves index the excitability of neurons that are central and spatially further from the central representation of the target muscle [15–17]. Therefore, MEP amplitude IO curve data provides additional information about the strength of overall corticospinal representation of a target muscle (ECR). Previous studies have shown that individuals with MS display decreased MEP amplitudes compared to healthy controls, and that this measure is associated with clinical function when single pulse TMS is applied at a single suprathreshold intensity over both upper and lower limb muscle representations in M1, and is suggested to be the result of axonal damage or

demyelination in the corticospinal tracts [1,2]. The current work extends these findings by demonstrating that capturing the strength of the overall corticospinal representation (via a MEP IO curve) provides useful information about the dysfunction of the corticospinal system, including the extents of the target muscle cortical representation and their corticospinal output, that relates to clinical disability (EDSS) in individuals with MS. Our findings of decreased slope in the MEP IO amplitude curve associated with increased disability may indicate that the neurons spatially further away from the central target muscle representation, or those that are intrinsically less excitable, have a greater degree of dysfunction due to advanced cortical damage and demyelination of corticospinal output that is associated with decreased clinical function.

The current study also confirms previous reports showing that abnormally prolonged iSP duration positively correlates with increasing disability measured by EDSS [10]. TCI measures interhemispheric inhibition on the contralateral homologous M1 representation [46–50], likely mediated by transcallosal pathways distinct from corticospinal output fibres [51–54]. Studies have shown abnormalities in the transmission time of interhemispheric interactions by a prolonged latency in onset and duration of the iSP [10,24–26], without displaying a change in the magnitude of the iSP. Interhemispheric transcallosal projections are known to be affected frequently by demyelinating white matter lesions in early MS [55–57], and prolonged latency and duration of TCI has been found to correlate with affected corpus callosum areas detected with mid-sagittal MRI slices [25]. It has been suggested that the reduction in transmission time of TCI and the prolongation of TCI duration, without a change in the magnitude, is potentially due to desynchronization of callosal activity from damage to transcallosal fibres. Past work has postulated that TCI duration is the most sensitive TMS measure of demyelination of the corpus callosum as changes in TCI magnitude and latency seem to occur with greater total callosal damage (≥50%) [25]. Therefore, TCI duration is potentially able to detect abnormalities in transcallosal connectivity in the earlier stages of the disease.

The current work extends previous findings by demonstrating that combining multiple TMS measures of corticospinal and interhemispheric excitability (i.e. slope of the MEP IO curve and iSP duration) accounts for a significant amount of unique variance in clinical disability as measured by EDSS, beyond that of clinical demographics (i.e. AO and DD). These results indicate the potential usefulness of multiple TMS measures as surrogate markers of clinical disability that complement currently used clinical assessment tools (e.g., EDSS) in individuals with MS. A combination of interhemispheric and corticospinal TMS excitability measures along with clinical demographics may be useful for prediction of disability in individuals with MS, as well as serving as a measure of disease state and treatment monitoring as similarly suggested in the prediction of recovery of function [58] and manual dexterity [41] in stroke. Decreased corticospinal and interhemispheric excitability in individuals with MS may result from a deficit in propagation of neural signals throughout the corticospinal system [2,6,13]. This might be caused by demyelination of the corticospinal tracts, loss of corticospinal fibres by a lesion in the motor cortices, irregular activity of spinal interneurons, and abnormal membrane potentials at the cortical and/or spinal levels. However, further work combining TMS-evoked potentials and novel

neuroimaging of the corticospinal system is warranted to further elucidate these speculations.

Lastly, the current study found that decreased cortical motor excitability (i.e. higher RMT and AMT values) was associated with increasing age only in the MS group, yet with a direct comparison of the correlation coefficients was not found to be significantly different between MS and controls. Moreover, higher resting motor threshold values were associated with increased DD. The finding that age correlated positively with excitability thresholds in MS and not in the healthy controls could possibly be further indication that the progression of corticospinal pathway demyelination in MS accentuates other age related changes in neurophysiological function [59], although with no difference in correlation coefficients when directly comparing MS and controls, the interpretation of these results should be tempered with caution. Further work employing longitudinal studies is needed to more carefully consider this issue.

4.2. Delayed CSP and MEP onset in MS

This is the first study to report differences in CSP onset between MS and healthy controls. The excitability of cortical inhibitory networks within M1 are integral to motor control [60,61]. Specifically, CSP duration is thought to indicate the state of cortical and spinal inhibitory networks [38,60–62]. Several studies suggest that the initial portion of CSP duration is due to spinal mechanisms, and the latter portion due to long-interval intracortical inhibition associated with gamma-aminobutyric acid-B ($GABA_B$)-like mechanisms at the cortical level (for review see: Terao and Ugawa [38]). The current study found CSP onset was significantly delayed bilaterally in MS compared to controls, without a difference in CSP duration. The finding that CSP duration was not different, but CSP onset was, may indicate a prolonged evoked potential period in individuals with MS compared to healthy controls, which may be indicative of similar neural underpinnings to the proposed mechanisms of the prolonged MEP and TCI duration.

Conversely, since CSP is thought to indicate the state of cortical and spinal inhibitory networks [38,60–62], it is also possible that the delayed onset of CSP could be due to abnormal regulation of local corticospinal inhibitory mechanisms within M1. CSP measures did not correlate with any clinical measure, which is in line with previous work [2]. Nevertheless, it has been suggested that measurements of CSP can be a useful marker to detect underlying motor tract abnormalities in those with paresis due to stroke and in those MS patients without overt motor deficits [2,63]. The present finding of a delayed onset of CSP suggests that CSP abnormalities may be an indicator of weakening of corticospinal tract integrity in the early stages of RRMS.

4.3. Prolonged MEP duration in MS

To our knowledge, one other study has reported prolonged duration of MEPs in MS compared to healthy controls [14]. They suggested that MEP duration may provide more information about impulse propagation down the descending corticospinal tracts even though there may be normal central motor conduction times [14]. Further, we suggest it may be that in the earlier stages of the disease (RRMS) there is variable demyelination of

corticospinal tracts, which could lead to a misfiring of individual groupings of corticospinal output neurons descending within the pyramidal tracts, leading to asynchronous propagation of actions potentials. Such asynchronous firing could then result in a prolonged evoked potential period, similar to a prolonged TCI duration [25]. It is possible that a prolonged MEP duration without a change in MEP amplitude could be mediated by similar variable axonal demyelination as a prolonged TCI duration [25]. There was a lack of relationship between MEP duration, age, clinical demographics (AO and DD) and disability (EDSS). This may be due to the earlier stages of RRMS displaying more sparse and variable demyelination in individual groupings of corticospinal neurons, which may become greater and more uniform as the disease progresses.

Additionally, there was longer MEP latency in individuals with MS confirming previous findings [1,2,8,11,12]. An increased MEP latency would indicate a disruption of overall corticospinal neural transmission, which could be due to demyelination of cortical interneurons, pyramidal cells or the descending corticospinal tracts. However, we did not find a relationship between MEP latency and EDSS as reported in previous studies [6]. A potential explanation for why we did not observe changes in MEP latency is that the current work only included RRMS patients, whereas previous studies included individuals with RRMS as well as individuals with primary and secondary progressive MS [6].

There are limitations to this study. The sample of participants were all diagnosed with RRMS, therefore the current results cannot be generalized to individuals with secondary or primary progressive MS. Further, the sample of participants was heterogeneous in terms of age of onset, disease duration and EDSS. Heterogeneity of sample population provides a potential increased generalizability of results, while conversely making it difficult to interpret the relationships between corticospinal excitability measures and clinical evaluation. We were not able to collect full data sets for the multiple TMS-based measures in all participants. The decreased numbers of individual participants within these data sets were due to contraindications to TMS, inability to elicit measurable MEPs, or that TMS maximum stimulator output was reached (e.g. during MEP IO curve collection). This decreased our overall sample size, especially for comparisons of TMS-evoked and clinical measures. We chose to include all data collected despite the fact that some participants did not have full datasets. We attempted to statistically control for potential biases associated with this decision by excluding participants from correlation and regression analyses if missing values were present. The cross-sectional research design provided information from a single time point only, making it unclear if the observed differences in corticospinal excitability and function were present prior to the clinical diagnosis and/or if there were changes in response to different intervention strategies. Overall, the limitations identified do not pose a significant threat to the validity of the results reported but do provide additional context for interpretation of results.

5. Conclusion

These results suggest that multiple measures of TMS-evoked potentials of corticospinal and interhemispheric excitability complement established clinical measures in individuals with MS as markers of disability. Combining multiple measures of corticospinal and

interhemispheric excitability (i.e. slope of the MEP IO curve and iSP duration) accounted for a unique amount of variance in clinical disability (i.e. EDSS), beyond that of clinical demographics (i.e. AO and DD). Also, RMT shows the most consistent difference between MS and controls, along with a relationship between age and clinical demographics (i.e. DD). These findings may be used as biomarkers to further current clinical evaluation, treatment monitoring, and prediction of disability in individuals with MS.

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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.

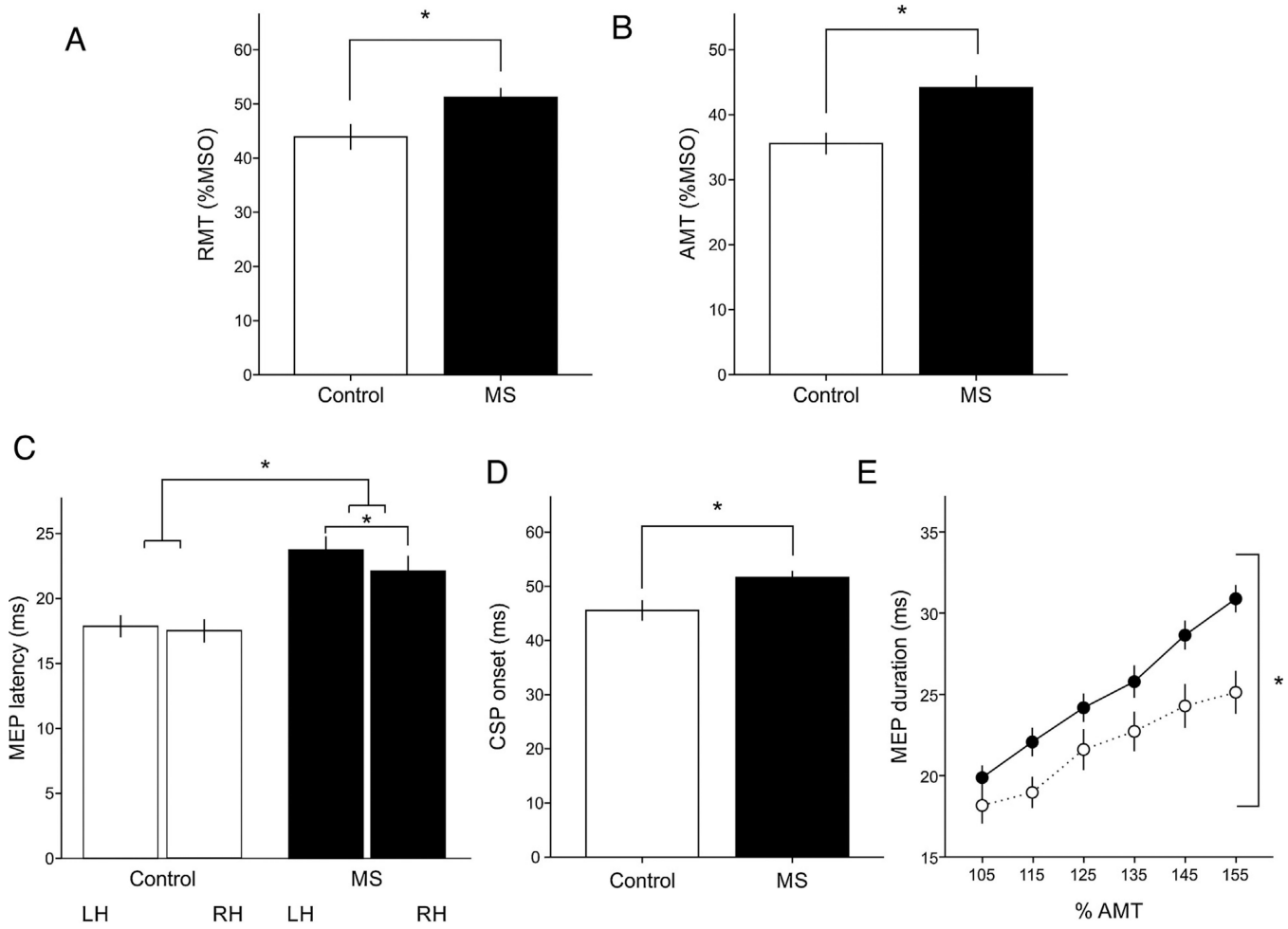

Fig. 1.

Mean values of all individuals in MS (black bars) and healthy control (white bars) groups. (A) Resting motor threshold (RMT) expressed as a percentage of maximum stimulator output (%MSO). (B) Active motor threshold (AMT) expressed as %MSO. (C) MEP latency shown in milliseconds. (D) Cortical silent period (CSP) onset shown in milliseconds. (E) Motor evoked potential (MEP) input-output curve data displaying MEP duration in milliseconds across TMS intensity. Bars represent standard error of the mean. *$p < 0.05$.

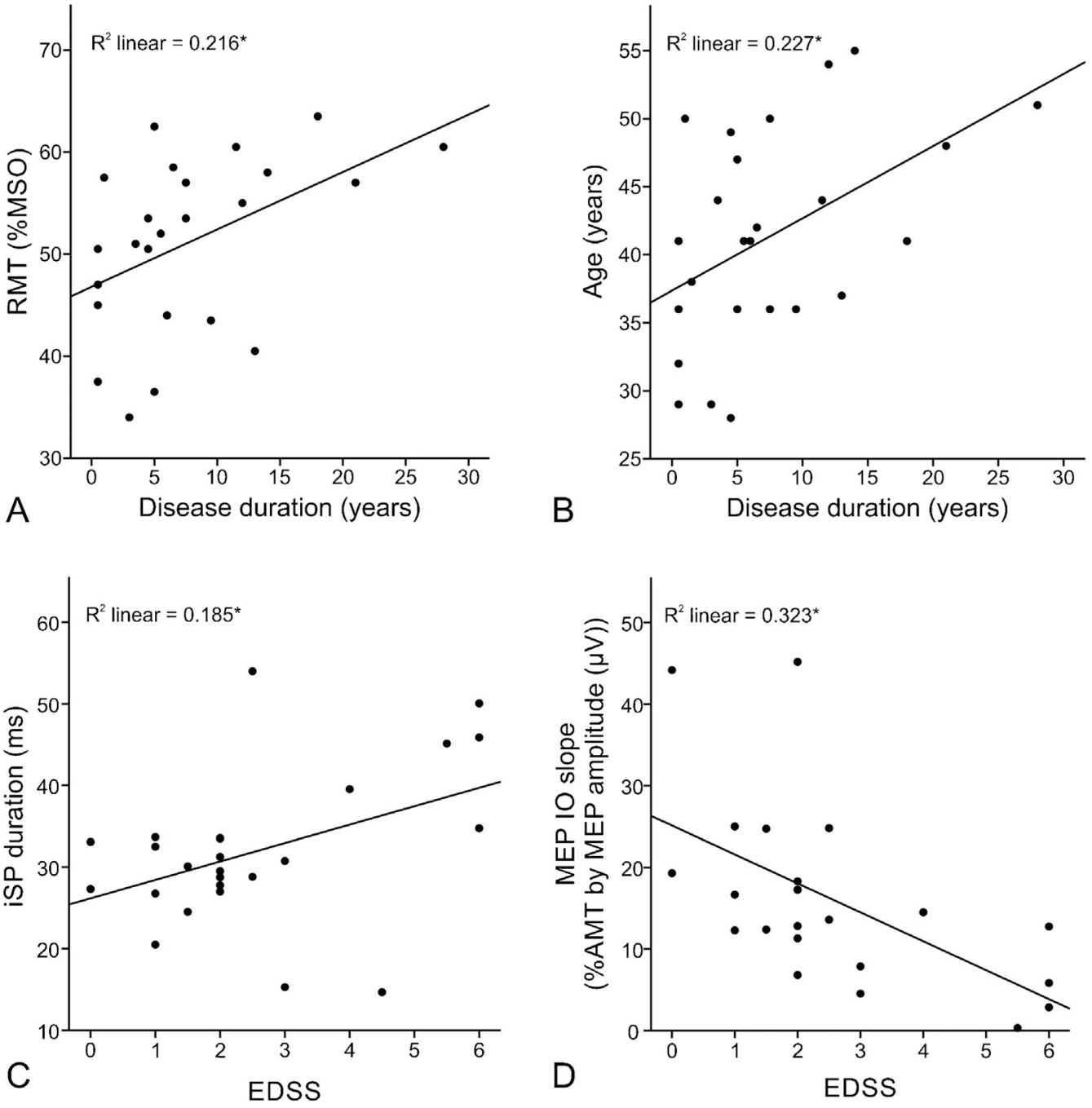

Fig. 2.

Scatterplots demonstrating the relationship with disease duration (DD), EDSS and TMS-based neurophysiological measures. (A–B) Relationships between DD (years) and (A) RMT (%MSO) and (B) age in MS. (C–D) Relationship between EDSS and (C) iSP duration (ms) and (D) MEP IO curve slope. DD was correlated with RMT and age and EDSS was correlated with iSP duration and MEP IO curve slope. *$p < 0.05$.

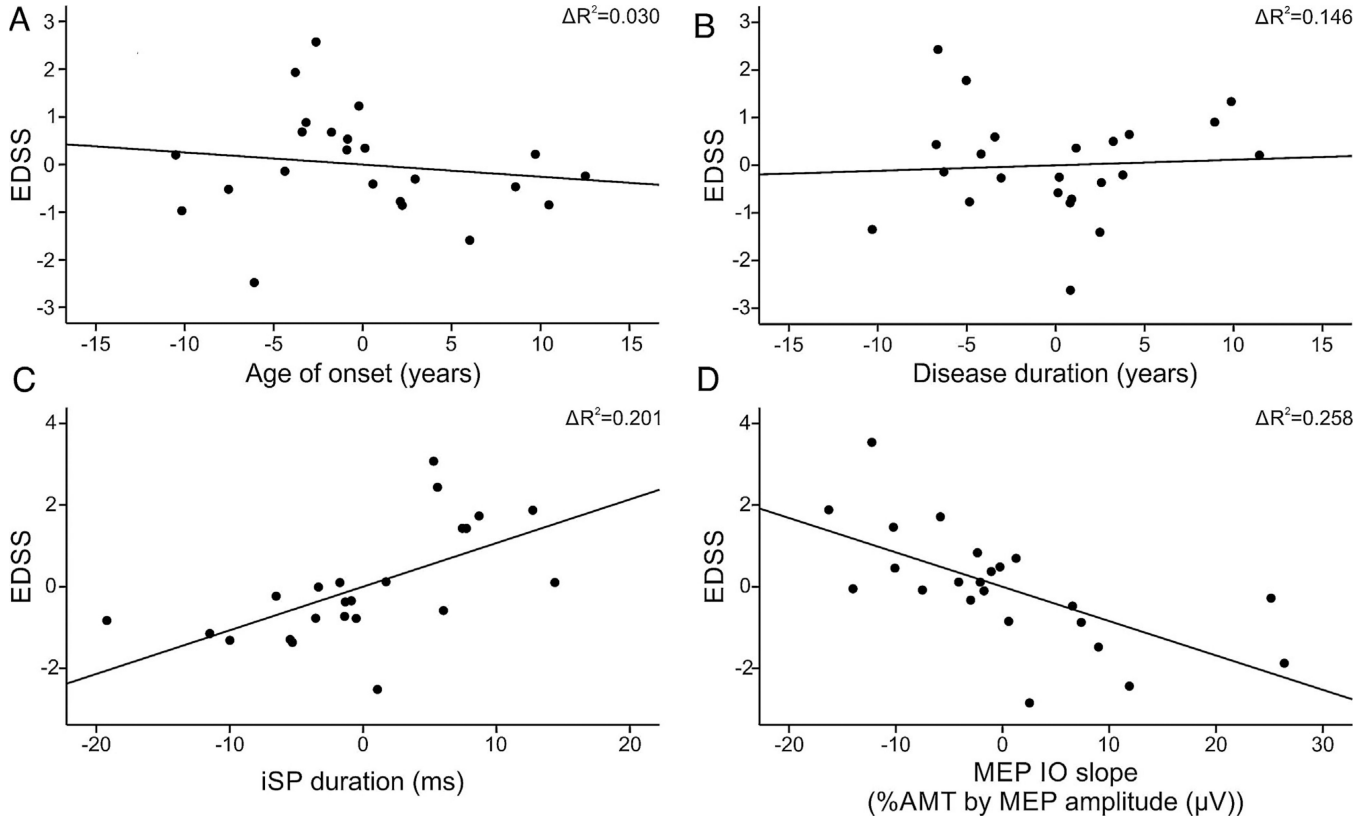

Fig. 3.

Partial plots generated by hierarchical regression analyses demonstrating the relationship with age of onset (AO), disease duration (DD), TMS-based neurophysiological measures and EDSS. Panels A–B depicts the relationship between EDSS with AO (years) and DD (years). Panels C–D depicts the relationship between iSP duration and linear slope of the MEP IO curve and EDSS. Asterisks indicate statistically significant ($p < 0.05$) ΔR^2 value in the hierarchical regression models.

Table 1

Summary of regression modeling for expanded disability status scale (EDSS).

Model	Predictors	R^2	*F* Statistic	Sig.	ΔR^2	Sig. (ΔR^2)	β_{AO}	β_{DD}	$\beta_{iSP\ duration}$	$\beta_{MEP\ IO}$
1	AO, DD	0.176	2.131	0.145	0.176	0.145	0.193	0.469	–	–
2	AO, DD, $iSP_{duration}$	0.376	3.824	0.027*	0.201	0.023*	−0.004	0.199	0.513	–
3	AO, DD, $iSP_{duration}$, slope of MEP IO curve	0.635	7.822	0.001*	0.258	0.002*	−0.108	0.047	0.541	−0.525

AO: age of onset, DD: disease duration, $iSP_{duration}$: ipsilateral silent period duration (ms), MEP IO: motor evoked potential input–output.

*$p<0.05$.