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Cortical Damage and Disability in Multiple Sclerosis: Relation to Intracortical Inhibition and Facilitation

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ABSTRACT

Background: Multimodal research combining biomarkers of intracortical activity and cortical damage could shed light on pathophysiological and adaptive neural processes related to the clinical severity of neurological conditions such as multiple sclerosis (MS).
Objective: Among people with relapsing-remitting and progressive forms of MS, we assessed the extent to which transcranial magnetic stimulation (TMS)-based biomarkers of excitatory and inhibitory cortical activity are related to cortical damage and clinical impairment.
Methods: Participants included 18 healthy individuals and 36 people with MS who had a relapsing-remitting or progressive clinical course. Using TMS, intracortical facilitation (ICF), short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), and cortical silent period (CSP) were obtained. Cortical volume and cortical magnetization transfer ratio (MTR) were quantified. Disability was assessed with Multiple Sclerosis Functional Composite (MSFC).
Results: Lower mean MTR within the cerebral cortex correlated with shorter CSP among MS participants with a progressive, but not a relapsing-remitting, clinical course. Within the cortical hand knob region targeted with the TMS, lower MTR was correlated with lower SICI only among individuals with relapsing-remitting MS. Longer CSP, higher ICF, lower cortical MTR, and sex were all independent significant predictors of poor upper extremity motor performance, while only cortical MTR was a significant independent predictor of total MSFC score among people with MS.
Conclusions: Cortical damage and cortical activity (both inhibitory and excitatory) may contribute to the severity of motor disability experienced by people with MS. When interpreting TMS-based outcomes, cortical integrity, clinical course, and symptom type should be considered.

Introduction

Multiple sclerosis (MS), a disease affecting the central nervous system, is a major cause of disability worldwide. Most people diagnosed with MS first experience a relapsing-remitting course, involving periods of clinical recovery between symptom relapses [1]. Others experience more continuous clinical deterioration, as can occur from disease onset (primary progressive MS) or after living with relapsing-remitting symptoms for several years (secondary progressive MS) [2]. While immunomodulatory and anti-inflammatory medications that mitigate relapsing-remitting symptoms are now widely available, effective therapeutic options for progressive disability and the associated neurodegeneration are less well established [3].

A potential contributor to neural and glial cell damage in many neurological conditions, including MS, is the over-activity of the brain's main excitatory neurotransmitter, glutamate [4,5]. This pathophysiological process, known as excitotoxicity, is also influenced indirectly by inhibitory neurotransmission, which is primarily driven by γ-aminobutyric acid (GABA) [6,7]. In humans, biomarkers of excitatory and inhibitory neurotransmission can be obtained non-invasively by analyzing characteristics of peripheral electromyographic activity evoked by transcranial magnetic stimulation (TMS) of the primary motor cortex [8]. Pharmacological studies involving the

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administration of neurotransmitter antagonists prior to TMS have linked glutamatergic activity at N-methyl-D-aspartate (NMDA) receptors to the TMS-derived measure of intracortical facilitation (ICF) [9,10]. TMS-based metrics primarily associated with inhibitory cortical activity include short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), and cortical silent period (CSP), each of which is believed to capture a relatively distinct aspect of inhibitory neurotransmission [8].

The relevance of excitatory and inhibitory cortical activity to structural brain damage, and ultimately to clinical impairment, is not fully understood. Notably, a disease-modifying therapy found to decrease ICF in people with MS, fingolimod [11], has been demonstrated in animal models to modulate glutamatergic neurotransmission in addition to having remyelinating and neuroprotective effects [12–14]. Moreover, cortical damage has been suggested to cause the SICI deficits observed in people with secondary progressive MS [15,16]. As previous studies have been limited to conventional neuroimaging sequences that are nearly blind to intracortical lesions and demyelination [17,18], links between intracortical damage and TMS-based outcomes remain unclear.

Structural damage within regions that appear normal on T1- and T2-weighted images can, however, be estimated with the magnetization transfer ratio (MTR) imaging technique [19]. MTR reflects the fraction of water bound to macromolecules and has been shown to correlate with the severity of demyelination and axonal loss observed in postmortem histology studies of the MS brain [20–22]. Compared to relapsing-remitting MS, cortical MTR reduction in progressive forms of MS is more pronounced, and is less strongly co-localized with cortical atrophy [23]. Cortical MTR of people with MS has been linked to more severe disability [24], including motor impairment [25]. Therefore, in combination with TMS and atrophy assessments, MTR could be a powerful tool to elucidate the relationship between cortical damage and intracortical activity associated with the motor system.

Empirical information on cortical integrity could also clarify the meaning of previously reported relationships between intracortical activity and clinical outcomes (e.g. [15,16,26–28]). It could be hypothesized that by combating excitotoxicity, maintaining low excitatory or high inhibitory activity prevents cell damage, and as a result, prevents clinical disability. This is challenged, however, by evidence that drugs that inhibit glutamatergic transmission have not been found to be clinically beneficial for people with MS [29–31], despite having neuroprotective effects [31]. Evidence that prolonged CSP (indicating high inhibition) is related to motor or cerebellar dysfunction in MS [26,27], and demonstrations that lower GABA facilitates motor learning and motor symptom recovery [32–35], further challenges this hypothesis. As excitatory and inhibitory activity and cortical damage may interact to produce, or prevent, clinical symptoms, assessing certain variables in isolation may conceal their contribution to clinical outcomes. A further important consideration regarding interpretation of TMS-based metrics, derived by stimulating the motor cortex, is that they are likely to be more closely related to motor system pathology than to more general disease progression.

Using a novel multimodal approach, we investigated the link between intracortical activity, cortical damage, and motor impairment. Our emphasis on motor dexterity was chosen due to its relevance to the primary motor cortex hand region stimulated in our TMS protocol, as well as its importance to daily activities and quality of life [36,37]. We predicted that cortical damage would be related to inhibitory (SICI, CSP, LICI) and excitatory (ICF) intracortical activity of people with MS. We additionally hypothesized that combining assessments of cortical damage, intracortical inhibition, and intracortical facilitation would predict motor disability better than a single variable alone.

Material and methods

Participants

MS patients who had a relapsing-remitting, primary progressive, or secondary progressive course were randomly selected for recruitment from a clinical database at the Montreal Neurological Institute and Hospital in Canada. Poster advertisements were used to recruit age- and sex-matched healthy control (HC) participants. Screening (through telephone interviews and clinical chart review) further excluded people for: (1) left handedness, (2) health conditions other than MS (e.g. history of head trauma or cancer), (3) relative contraindications for undergoing MRI or TMS [38], (4) medications with documented effects on intracortical facilitation or inhibition (e.g. baclofen), and (5) relapse occurrence within 3 months prior to participation. Further exclusions occurred if valid TMS data could not be collected due to unacceptable noise in the electromyographic signal (i.e. movement artifact) and/or having a resting motor threshold (rMT) beyond the limit of our equipment when stimulating the central scalp region overlaying the left hemisphere (1 HC and 2 MS participants excluded). One HC participant was additionally excluded for being an extreme outlier (>3 standard deviations outside of mean) on several TMS-based outcome measures. Five MS participants were excluded from the analysis because they were taking Gilenya, which has been shown to influence ICF [11]. The resulting sample included 18 HC and 36 MS participants. Data from some participants was also included in a study on a larger cohort of relapsing-remitting MS and healthy participants that focused on the relationship between conventional imaging metrics (i.e. white matter lesion volume), CSP prolongation, and clinical impairment persisting during remission [26].

All participants provided informed consent. The Research Ethics Board at the Montreal Neurological Institute and Hospital approved this protocol.

Demographic and clinical outcomes

Demographic and clinical variables (age, sex, diagnosis date, age of disease onset, clinical course, date of most recent relapse, EDSS, medications) of MS participants were extracted from the clinical database. Age, sex, and medications of healthy participants were self-reported. The Multiple Sclerosis Functional Composite (MSFC) was performed and scored according to standard procedure to assess clinical disability [39,40]. This included the 9-hole peg test (9HPT), which is a valid and reliable measure of upper extremity function among people with MS [41]. Z-scores for the 9HPT and MSFC [39,40] were used in analyses involving clinical outcomes.

TMS data collection

TMS was performed using a Magstim 2002 stimulator and figure-of-8 coil (9.5 cm outer wing diameter). With the handle oriented posteriorly, the coil was held against the left hemisphere at 45-degrees to the sagittal plane. Electromyographic data was recorded from surface electrodes in a belly-tendon montage, with the recording electrode over the first dorsal interosseus (FDI) muscle of the right (dominant) hand. The electromyographic signal was amplified, filtered (bandwidth = 10–3000 Hz) and collected at a sampling rate of 6000 Hz. A conventional hot-spotting technique was used to identify the target cortical region for the FDI muscle. Using BrainSight 2 stereotaxic navigation software (Rogue Research, Inc.), this location was referenced as the stimulation site for all subsequent TMS protocols. For all protocols described below, invalid trials (e.g. movement artifact) were identified during the TMS procedure and replaced with additional trials at the end of each section,