Clinical Neurophysiology 127 (2016) 1503–1511

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Intracortical inhibition abnormality during the remission phase of multiple sclerosis is related to upper limb dexterity and lesions

Julia C. Nantes [a,b,*], Jidan Zhong [b,c], Scott A. Holmes [a,b], Benjamin Whatley [a,b], Sridar Narayanan [c,d], Yves Lapierre [d], Douglas L. Arnold [d], Lisa Koski [b,c]

[a] Integrated Program in Neuroscience, McGill University, 3801 University Street, Room 141, Montreal, Que. H3A 2B4, Canada
[b] Research Institute of the McGill University Health Centre, 2155 Guy Street, 5th Floor, Montreal, Que. H3H 2R9, Canada
[c] Department of Neurology and Neurosurgery, McGill University, 845 Rue Sherbrooke Ouest, Montréal, Que., Canada
[d] Montreal Neurological Institute, McGill University, 3801 University Street, Montreal, Que. H3A 2B4, Canada

ARTICLE INFO

Article history:
Accepted 24 August 2015
Available online 31 August 2015

Keywords:
Multiple sclerosis
Motor control
Brain damage
Transcranial magnetic stimulation
Intracortical inhibition
Cortical silent period

HIGHLIGHTS

- Cortical silent period (CSP) prolongation is related to upper extremity impairment of people with relapsing-remitting multiple sclerosis (RRMS) in remission.
- Normalized lesion volume is correlated with longer CSP duration, while cortical thickness is not.
- CSP duration predicts motor impairment independently of lesion volume.

ABSTRACT

Objective: The impact of inhibitory cortical activity on motor impairment of people with relapsing-remitting multiple sclerosis (RRMS) has not been fully elucidated despite its relevance to neurorehabilitation. The present study assessed the extent to which transcranial magnetic stimulation (TMS)-based metrics of intracortical inhibition are related to motor disability and brain damage.
Methods: Participants included forty-three persons with RRMS in the remitting phase and twenty-nine healthy controls. We stimulated the dominant hemisphere and recorded from the dominant hand to assess short-interval intracortical inhibition (SICI) and cortical silent period (CSP) duration. Disability was evaluated with the Multiple Sclerosis Functional Composite (MSFC). Regional cortical thickness and lesion volume were measured.
Results: RRMS participants with dominant upper limb dexterity impairments had prolonged CSP, but equivalent SICI, compared to participants with preserved function. CSP was not related to walking or cognitive performance. Higher normalized lesion volume correlated with longer CSP duration. When adjusting for normalized lesion volume, longer CSP significantly predicted worse dominant upper extremity impairment.
Conclusions: High intracortical inhibition possibly contributes to (or prevents remission from) motor impairment. Lesions may be associated with intracortical inhibition shifts.
Significance: CSP duration and lesion burden should be considered when developing interventions aiming to mitigate motor impairment.

Abbreviations: RRMS, relapsing-remitting multiple sclerosis; RRMS-P, RRMS participant with preserved motor function; RRMS-I, RRMS participant with impaired motor function; HC, healthy control; GABA, γ-aminobutyric acid; TMS, transcranial magnetic stimulation; M1, primary motor cortex; SICI, short-interval intracortical inhibition; CSP, cortical silent period; EDSS, Expanded Disability Status Scale; CST[i], intracortical cortico-spinal tract; MSFC, Multiple Sclerosis Functional Composite; T25FW, Timed 25-foot walk; 9HPT, 9-hole peg test; PASAT, the Paced Auditory Serial Addition Test; RMT, resting motor threshold; MEP, motor-evoked potential.

* Corresponding author at: 835 Pine Avenue West, Montréal, Que. H3A 1A1, Canada. Tel.: +1 514 226 5104.
E-mail addresses: julia.nantes@mail.mcgill.ca (J.C. Nantes), jidan.zhong@mail.mcgill.ca (J. Zhong), scott.holmes@mail.mcgill.ca (S.A. Holmes), bwhatley@dal.ca (B. Whatley), sridar.narayanan@mcgill.ca (S. Narayanan), yves.lapierre@mcgill.ca (Y. Lapierre), douglas.arnold@mcgill.ca (D.L. Arnold), lisa.koski@mcgill.ca (L. Koski).

http://dx.doi.org/10.1016/j.clinph.2015.08.011
1388-2457/

1. Introduction

Multiple sclerosis is a chronic neuroinflammatory disease that can cause motor impairments, among other debilitating symptoms (Compston and Coles, 2008). For people with the relapsing-remitting course of multiple sclerosis (RRMS), symptoms associated with transient neuroinflammatory events greatly improve during spontaneous clinical remission phases despite the persistence of structural brain damage (Hauser and Oksenberg, 2006; Steinman, 2014). Physiological mechanisms contributing to the severity of residual disability present during the remission phases of RRMS have not been fully elucidated.

Symptom recovery after neurological damage may be influenced by the brain's main inhibitory neurotransmitter, γ-aminobutyric acid (GABA), which has a key role in synaptic plasticity and motor learning (Sanes and Donoghue, 2000; Stagg et al., 2011; Kim et al., 2014; Sampaio-Baptista et al., 2014; Blicher et al., 2015). In humans, intracortical inhibitory activity can be studied non-invasively through a variety of protocols that involve analyzing peripheral electromyographic signals associated with transcranial magnetic stimulation (TMS) of the primary motor cortex (M1). Pharmacological evidence supports that the short-interval intracortical inhibition (SICI) metric is linked to inhibitory activity at ionotropic $GABA_A$ receptors, while the cortical silent period (CSP) primarily reflects metabotropic $GABA_B$ receptor activity (Ziemann, 2013).

The relationship between these TMS-based metrics and clinical manifestations of multiple sclerosis is not fully known. While CSP prolongation (indicating higher intracortical inhibition) has been reported to occur during the clinical remission phase of RRMS (Caramia et al., 2004), it is not clear if this alteration is related to the preservation or impairment of function. As divergent areas of research support that plasticity and motor learning favor a low inhibitory state (Levy et al., 2002; Floyer-Lea et al., 2006; Stagg et al., 2011), it could be hypothesized that higher intracortical inhibition during remission is linked to more severe persisting impairment. However, the reverse could also be true, as intracortical inhibition deficits are common during relapses (Caramia et al., 2004) and among individuals with the later, secondary progressive form of multiple sclerosis (Conte et al., 2009; Vucic et al., 2012). Moreover, it has not been directly assessed if intracortical inhibition is related specifically to impairment of the limb contralateral to the TMS stimulation site, as opposed to other neurological symptoms of this complex disease.

Of further consideration is the impact of brain damage on TMS-based outcomes. Conte et al. (2009) reported that SICI of people with multiple sclerosis is not correlated with lesion load within the whole brain nor within the intracranial cortico-spinal tract (CST_i). While not previously assessed among people with multiple sclerosis, it is possible that neuroimaging analysis techniques that estimate atrophy and lesion impact near the stimulated cortex may provide metrics of damage relevant to intracortical inhibition abnormities. Understanding how inhibitory cortical activity may interact with brain damage to produce (or prevent) motor disability may support the development of optimal tools to assess disease burden and to treat symptoms of people with neurological conditions such as RRMS.

The primary objective of this study was to assess the extent to which TMS markers of intracortical inhibition (SICI, CSP) are abnormal among people with RRMS in remission that have upper limb dexterity impairments when compared to those with preserved upper limb function. Secondly, we investigated the specificity of the identified neurophysiological abnormalities in predicting poor performance of the limb contralateral to the TMS stimulation site compared to other types of disability. The relationship between intracortical inhibition and structural brain damage (as measured throughout the whole brain and near the stimulation site) was also investigated. We predicted that among RRMS participants, intracortical inhibition would be related to upper limb disability, as well as to damage around the cortical region stimulated. Our additional multimodal analysis explored whether intracortical inhibition is related to disability independently of brain damage measured with MRI.

2. Methods

2.1. Participants

A random selection process was used to recruit people with RRMS from a clinical research database at the Montreal Neurological Institute and Hospital in Canada. Age- and sex-matched healthy control (HC) participants were recruited through advertising posters in the community. Age, sex, time since diagnosis, date of most recent relapse, medications, and Expanded Disability Status Scale (EDSS) score were extracted from the clinical database for RRMS participants, and applicable variables for HC participants were self-reported. People were not invited to participate if they: (1) had risk factors for undergoing TMS or MRI (e.g. medications lowering seizure threshold, history of seizure, pregnancy, ferromagnetic metal in body), (2) were taking medications known to affect intracortical inhibition (e.g. baclofen), (3) had a pre-existing health condition not attributed to MS (e.g. bipolar disorder, limb amputation), (4) had experienced a clinically-significant relapse within the three months prior to participation, or (5) were left-handed. Of people who took part in the study, two HC participants were excluded for abnormally poor motor performance (>2 standard deviations worse than published norms (Oxford Grice et al., 2003)). Two participants (1 RRMS, 1 HC) did not complete the study because their resting motor threshold was too high to assess SICI or CSP with our protocol. All participants provided informed consent. The Research Ethics Board at the Montreal Neurological Institute and Hospital in Canada approved this study. The final sample included 29 HC and 43 RRMS participants.

2.2. Multiple Sclerosis Functional Composite

The Multiple Sclerosis Functional Composite (MSFC) (Fischer et al., 1999), an assessment of performance across functional domains that has been validated among people with MS (Cutter et al., 1999), was used to measure disability. The MSFC consists of three subscales: Timed 25-foot walk (T25FW), 9-hole peg test (9HPT), and the 3 second version of the Paced Auditory Serial Addition Test (PASAT), which measure leg function/ambulation, hand/arm dexterity, and cognitive function, respectively.

2.3. Neurophysiological assessments

TMS pulses were delivered with a Magstim 200[2] stimulator and figure-of-8 coil (outer wing diameter = 9.5 cm) held against the head (left hemisphere) at a 45-degree angle to the sagittal plane (handle oriented posteriorly). Electromyographic data was collected with surface electrodes placed in a belly-tendon montage on the dominant hand (contralateral to the TMS stimulation site), with the recording electrode over the first dorsal interosseus (FDI) muscle. Data was amplified and filtered (bandwidth = 10–3000 Hz, Grass P511 AC Amplifiers) and collected at a sampling rate of 6 kHz. Using BrainSight 2 stereotaxic navigation software (Rogue Research Inc), the optimal target site to elicit an MEP from the target FDI was identified (Thielscher and Kammer, 2002), marked, and referenced for all further stimulations. Resting motor threshold (RMT) was defined as the lowest intensity of stimulation