

## Correlations between corpus callosal myelin water fraction and measures of transcallosal inhibition in multiple sclerosis patients on glatiramer acetate treatment

Eric Y. Zhao<sup>1</sup>, Irene Vavasour<sup>2</sup>, Marjan Zakeri<sup>3</sup>, Michael Borich<sup>3</sup>, Cornelia Laule<sup>4</sup>, Anthony Troubsee<sup>5</sup>, David K. B. Li<sup>2</sup>, Lara Boyd<sup>3</sup>, and Alex Mackay<sup>2,6</sup>  
<sup>1</sup>Department of Cellular & Physiological Sciences, The University of British Columbia, Vancouver, BC, Canada, <sup>2</sup>Department of Radiology, The University of British Columbia, Vancouver, BC, Canada, <sup>3</sup>Brain Behavior Lab, Department of Physical Therapy, The University of British Columbia, Vancouver, BC, Canada, <sup>4</sup>Department of Pathology & Laboratory Medicine, The University of British Columbia, Vancouver, BC, Canada, <sup>5</sup>Division of Neurology, Department of Medicine, The University of British Columbia, Vancouver, BC, Canada, <sup>6</sup>Department of Physics & Astronomy, The University of British Columbia, Vancouver, BC, Canada

**BACKGROUND:** Multiple sclerosis (MS) is a disease of the central nervous system (CNS) characterized by acute clinical and subclinical attacks of inflammation and progressive neurodegeneration. Demyelination of the corpus callosum (CC), a structure which connects the two hemispheres of the brain, is believed to be closely related to brain function deficits<sup>1</sup>. In MRI, it has been shown that the signal fraction of short T<sub>2</sub> relaxation arises from water trapped in myelin sheaths, yielding a measure of myelin water fraction (MWF)<sup>2</sup>. This allows monitoring of myelination state. Transcranial magnetic stimulation (TMS) can assess cortical excitability and neurophysiologic function between homologous regions of the motor cortex mediated by transcallosal connections. Transcallosal inhibition (TCI) is observed as a transient weakening of voluntary muscle contraction on the side ipsilateral to TMS stimulation due to inhibition through the transcallosal pathway. Demyelination of the CC can decrease transcallosal conduction velocity, delaying TCI onset. Demyelination can also disrupt spatiotemporal summation of action potentials, resulting in decreased inhibition magnitude<sup>3</sup>. This may shorten the duration of suprathreshold stimulation of  $\alpha$ -motor neurons and thus shorten the ipsilateral silent period (iSP). Glatiramer acetate (GA, Copaxone<sup>®</sup>) is an effective treatment for MS to prevent relapses and disability progression, demonstrating neuroprotective and anti-inflammatory properties<sup>4</sup>.

**PURPOSE:** To characterize the relationship between MWF in the CC and TCI assessed by TMS-evoked potentials in MS subjects on GA. This may guide the use of MWF for evaluating treatments that have potentially neuroprotective effects and improve the design of clinical trials for more efficient development of new treatments.

**METHODS:** Twelve MS patients (mean age 43.3; range 28-54y, EDSS range 1.0-6.0, disease duration range 1-35y) who had been on GA from 0-5 years underwent both MRI and TMS testing. The MRI protocol was performed on a Philips 3.0T Acheiva system and consisted of a sagittal T<sub>1</sub>IR, a sagittal 3D T<sub>2</sub> 32 echo GRASE sequence<sup>5</sup> (TR=1000 ms, 10 ms echo spacing, six 5 mm slices), FLAIR, and T<sub>1</sub> spin echo post-gadolinium. The 3D T<sub>2</sub> echo sequence was modelled via multiple exponential components and T<sub>2</sub> relaxation was deduced using a non-negative least squares with extended phase graph algorithm<sup>6</sup>. MWF was computed as the ratio of area under the T<sub>2</sub> distribution from 10-40 ms to the total area (Figure 2)<sup>6,7</sup>. MWF values were averaged for the whole CC as well as motor and sensory regions proposed by Hofer and Frahm<sup>8</sup> (Figure 2). TMS was performed using a figure-of-eight coil attached to a Magstim 200<sup>2</sup> stimulator targeting the motor cortex representation of the contralateral forearm extensor musculature. Subjects performed an isometric grip contraction using the hand ipsilateral to the stimulation site. Electromyographic (EMG) data were collected from the extensor carpi radialis muscle bilaterally. Transient suppression in voluntary EMG activity was used to quantify the iSP (Figure 1). Stimulation protocol was performed bilaterally. iSP onset time, duration, area under the curve, and mean magnitude normalized against prestimulatory magnitude (iSP/Prestim) were calculated in both hemispheres and averaged.

**RESULTS:** No enhancing lesions were detected. Significant correlations were observed between onset of iSP and MWF in motor and sensory regions of the CC (Figure 3). In addition, motor region MWF correlated with iSP/Prestim and iSP duration. Pearson correlations were weaker than Spearman ranked correlations, suggesting nonlinearity. Onset and magnitude correlated negatively with MWF, whereas duration correlated positively. In contrast, no consistent correlations were observed with whole CC measures.

**DISCUSSION AND CONCLUSION:** The observed effects of decreased MWF, specifically in the motor and sensory regions of the CC, agree with those expected of increased demyelination, as confirmed by TMS based measures of TCI. It is notable that significant correlations were not observed in the whole CC but primarily in the fraction known to carry motor information. This provides functional neurophysiological evidence that the measured iSP parameters were indeed affected by regional demyelination of normal appearing white matter of the CC. Significant correlations displayed nonlinearity, and further analysis and data collection will be required to detail the specific nature of TMS dependence on MWF. Based on our data, MWF is a good estimator of neurophysiologic function as assessed by TMS.

**ACKNOWLEDGEMENTS:** MS subjects and their families. Funding support from Teva Canada Innovation.

**REFERENCES:** <sup>1</sup>Ozturk A, Smith SA, Gordon-Lipkin EM *et al*, *Mult Scler* 2010;16(2):166. <sup>2</sup>Whittall KP, MacKay AL, Graeb DA *et al*, *Magn Reson Med* 2009;37:34-43. <sup>3</sup>Britton TC, Meyer BU and Benecke R, *Biol Cybernetics* 1979;33:97-111. <sup>4</sup>Ge Y, Grossman RI, Udupa JK *et al*, *Neurology* 2000;54(4):813-17. <sup>5</sup>Prasloski Neuroimage 2012;61:533-9. <sup>6</sup>Prasloski MRM 2012;67:1803-14. <sup>7</sup>Whittall JMR 1989; 84:134-52. <sup>8</sup>Hofer S and Frahm J *NeuroImage* 2006; 32:989-94.

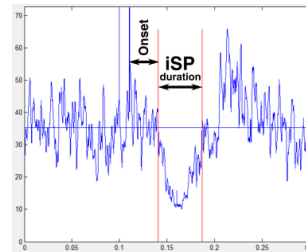


Figure 1: Transcallosal inhibition (TCI) is observed as a drop in EMG signal below average. iSP onset and duration in 20 averaged MEP replicates is shown.

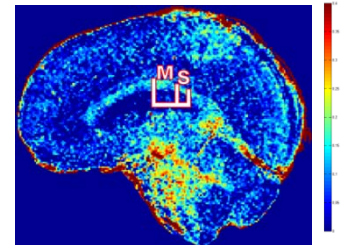


Figure 2: Sagittal map of short T<sub>2</sub> fraction computed from 3D T<sub>2</sub> echo sequence. The motor (M) and sensory (S) regions of the corpus callosum are labelled.

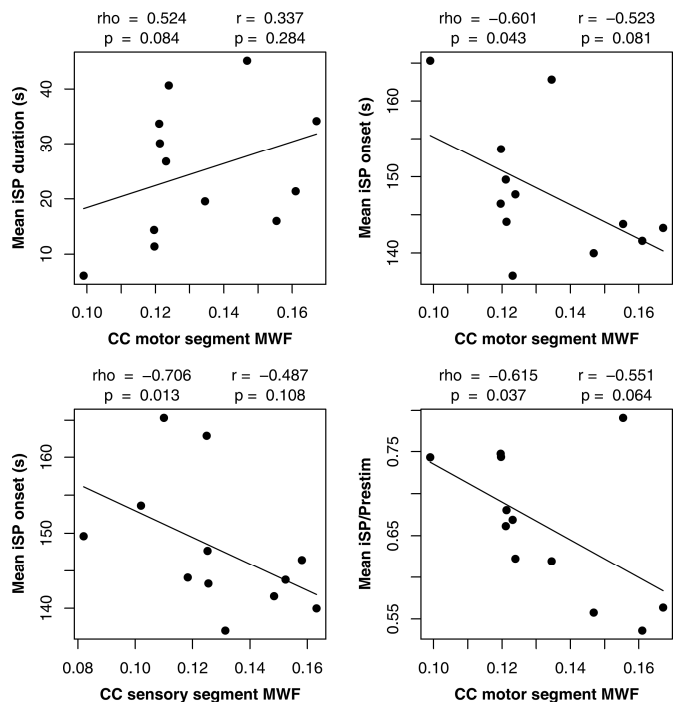


Figure 3: Correlations between TCI parameters and MWF in 12 MS patients. MWF averaged over the whole CC as well as motor and sensory regions was correlated with iSP/Prestim, onset time, and duration. Pearson's  $r$ , Spearman  $\rho$ , and corresponding  $p$ -values are shown.