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

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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 deficits1. In MRI, it has been shown that the signal fraction of short T2 relaxation arises from water trapped in myelin sheaths, yielding a measure of myelin water fraction (MWF)2. 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 magnitude3. This may shorten the duration of suprathreshold stimulation of α-motor neurons and thus shorten the ipsilateral silent period (iSP). Glatiramer acetate (GA, Copaxone®) is an effective treatment for MS to prevent relapses and disability progression, demonstrating neuroprotective and anti-inflammatory properties4.

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 Achieva system and consisted of a sagittal T1, T2, a sagittal 3DT 32 echo GRASE sequence5 (TR=1000 ms, 10 ms echo spacing, six 5 mm slices), FLAIR, and T1 spin echo post-gadolinium. The 3DT echo sequence was modelled via multiple exponential components and T2 relaxation was deduced using a non-negative least squares with extended phase graph algorithm. MWF was computed as the ratio of area under the T2 distribution from 10-40 ms to the total area (Figure 2). MWF values were averaged for the whole CC as well as motor and sensory regions proposed by Hofer and Frahm6 (Figure 2). TMS was performed using a figure-of-eight coil attached to a Magstim 200® 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 differentially affecting 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.

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