Transient Decrease in Water-Soluble Choline Metabolites Following a Single Session of repetitive Transcranial Magnetic Stimulation

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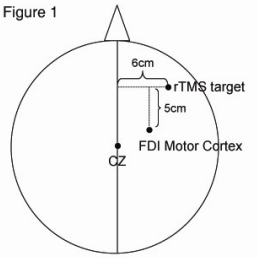
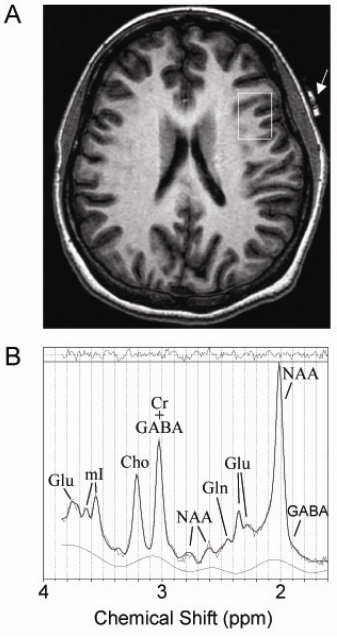
Background: Repetitive transcranial magnetic stimulation (rTMS) is being used in studies of higher cognitive functions and modulation of neuroplasticity and behavior in healthy subjects, as well as a therapeutic approach in neuropsychiatric disorders. The existence of long term effects of rTMS is evident from its therapeutic success, even if the successful treatment is limited to a selected group of patients. However, the underlying mechanisms of these long term effects are not known. It is important to understand these mechanisms, for optimization of treatment and identification of the individuals for whom treatment will be beneficial, and for understanding the consequences of the application of rTMS to healthy subjects in behavioral studies. We used ^{1}H-MRS at 3 Tesla to monitor potential metabolic alterations following a single rTMS session.

Figure 1



Methods: Fourteen subjects randomly assigned to real and sham rTMS underwent MRI and ^{1}H-MRS prior to and up to 36 min after a single rTMS session. Slow (1 Hz) rTMS was applied for 15 min to the dorsolateral prefrontal cortex at the target location shown in **Figure 1**. A fiduciary marker, placed at the target location (arrow in **Figure 2A**) aided in reproducible ^{1}H-MRS voxel positioning. Single voxel (10.5 ± 1.1 cm^3, n=14) PRESS ^{1}H spectra were acquired with a repetition time of 2 sec, time to echo of 35 msec, spectral width of 5000 Hz, 2048 time points, and 272 acquisitions (9 min). The levels of N-acetylaspartate, glutamate, creatine, myo-Inositol, glutamine, choline and GABA were analyzed using LC-Model.

Figure 2



Results: A typical axial image of the brain showing the fiduciary marker and the position of the ^{1}H-MRS voxel in the dorsolateral prefrontal cortex is shown in **Figure 2A**. **Figure 2B** demonstrates a typical ^{1}H-MRS spectrum of the dorsolateral prefrontal cortex. The levels of the metabolites and neurotransmitters in this region, prior to and after a single session of rTMS, are summarized in **Figure 3**. The bars in **Figure 3** show the mean (+ standard deviation) of the results of ten subjects prior to rTMS (white), 8-14 min (median time 11 min, darkest gray), 18-26 min (median time 22 min, medium dark gray), and 30-36 min (median time 33 min, light gray) after rTMS. During the initial time frame of 8 - 14 min after rTMS, we did not observe any changes in metabolite concentration ratio in either the real or the sham rTMS population. During the following period of 18-26 min post real rTMS, we observed a significant 6.0 % decrease in the choline/creatine concentration ratio, (mean difference=0.015, P=0.0037, 95 % CI = -0.023 to -0.007, two-tailed paired t-test, **Figure 3**). In agreement, the absolute concentration of choline decreased by 10.3 % (mean difference=0.23 mM, P=0.0017, 95 % CI = -0.34 to -0.12, two-tailed paired t-test) (**Figure 4**). This decrease was not observed in the sham group. During the later time frame of the study (30-36 min after rTMS stimulation), no significant changes in metabolite or neurotransmitter concentration ratio were observed in either the real or the sham rTMS group. Specifically, the levels of the choline/creatine ratio as well as the absolute choline concentration were similar to the levels prior to the rTMS.

Figure 3

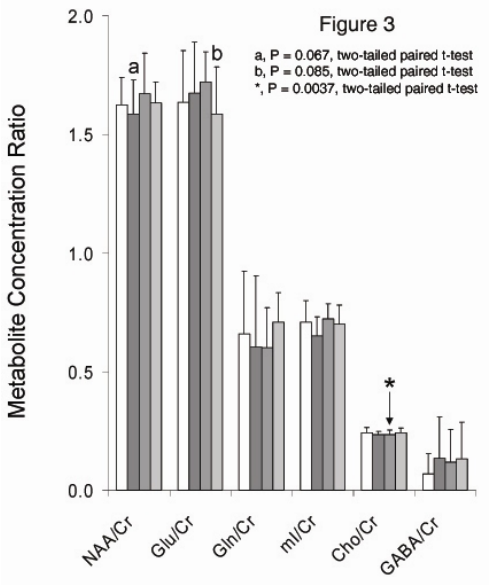
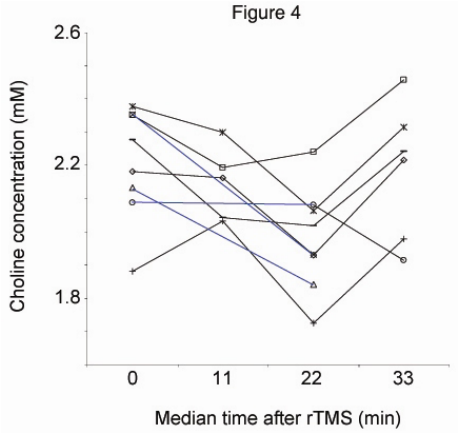


Figure 4



Discussion: The transient decrease in water-soluble choline metabolites may suggest a transient increase in the incorporation of phosphocholine into phosphatidylcholine via the CDP-choline pathway. Such an increase may suggest a transient increase in CDP-choline and a transient decrease in diacylglycerol, which may explain the long term effects of rTMS at the molecular level by modulating signal transduction and protein synthesis.