^{1}H MRS Demonstrates Elevations of Prefrontal Cortex GABA in Major Depressive Disorder after Treatment with Repetitive Transcranial Magnetic Stimulation

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Target Audience

Researchers and clinicians with interest in neuropsychiatric disorders and/or in MRS studies of such disorders

Purpose

To investigate the potential involvement of the GABAergic and glutamatergic neurotransmitter systems in the mechanism of action of repetitive transcranial magnetic stimulation (rTMS) for the treatment of major depressive disorder (MDD).

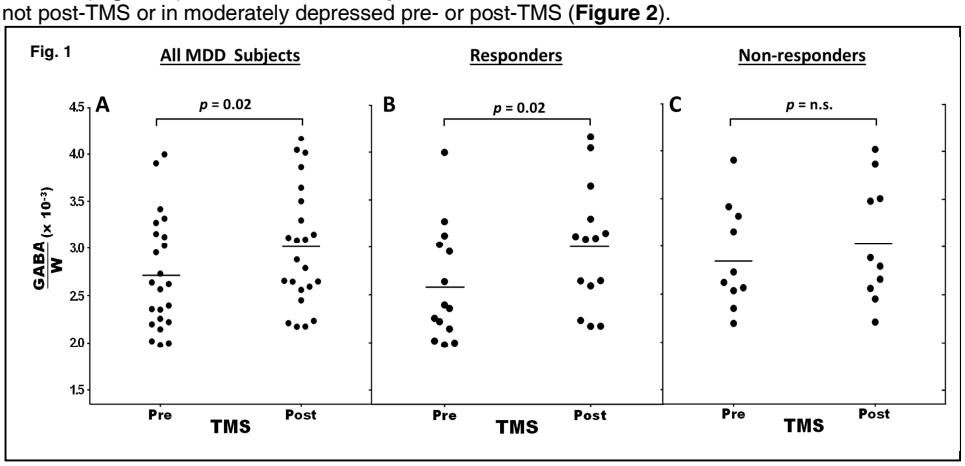
METHODS

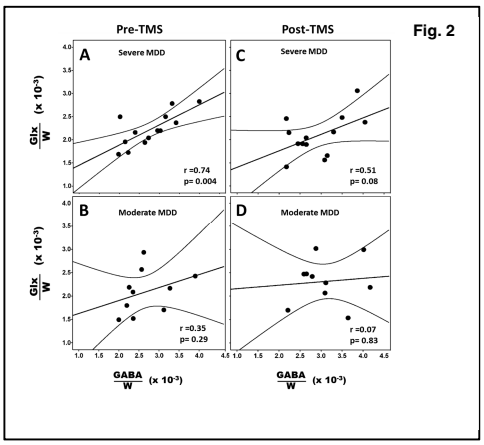
Subjects: A consecutive sample of 23 subjects (7 male) between the ages of 23-68, living in the greater New York City area was enrolled into the study. All subjects fulfilled criteria for a current major depressive episode and had failed at least two antidepressant trials of adequate dose and duration. Of the 23 subjects, 19 were on a stable regimen of psychotropic medications throughout the study period, and 4 were not currently taking any medication for the duration of the study.

Treatment with rTMS and ^{1}H MRS Measurements: All 23 MDD patients completed 25 sessions of rTMS over the left dorsolateral prefrontal cortex (DLPFC) over a 5-week period using the NeuroStar TMS Therapy System and a standard "Figure 8" coil. Individual sessions consisted of 37.5 min (3000 pulses; 30-second duty cycle, 4 seconds on, 26 seconds off) of 10-Hz excitatory TMS daily for 25 days (Monday-Friday for a 5 week period). Treatment response was assessed using the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) at baseline and 1–3 days after completing the 5-week course of treatment. Levels of GABA and glutamate+glutamine (Glx) in the medial prefrontal cortex (MPFC), including the anterior cingulate cortex (ACC), were obtained at baseline and after 5 weeks of treatment using the standard J-editing technique. GABA and Glx peak areas were derived by frequency-domain spectral fitting and expressed as ratios relative to the area of synchronously acquired unsuppressed voxel tissue water (W).

RESULTS

MPFC GABA/W increased 12.3% (p=0.02) in all depressed subjects and 18.3% (p=0.02) in subjects with partial or full responses as assessed by $HDRS_{17}$ (**Figure 1**). rTMS showed no significant effects on Glx/W. GABA/W and Glx/W were correlated in severely depressed patients at baseline but not post-TMS or in moderately depressed pre- or post-TMS (**Figure 2**).





DISCUSSION

The novelty of this study is its focus on examining changes in brain GABA and Glx levels in patients with depression before and after a course of therapeutic rTMS, finding GABA elevations in the MPFC post-TMS relative to levels at baseline in a cohort of adults with MDD. In addition, this increase in GABA was most pronounced in the subgroup of patients most sensitive to the antidepressant effect of rTMS (**Fig. 1**). In contrast, we found no differences or changes in Glx between baseline and post-TMS. Our finding of an association between the antidepressant effect of rTMS and elevation of MPFC GABA relative to baseline is consistent with and extends prior observations about GABA in depression and the effects of antidepressant treatments. GABA levels are low in the depressed brain, supported by convergent evidence from CSF samples[1], GABAergic neuronal density[2] and GAD67 expression[3] in postmortem brains. Prior MRS studies in depressed individuals revealed GABA reductions compared to healthy controls[4,5] with more pronounced MPFC reductions in a treatment refractory subgroup[5]. Further and also supporting the GABA-deficit hypothesis of depression, a variety of antidepressants seem to function, in part, by elevating GABA. These include serotonin-selective reuptake inhibitors[4], the GABA-reuptake inhibitor tiagabine[6] and ECT[7]. Interestingly (**Fig. 2**), we found MPFC GABA and Glx to correlate at baseline but not after TMS, and this was clearly due to elevations in GABA that were not accompanied by those of Glx. While the reason for this apparent "unlinking" of GABA and Glx after TMS is unclear, it could indicate an unlinking of the metabolism of the two neurotransmitters, a change in the proportions of the neurotransmitter pools that are protein-bound and hence MRS-visible, or change in compartmental localization, which might also affect MRS visibility.

CONCLUSION

Treatment with rTMS over the left DLPFC improves depressive symptoms. This response correlates with selective elevations of GABA in the MPFC, which has dense reciprocal connections with the DLPFC. These findings may indicate restoration of GABAergic synapses as well as improved homeostatic balance with the potentially excitotoxic glutamatergic system.

REFERENCES

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