Multi-Voxel Imaging of GABA Temporal Dynamics: A Double-blind Drug-Challenge Crossover Study at 4 Tesla

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Purpose: We have developed a technique for multi-voxel imaging of pharmaco-dynamic changes in GABA based on combining MRSI with the well-known MEGAPRESS-based [1] difference-editing acquisition. Our "functional" MRSI (fMRSI) technique was developed to permit the quantitative measurement of brain GABA levels in vivo, both spatially and temporally. We aimed to demonstrate the method by challenging the GABA system with oral administration of stimulant and sedative drugs in a double-blind crossover design of placebo, dextroamphetamine(D-amph) and alprazolam (Alp), and measuring brain GABA over time.

Methods: Data were collected on a 4T Varian/Agilent MRI/MRS scanner. MRSI combined the MEGAPRESS GABA-editing technique with a reduced-sampling k-space method [2] (FOV=180x180mm; matrix=16x16; sw=2kHz; TR/TE-1s/68ms). MEGACSI spectra were collected, resulting in MRSI images of GABA (Fig.2 right). Seven healthy male volunteers received placebo, stimulant (20mg D-amph {Dexidrine™}) and sedative (1mg Alp {Xanax™}) in a counterbalanced order over three separate study visits. fMRSI commenced 45 minutes post-dose. Each fMRSI scan spanned 19 min, with 4 repeated fMRSI scans over a 2-hour period. GABA was measured from the basal ganglia, temporal-insular cortex, thalamus, and posterior cingulate.

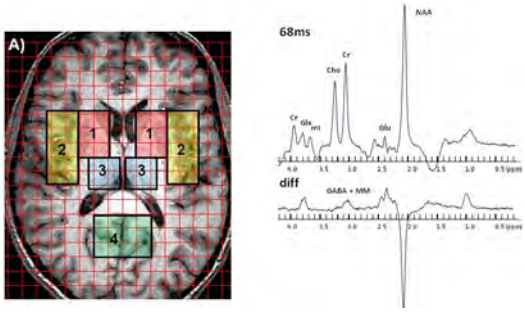

Figure 1 – (A) voxel clusters in the L/R basal-ganglia(1); temporal-cortex(2); thalamus(3) and POC(4). Sample MEGACSI spectra displayed from the POC.

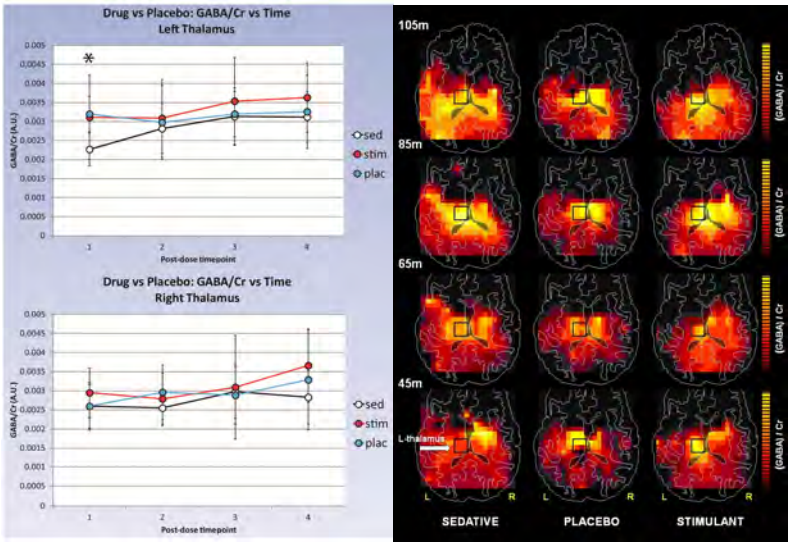

Figure 2 – (left) Metabolite plots of GABA/Cr in 7 regions over 4 timepoints for 3 conditions. Bars are standard deviation in the mean (n=7). (right) GABA maps depicting spatial and temporal changes in GABA over 4 timepoints and 3 conditions. Left thalamus is labeled where a significant effect was found.

Results: Relative to placebo, GABA was reduced significantly in the sedative condition (Alp) within the left thalamus. There was a significant interaction between drug and time (df=3, F=6.04, p=0.005, 2-tailed). Specifically, GABA was reduced by 40.9±19.0% at the 1st time point (ie, 45-min post-dose) (n=7, F=15.0, p=0.002, 2-tailed) . Alpha was Bonferroni-corrected to p=0.007 for multiple comparisons across 7 regions. No effects were found in any other region or for the stimulant condition.

Discussion/Conclusions: Results are consistent with previous findings of reduced GABA in the thalamus following sedative administration. Functional MRSI may be a useful tool for quantitatively imaging the spatial and temporal dynamics of brain GABA in vivo in response to a drug challenge. Further refinements of this methodology should place fMRSI in the same functional realm of other functional imaging modalities, e.g., positron-emission tomography (PET) with the added advantage of being completely non-invasive. Noteworthy limitations in the current study are the presence of macromolecules in the 3.00ppm GABA resonance as well as the use of total creatine as a denominator. As well, voxel gray matter content will influence these results and will need to be accounted for in future analyses. Nonetheless, these preliminary results do suggest efficacy of the fMRSI modality in quantitative and dynamic neurotransmitter imaging in vivo.

References:

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