An Experimental Methods Based Approach to Understanding the Mechanisms Underlying MEG Indices of Auditory/Language Processing

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Background:
Language/auditory processing deficits are a hallmark feature of autism spectrum disorder (ASD). Magnetoencephalography (MEG) studies have shown delayed M100 auditory evoked field responses and altered induced gamma-band activity in individuals with ASD. MEG indices of language/auditory processing, as a result, have been proposed as putative biomarkers for ASD. The mechanisms underlying these aberrant MEG measures, however, are not clearly understood. Excitatory/Inhibitory (E/I) imbalance has been suggested as a potential explanation for these deficits and the general pathophysiology of ASD. Abnormal structural and functional network connectivity have similarly been associated with language deficits in children with ASD. The current study utilizes an experimental therapeutics approach to better understand how mechanisms of E/I balance and structural and functional network connectivity contribute to MEG outcomes of language/auditory processing in ASD. Here, we present data from the healthy volunteer pilot phase of this study, investigating how measures of E/I balance, structural connectivity, and functional connectivity are related to MEG measures of language/auditory processing.

Methods:
Twenty healthy adult volunteers completed MEG, MRI, functional MRI (fMRI), and Magnetic Resonance Spectroscopy (MRS) at baseline and then immediately before and after continuous theta burst stimulation (cTBS) applied at 80% active motor threshold. Brain stimulation targets were individualized and determined by peak BOLD activation during an fMRI language-based task. fMRI data were additionally processed to measure task-based functional connectivity between the left posterior superior temporal cortex (psTC) and left frontal language areas. Diffusion weighted imaging (DWI) data were acquired and analyzed to quantify fractional anisotropy (FA), radial diffusivity (RD), mean diffusivity (MD), and axial diffusivity (AD) in specific left white matter tracts (e.g., arcuate fasciculus and auditory radiation fiber bundles). A spectroscopy voxel of 2.5 cm^3 was placed within the left pSTC for MRS. MRS data were then processed to measure creatine-normalized concentrations of glutamate and gamma-amino butyric acid (GABA), as well as the ratio of glutamate/GABA. MEG data were collected while participants listened to validated auditory stimuli and then processed to measure M100 latency and induced gamma power in the left pSTC.

Results:
M100 latency negatively correlated with glutamate [$r(n=9) = -0.907$, $p < 0.001$] and the ratio of glutamate/GABA [$r(n=9) = -0.681$, $p < 0.05$] at baseline, while changes in M100 latency positively correlated with changes in glutamate/GABA pre-post cTBS [$r(n=9) = 0.757$, $p < 0.05$]. Significant correlations ($p < 0.05$) were also observed between M100 latency and FA [$r(n=9) = 0.757$], RD [$r(n=9) = -0.767$], and MD [$r(n=9) = -0.742$] measures in the arcuate fasciculus, but none were observed between M100 latency and fMRI task-based functional connectivity. Induced gamma power negatively correlated with task-based functional connectivity [$r(n=11) = -0.678$, $p < 0.05$] at baseline but did not correlate with other MRS or DWI measures.

Conclusions:
These findings suggest a relationship between E/I balance, structural and functional network connectivity, and language/auditory processing in a non-clinical sample. This dataset will serve as a normative reference for our ongoing clinical study, in which we will utilize the same experimental therapeutics approach to probe these outcomes to explore how E/I balance, structural cortical architecture, and network functioning contribute to language/auditory processing in adolescents with ASD. We have begun this phase of the study and are currently enrolling.