Disruption of Medial Geniculate Nucleus Connectivity to Auditory Cortex in Patients with Schizophrenia

Jared X. Van Snellenberg,1,2,3 Guillermo Horga,1,2 Roberto Gil,1,2,3 Juan Sanchez-Pena,2 Seth Baker,2 Rachel J. Rosengard,2 & Anissa Abi-Dargham1,2,3

1. Background
Recent work in a 22q11 deletion syndrome (22q11DS) mouse model of schizophrenia identified a specific disruption of synaptic transmission from the medial geniculate nucleus (MGN) of the thalamus to auditory cortex, which was sensitive to treatment with antipsychotic medication (Chun et al., 2014). However, no direct evidence for such a disruption exists in clinical samples of patients with schizophrenia. Consequently, we employed high-resolution multiband functional Magnetic Resonance Imaging (fMRI) during a resting state and during a novel task designed to identify MGN and lateral geniculate nucleus / pulvinar (LGN/P) voxels in fMRI images, in order to directly assess the connectivity of MGN and LGN/P to auditory and visual cortices (AC and VC) in unmedicated patients with schizophrenia.

2. Methods
Eighteen unmedicated patients with schizophrenia and 18 healthy controls participated in the study. The below methods failed to identify anatomically plausible MGN or LGN/P regions-of-interest (ROIs) in 4 patients and 2 controls, leaving 14 patients (10 male, mean age 36.4 ± 9.5 years) and 16 controls (11 male, 28.9 ± 2.9 years). All participants were scanned on a 3 T Siemens MR 750. We acquired functional EPI volumes with 2 mm isotropic voxels and 850 ms TR with a multiband acceleration factor of 6, no in-plane acceleration, 192 mm FOV, 66 slices, 60° FA, and 25 ms TE. The localizer task used a sparsely temporal sampling sequence, with acquisition clusters of 3 volumes (2550 ms) followed by a 9450 ms inter-cluster interval, during which the scanner was not collecting data and either auditory or visual stimuli were presented in random order. The visual stimulus was a circular checkerboard alternating between black and white at 7.5 Hz, with maximum contrast. Participants also completed 4 resting state runs (with fixation) of 7.5 minutes each.

3. Task and Functional MRI Sequence Design
Stimulus Presentation
Sparse fMRI Acquisition

4. Functional Localizer Task Analysis

5. Functionally Identified Thalamic Nuclei (Examples)

Lateral geniculate nucleus / pulvinar (yellow) and medial geniculate nucleus (blue) ROIs displayed on the MNI normalized T2* images for each participant.

6. Methods (Cont’d)

Data were preprocessed through the Human Connectome Project pipeline. MNI Template aligned images were smoothed with a 4 mm FWHM Gaussian filter. Template masks were obtained from the SPM WFU PickAtlas for Brodmann’s Areas (BA) 41 and 42 in each hemisphere (MGN mask), BA 17 and 18 (VC mask), and medial and lateral geniculate bodies (ST mask). The VC and AC masks were dilated by 1 voxel in 3 dimensions while the ST mask was dilated by 2 voxels, but with voxels showing greater than 97.5% probability of white matter in SPM tissue probability maps removed, along with voxels within 2 mm of the PickAtlas hippocampus. An Auditory – Visual condition contrast was calculated for each subject, and voxels showing contrast values in the top 10% within each mask were identified. A single contiguous cluster of at least 10 voxels in each hemisphere was retained as an ROI for auditory or visual cortex for each subject. ROIs for auditory thalamus were then identified as the largest contiguous cluster of voxels within the ST mask showing a correlation with the average signal in the AC mask that was in the top 7.5% of ST mask voxels, but that was not also in the top 7.5% of voxels in terms of their correlation with the VC mask. The visual thalamic ROI was identified in the converse manner. These correlations were determined after regressing out run- and volume-specific regressors, to account for run effects as well as T1 relaxation effects.

The MGN and LGN/P ROIs were then used as seeds to evaluate whole-brain connectivity during resting state, by averaging the time series of all voxels within each ROI to create a single time series. Connectivity data was ‘scrubbed’ for both high-motion volumes and volumes during which participants closed their eyes, and bandpass filtered between 0.008 and 0.09 Hz. Pearson correlations between each thalamic ROI and every voxel in the brain were calculated for each subject. Fisher r-to-z transformed, and averaged together for right- and left-hemispheres. Voxels exhibiting significant connectivity were assessed within each group, as well between-group differences in connectivity, using robust regression and correction for multiple comparisons (alphasim corrected P < 0.05).

7. Resting State Analysis of ROI Connectivity

8. Validation of ROIs With Resting State Functional Connectivity

Applying the functionally identified ROIs to the resting state data, in 16 healthy controls A) the MGN ROI showed stronger connectivity to the AC than the LGN/P ROI (one-tailed t(15) = 2.06, P = 0.029), while the LGN/P ROI showed stronger connectivity to the VC than the MGN ROI (one-tailed t(15) = 3.31, P = 0.002). In addition, in a voxelwise comparison of the B) MGN and C) LGN/P ROI with the PickAtlas ROI, the functionally localized ROIs showed stronger connectivity to primary auditory and visual cortices, respectively (P < 0.005, alphasim corrected).

9. Alteration of MGN-AC and LGN/P-VC Connectivity in Patients

Patients showed significantly reduced connectivity relative to healthy controls between the MGN ROI and primary AC, as well as between the LGN/P ROI and primary/secondary VC (P < 0.05, alphasim corrected).

10. Results
Both groups exhibited significant connectivity between MGN and primary and secondary auditory cortex, as well as between LGN/P and primary and secondary visual cortex. Moreover, patients with schizophrenia showed significantly reduced connectivity between MGN and primary auditory cortex in the right hemisphere, as compared to healthy control participants, confirming our hypothesis. A similar finding was not observed between the nearby LGN/P and auditory cortex, suggesting this result is specific to MGN. In addition, patients demonstrated a reduction in connectivity between LGN/P and primary and secondary visual cortex, although a similar reduction was also observed between MGN and visual cortex.

11. Conclusion
We demonstrate a reduction in MGN-auditory cortex connectivity in unmedicated patients with schizophrenia, which was directly hypothesized on the basis of a 22q11DS mouse model of schizophrenia. These findings directly support the notion that the mechanism of impaired synaptic transmission identified in this model is also impaired in human patients with schizophrenia.

References: