Alterations of Mismatch Negativity (MMN) in Schizophrenia Patients Differing on Perceived Spatial Location of Auditory Hallucinations

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Auditory verbal hallucinations (AHs), or hearing 'voices', are one of the hallmark symptoms of patients with schizophrenia (SZ). The primary objective of this study was to examine whether SZs with differing perceived locations of AHs also differ in the processing of auditory deviance, as indexed by the auditory mismatch negativity (MMN). MMNs to duration, frequency, gap, intensity and location were recorded in 21 SZ patients with persistent AHs and 15 healthy controls (HC). Patients were divided into those who experienced AHs as being inside the head only (SZI) and those with AHs outside the head (SZO). MMN amplitudes and latencies for each deviant were compared between groups. Duration-MMN was reduced in both patient groups relative to HCs. SZOs were found to have reduced right frontal location-MMN amplitudes compared to SZIs and HCs. Overall, we report differences in auditory change detection for location deviants between schizophrenia patient groups that differ in the perceived location of auditory hallucinations. Whether these differences are due to structural abnormalities and/or functional differences between the groups remains unanswered.

Abnormal Functional Connectivity Associated with Auditory Hallucinations Across the Psychosis Spectrum

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Auditory hallucinations (AH) are most commonly associated with schizophrenia (SZ), but they are non-specific, also occurring in bipolar disorder (BP). In this transdiagnostic investigation, we sought to identify functional connectivity (FC) abnormalities associated with AH across SZ and BP. Participants were 95 individuals with lifetime AH (71 SZ, 24 BP) and 62 without (NAH) (16 SZ, 46 BP), categorized using item B16 in the Structured Clinical Interview for DSM-IV-TR (SCID). We acquired high-resolution structural scans and resting state blood oxygenation level dependent (BOLD) images (124 volumes, TR/TE 3000ms/30ms) on a 3T Siemens Tim Trio scanner at McLean Hospital. We used CONN v17e for resting state FC analysis. In addition to standard preprocessing, we used the ARtifact detection Tool (ART) to identify outlier time points, included only individuals with < 20 motion outliers, and performed rigorous denoising. For group-level analysis, we compared AH to NAH, adjusting for motion and other symptom dimensions. We performed ROI-to-ROI analysis, looking at BOLD time-course correlations across the 48 cortical and 21 subcortical regions of the Harvard-Oxford atlas and 26 cerebellar regions from the Automated Anatomical Labeling (AAL) atlas, using a significance threshold of $p<0.05$, FDR-corrected. We found multiple brain region pairs showing hyperconnectivity (either from reduced anti-correlations or increased positive correlations) in AH relative to NAH. Regions of the cerebellum, pre- and post-central gyri, and auditory cortices featured prominently among the FC

abnormalities. These results, highlighting cerebellar abnormalities, are particularly intriguing in light of growing evidence for the cerebellum's role in integrating higher-level brain processes.

Associations of Resting State Cerebral Blood Flow with Auditory Verbal Hallucinations with and Without Emotional Content in Schizophrenia

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Auditory verbal hallucinations (AVH) are a core symptom in schizophrenia. Here we focus on resting state cerebral blood flow (rCBF) linked to AVH and explored rCBF in patients with AVH with and without emotional content. We included 48 schizophrenia spectrum patients and 40 age and gender matched healthy controls. We assessed AVH with the comprehensive assessment of schizophrenia history and the hallucination change scale as well as imaging on a 3T MRI scanner. AVH were currently present in 33 patients and 18 patients had AVH with emotional content. Patients did not differ in antipsychotic medication or positive symptoms. We compared whole brain perfusion using arterial spin labeling (ASL) over all, and between the groups using one-way ANCOVAs (F-test and T-tests). We applied threshold-free cluster enhancement (TFCE) and a statistical threshold of $p < 0.05$ family wise error corrected for multiple testing (FWE-corr). We found a group effect (F-test) within the superior temporal gyrus and T-tests revealed that patients with AVH had increased perfusion most prominently within the left superior temporal gyrus compared to heathy controls and patients without AVH. Furthermore, T-tests indicated perfusion within the limbic system to be specific to AVH with emotional content. The STG has been suggested to play a key role in AVH in patients with schizophrenia. Thus, our results are highly compatible with increased superior temporal perfusion as a marker of AVH. Furthermore, distinguishable associations of rCBF with AVH with and without emotional content point to distinct underlying pathophysiology.

Microstructural White Matter Abnormalities Associated with Auditory Verbal Hallucinations

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Auditory verbal hallucinations (AVH) are one of the hallmarks of psychosis, but they also appear in 5-10 % of healthy individuals. Structural and functional imaging studies implicate the superior temporal gyrus and inferior frontal language areas in generation of AVH. Here, we examined white matter in tracts interconnecting these regions with advanced diffusion imaging methods. We aimed to reveal pathophysiologic substrates for AVH across several datasets, consisting of first episode and chronic schizophrenia patients as well as healthy individuals with and without AVH. Diffusion MRI data were analyzed using voxel-wise analyses, as well as stochastic and deterministic tractography to extract fiber connections forming language networks: arcuate fasciculus, inferior occipito-frontal fasciculus, and the genu and isthmus of the corpus callosum. Several measures of white matter microstructure were examined, including extracellular free water (FW) and tissue-specific fractional anisotropy (FAt), axial and radial diffusivity (Rdt). We identified significant microstructural abnormalities in language connections across patients with established schizophrenia and healthy individuals with AVH, albeit to lesser degree. These changes were characterized by increased extracellular FW and RDt, as well as decreased FAt. Notably, microstructural variability was associated with positive symptoms and AVH, independent of diagnostic status and illness stage (first episode and chronic schizophrenia). Our data point to

shared neural substrates for auditory verbal hallucinations across heterogeneous schizophrenia populations and healthy individuals; compatible with dimensional models of psychosis.

Auditory and Language System White Matter Connectivity Abnormalities and Auditory Hallucinations in the First Episode Schizophrenia Spectrum

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Auditory verbal hallucinations (AVH) are common in schizophrenia and may be related to impaired cortical connectivity between left language centers via the arcuate fasciculus, and between the left and right the auditory cortices across the corpus callosum. We examined white matter auditory cortex connectivity using diffusion spectrum imaging (DSI) in 40 first-episode psychosis (FEP) and 32 matched healthy comparison subjects (HC). Our primary measure was generalized fractional anisotrophy (gFA), the DSI analogue of FA reported in studies using diffusion tensor imaging (DTI). Across the auditory transcallosal (ATC) fibers, groups did not differ in gFA. However, AVH+ FEP (n =23) had reduced gFA within the ATC compared to AVH- FEP (n =17, p =.009). For bilateral arcuate fasciculus (AF) fibers, there were no significant group differences in gFA and no asymmetry between hemispheres in either group. AVH+ FEP had reduced gFA within the left hemisphere AF compared to AVH- FEP (p =.040). By contrast, AVH+ FEP and AVH- FEP did not differ in right hemisphere AF gFA. FEP showed white matter structural connectivity abnormalities in the left hemisphere language circuit and inter-hemispheric auditory fibers that were associated with AVH. Although the precise microstructural abnormality giving rise to gFA reductions is unknown, it is thought to indicate more “leaky” axons, and is likely manifest in slowed conduction times. Thus, at the first psychotic episode, AVH are associated with impaired left-language system and inter-hemispheric auditory communication, likely reflecting mistiming of information flow between language-related cortical centers.

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