Altered anterior cingulate chemistry, blood flow, and functional connectivity in schizophrenia

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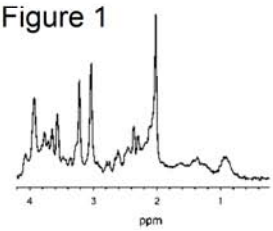
Target audience: Researchers interested in schizophrenia, MRS, ASL, and functional connectivity

Introduction: The anterior cingulate cortex has been implicated in the pathophysiology of schizophrenia ranging from post-mortem and neuroimaging studies (1). This study combined proton magnetic resonance spectroscopy (MRS) and arterial spin labeling (ASL), and resting state fMRI to investigate anterior cingulate neurochemistry, regional cerebral blood flow, and functional connectivity in participants with schizophrenia and healthy controls.

Methods: 14 stable outpatients with schizophrenia treated with antipsychotic medication and 8 age-matched healthy controls participated in this project. Each participant was scanned using a Siemens TIM Trio 3T MRI system with a 32-channel phased array head coil. Spectra were acquired from the anterior cingulate (AC) with PRESS (TR/TE=2000/30ms, VOI = 6cm^3, NEX= 128 (water-suppressed); 16 (water-unsuppressed), 2.5kHz spectral width, 2048 complex points). Spectra were analyzed using fully automated curve fitting software, 'LCModel' with a simulated basis set (2). The spectroscopic voxel was segmented into gray, white, and CSF tissues using SPM8, and metabolite concentrations were corrected for the proportion of gray, white, and CSF tissues using MATLAB in house code. fMRI was acquired while participants were at rest with eyes closed for 8 minutes with an echo-planar image (EPI) pulse sequence (TR=2000 ms, TE = 27 ms, flip angle = 80, slice thickness = 4.0 mm, interleaved, and FOV = 220 x 220). Figure 1 illustrates spectroscopic voxel placement and a representative spectrum. Functional connectivity analysis was performed with in house MATLAB code. Functional connectivity with ACC spectroscopic voxel as seed region was computed for each subject and group differences were determined. ASL was acquired using Psuedo-Continuous Arterial Spin Labeling (TR/TE = 4000/16ms, FOV = 220x220mm, Number of slices = 23, Slice thickness = 5 mm, Voxel size = 3.4x3.4x5.0 mm3, Bandwidth=1594 Hz/pixel, 136 measurements, labeling offset = 90 mm, labeling duration of 1.85 s, post labeling delay of 0.93s). ASL data were processed with pCASL MATLAB scripts and with SPM8 using ASL tbx.

Figure 1



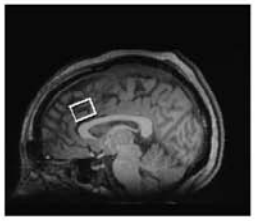
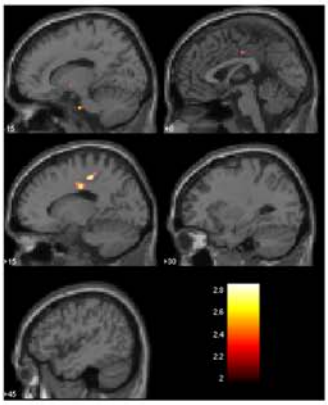


Figure 2



Results: MRS results only revealed significantly reduced NAA in the patients compared to controls ($t = 2.68$, $p < .05$) and ASL results revealed no significant difference for anterior cingulate blood flow. Controls had greater magnitude of anterior to mid cingulate functional connectivity compared to patients ($p<0.05$; see Figure 2). NAA was strongly positively correlated with both whole-brain rCBF($r=0.866$ $p < .05$) and AC rCBF ($r =0.807$ $p < .05$) in controls and at trend level for whole-brain CBf ($r = 0.523$ $p< 0.1$) and AC CBF ($r = 0.55$, $p <.05$) in patients. NAA was not significantly related to anterior cingulate functional connectivity.

Discussion: This is the first study to combine MRS, ASL, and resting state fMRI functional connectivity to investigate anterior cingulate in schizophrenia. Results show reduced anterior cingulate NAA and altered functional connectivity in schizophrenia. The strong relationship of NAA and CBF lends support to the tight coupling between neuronal function and blood flow in controls that may be slightly compromised in patients. The combination of these results provides support for anterior cingulate neuronal dysfunction and disconnection that may contribute to clinical features of schizophrenia.

References: (1) Fornito et al. (2009).Schizophr Bull 35(5):973-93, (2) Provencher SW (2001). NMR Biomed 14(4):260-4

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