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Abnormal Anterior Cingulate Cortex Activity Predicts Functional Disability in Schizophrenia

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The anterior cingulate cortex (ACC) may play a critical role in mediating cognitive deficits in schizophrenia (Szeszko et al., 2000). The ACC plays a critical role in conflict monitoring (e.g. Bush et al., 2000) and functional neuroimaging studies have implicated abnormal ACC activation during selective attention tasks in schizophrenia (Carter, Mintun, Nichols, & Cohen, 1997) and, in particular, while patients monitor conflict (Harrison et al., 2007). The relationship between these brain imaging deficits and real-world functioning has not been investigated and may be useful in predicting long-term outcome.

We therefore examined functional magnetic resonance imaging (fMRI) measures of conflict monitoring in patients with schizophrenia in relationship to functional disability using a reliable and validated measure, the Multidimensional Scale for Independent Functioning (Jaeger et al., 2003). Nine (4M/5F, 32.6±7.33 years old) patients with schizophrenia, who met criteria for schizophrenia (n = 5) or schizoaffective disorder (n = 4) using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P), and nine (6M/3F, of 34.59±7.88 years old) healthy comparison subjects as determined by the SCID-NP participated in the study.

To activate the dorsal ACC during conflict monitoring while undergoing fMRI, the Multisource Interference Task was adapted for use in the current study from prior work (Bush et al., 2000; Bush & Shin, 2006). In particular, the contrast of Interference minus Control conditions has been demonstrated to reliably activate the dorsal ACC (see Bush & Shin (2006) for task specifications).

A total of 536 EPI volumes were acquired on a GE 3T HDx MR imaging system (TR=1500ms, TE=27ms, matrix=64*64, FOV=220mm, slice-thickness=5mm, 26 continuous slices) axially aligned along the anterior and posterior commissures. Imaging data were processed using SPM5 (<http://www.fil.ion.ucl.ac.uk/spm>). Patients demonstrated significantly lower activation compared to healthy volunteers during the contrast of

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Contributors Dr. Ikuta designed the study, conducted the literature search and statistical analyses, and wrote the first draft of the manuscript. Dr. Szeszko wrote the protocol, conducted statistical analyses and edited the manuscript. Drs. DeRosse and Gruner recruited the patients and conducted the clinical assessments. Dr. Malhotra supervised patient recruitment and edited the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest My co-authors and I affirm that we do not have any conflicts of interest that may have influenced this work, and we have reviewed and approve the manuscript in this form.

interference minus the control condition in the anterior cingulate cortex (Figure 1, MNI coordinates: [12,15,45], $K=2$, $p < 0.001$, $Z=3.39$); a 5mm-sphere Region of Interest (ROI) was defined from this coordinate; and BOLD signal change between Interference and Control conditions was extracted by MarsBar SPM extension (<http://marsbar.sourceforge.net/>).

We investigated the correlation between BOLD signal change and the Multidimensional Scale of Independent Functioning in patients. There were significant positive correlations between BOLD signal and global residential functioning ($r = .68$, $df = 9$, $p = .04$) and global role position ($r = .74$, $df = 9$, $p = .02$) suggesting that greater susceptibility to conflict monitoring was associated with more functional impairment.

BOLD activity in the anterior cingulate cortex, as assessed during the performance of a conflict monitoring task, is associated with psychosocial functioning in patients with schizophrenia. It suggests that functional abnormalities during a conflict-monitoring task predict greater disability in patients. Our findings converge with prior studies linking gray matter volumes to functional outcome in schizophrenia (e.g., Buchsbaum et al., 2003) and more specifically, a report that cingulate volume predicted outcome in patients (Mitelman et al., 2005). Similarly, a recent study indicated that pretreatment gray matter volume significantly predicted the effects of cognitive therapy on social cognition (Keshavan et al., 2011) suggesting that MR imaging measures may be useful biomarkers in assessing a broad range of functional outcome measures. It is conceivable that deficits in the ability to monitor conflict and adjust behavioral patterns accordingly, as reflected by abnormal ACC activation (e.g., Harrison et al., 2007; Polli et al., 2008), could contribute to functional deficits in patients across a range of measures, including those related to independent functioning. Study limitations include the small sample size, possible influence of antipsychotic medications and illness severity on dependent measures, potential effect of sex differences (Clayson et al., 2011), and lack of functional outcome measures in healthy volunteers.

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Figure 1.
Lower BOLD response in patients compared to healthy volunteers during the Interference – Control Condition (peak MNI coordinates: x = 12, y = 15, z = 45)