

Widespread Cortical Dysfunction in Schizophrenia: The FBIRN Imaging Consortium

Steven G. Potkin^{1,2} and Judith M. Ford³

²Department of Psychiatry and Human Behavior, 5251 California Avenue, Suite 240, University of California, Irvine, CA 92617;

³Department of Psychiatry, SFVA, Building 8, Room 9B-30 116D, 4150 Clement Street, University of California, San Francisco, CA 94121

This Special Theme issue presents a series of related papers describing fMRI data collected as part of a multi-site brain imaging consortium, the Functional Imaging Biomedical Informatics Research Network (FBIRN) on the same subject population (C125 patients and C125 controls), a larger sample than would have been possible from a single-site, and from a broader clinical and demographic range of patients. Potkin et al observe cortical inefficiency during retrieval of items from memory but not during encoding of those items; Brown et al showed that the lawful relationship between memory retrieval time and neural activation is decoupled in patients with schizophrenia. Wible et al analyzed the same memory data and report activations of left auditory and parietal cortices are especially abnormal in patients who tend to hallucinate. Using an auditory target detection task, Ford et al report abnormal activation of left primary auditory cortex in the hallucinators. A multivariate analysis of those auditory data by Kim et al found differences in connectivity in patients and controls. These studies on the same patient sample suggest that abnormal circuitry characterizes schizophrenic performance in both auditory target detection and memory retrieval, and that patients who hallucinate have reduced left auditory cortical activation on both tasks. Segall et al report anatomical differences between patients and controls in the largest sample yet published. Finally, Potkin et al. identified six genes that influence DLPC activation and have functions related to forebrain development and stress responses in schizophrenia. These related publications indicate the power of multisite neuroimaging.

Key words: multi-site neuroimaging studies/cortical dysfunction/sternberg item recognition paradigm/detection paradigm/auditory oddball paradigm/working memory/genome wide association study

¹To whom correspondence should be addressed; tel: 949-824-8040, fax: 949-824-3324, e-mail: sgpotkin@uci.edu.

This *Special Theme* issue of *Schizophrenia Bulletin* describes a series of related articles using the same subjects studied by the Functional Imaging Biomedical Informatics Research Network (FBIRN) consortium. The FBIRN consortium uses functional magnetic resonance imaging (fMRI) and structural MR brain imaging to explore clinical and cognitive abnormalities in large samples of schizophrenia patients collected across many sites. The FBIRN had as its initial aim to measure intersite fMRI variability; it accomplished its primary aim initially by developing a MRI calibration method, a common functional protocol and recruiting subjects who traveled to all sites for multiple imaging sessions. This resulted in the Traveling Subjects (phase I) study.¹⁻⁴ These data are now available as part of the BIRN Data Repository (www.nbirn.net). The FBIRN phase II study was the first multisite functional neuroimaging study of a clinical population; it began in February of 2005 and was built upon lessons learned and methods developed during the Traveling Subjects phase I study. The dataset includes structural MRI images, fMRI images, behavioral data, and demographic and clinical assessments on approximately 125 schizophrenic patients and 125 age- and gender-matched controls from around the United States. The articles in this special issue are the initial analyses and publication of these phase II data.

Through this large collaborative study, the FBIRN sites collected MR data from a larger sample than would have been possible from a single site and from a broader range of patients, both clinically and demographically. Multisite neuroimaging studies create several challenges, most of which are related to unwanted variability. In essence, the statistical advantages of a large number of subjects are undermined if between-site differences due to machine or paradigm differences are not addressed at both the planning and analysis stages. FBIRN has been funded to develop methods to do precisely this. In particular, standard criteria for inclusion and exclusion of subjects were adopted, raters were trained in a cross-site session to do symptom assessment before the study was launched, months were spent optimizing the parameters for fMRI paradigms and calibrating the scanner with phantom and human volunteers, data were carefully assessed for quality, and finally statistical methods for combining data cross-sites were implemented. In so doing, many of the problems associated

with combining data in previous multisite studies were avoided, and data could be amassed and analyzed with sample sizes large enough to address previous confounds in the literature to contrast analysis methods on the same subjects and facilitate correlating clinical, behavioral, and genetics data with MR data.

Two cognitive tasks were chosen and modified for FBIRN use, the visual Sternberg Item Recognition Paradigm (SIRP), and the auditory target (oddball) detection (AOD) paradigm. The articles in this special issue begin with a series of articles on the SIRP. Potkin et al observe cortical inefficiency during memory retrieval but not during memory encoding (SIRP). Analysis of these same data by Brown et al focused on memory retrieval times, and they report that the lawful relationship between memory retrieval time and neural activation is decoupled in patients with schizophrenia. Analysis of these data by Wible et al focused on relating symptoms to neural activations during memory retrieval, and they report that activation of left hemisphere auditory and parietal cortices are especially abnormal in patients who tend to hallucinate. This finding is consistent with Ford et al who report abnormal activation of left primary auditory cortex during the AOD paradigm in patients who tend to hallucinate. A multivariate analysis of the AOD data by Kim et al focused on connectivity between different regions, and they report functional connectivity differences between patients and controls in networks related to auditory processing and executive control. These findings together suggest that abnormal circuitry characterizes schizophrenia performance in both auditory target detection (Kim et al) and memory retrieval (Brown et al, Potkin et al, SIRP) and that patients who hallucinate have reductions of activity in left auditory cortex regardless of whether the task is visual working memory (Wible et al) or auditory (Ford et al). Another manuscript in this Theme issue reports structural MR findings from the largest sample yet published (Segall et al).

The strength of large sample sizes is most evident in the first article by Potkin et al (SIRP). The large FBIRN sample, collected across 10 different universities, allowed matching for performance accuracy with the identical level of memory load, addressing possible confounds in previous efforts. In the FBIRN sample, the major difference in brain activation between schizophrenia subjects and controls was during the retrieval condition of a working memory task. The lack of differences observed in the encoding condition suggested that schizophrenia subjects were able to store the memoranda similarly to controls (over a range of 1–5 items) but required greater activation of the dorsolateral prefrontal cortex (DLPFC) to achieve the same level of performance accuracy as controls during item retrieval from memory. Potkin et al (SIRP) demonstrated that successful working memory performance in schizophrenia is associated with inefficient DLPFC function compared with healthy normal controls, even

at the same level of accuracy. Rather than supporting the concept of hyper- or hypofrontality in schizophrenia, these data suggest that reduced efficiency of prefrontal function in schizophrenia may be manifest in either direction depending on task demands. These findings suggest that mechanisms of inefficiency in the DLPFC, and not direction of difference, are key to understanding the working memory deficit in schizophrenia.

In the next article in this series, Brown et al apply response time cognitive models to the same data to distinguish between a deficit interpretation of diminished neural activity of unresponsive neurons and an inefficiency interpretation assuming that mildly impaired schizophrenia individuals will have reduced computational power that will require increased neural activity of neurons to achieve correct performance. Brown et al observe that fast-scanning healthy volunteers require little additional neurocognitive capacity to scan working memory as scanning load increases, while slower scanning volunteers show a linear increase in blood oxygen level-dependent (BOLD) response to increasing scanning load. Unlike healthy participants, schizophrenia patients showed an uncoupling of performance to brain response in the left PFC and caudate as memory load increased most compatible with an inefficiency interpretation. In the left perirhinal/entorhinal cortex, however, schizophrenia patients show either an inefficient or disordered pattern of inhibition as WM load increases reflecting a complex and disordered pattern of activation and inhibition even when performing a task as simple as memory scanning.

In the next article, Wible et al report that neural activation during memory retrieval was correlated with symptom measures of auditory hallucinations. Patients who tended to hallucinate showed less activity in verbal working memory/language processing regions, including the superior temporal and inferior parietal regions, than did patients who did not tend to hallucinate. The more severe the hallucinations the less activity was observed. A relationship with auditory hallucinations and left hemisphere auditory cortical activation was also reported by Ford et al but in the auditory target detection task. They reported that patients who tended to hallucinate had less activation to probe tones in left primary auditory cortex (BA41) than did subject who did not hallucinate. Although “voices” are the subject’s subjective sensory experience and tones were used to probe auditory cortex, the data suggested that primary auditory cortex is “turned on” and “tuned in” to process internal acoustic information at the cost of processing external sounds.

In a connectivity analysis of these data, Kim et al used independent components analysis to extract signals that represent possible task-related functional networks. They identified multiple functionally connected networks involved in auditory target detection that were decreased

in schizophrenia patients, including the bilateral temporal lobes, default mode regions, and DLPFC, areas commonly implicated in schizophrenia. These findings suggest that the dysfunction in schizophrenia is diffuse and widespread and could reflect a defect in transition from primary auditory sensory areas to higher association cortex.

All together the findings from these articles suggest that the underlying pathophysiological abnormalities involving the DLPFC, temporal lobe, and basal ganglia in schizophrenia are not limited to a single cognitive task but are more widespread and represent circuitry dysfunction involved in multiple cognitive tasks.

These functional studies are further supported by the Segall et al VBM study of the FBIRN sample augmented by additional subjects from the MIND consortia comprising the largest morphometry study of schizophrenia to date. A consistent pattern of reduced cortical gray matter in schizophrenia patients compared with controls was found particularly in the temporal lobes, as well as anterior cingulate and some frontal regions. Schizophrenia subjects had reduced cortical gray matter in areas of the superior, middle, medial, and inferior frontal gyri. The structural differences were not limited to the DLPFC but were widespread across the frontal cortex (as well as superior temporal and other areas).

The strong relationship between cognitive demands on the SIRP and auditory odd ball and the neural dysfunction reflected in the BOLD signal in the DLPFC, in conjunction with the structural frontal differences, makes the BOLD signal changes in the DLPFC a good choice for a cognitive biomarker in schizophrenia. In the second Potkin et al publication employing to Genome Wide Association Scan (GWAS), DLPFC activation was used as a quantitative trait to identify unanticipated genes related to DLPFC inefficiency by examining the role of individual genetic variation on this quantitative phenotype 235 at an individual level, ie, how each single-nucleotide polymorphism (SNP) predicts activation in the DLPFC. This approach reverses the candidate gene strategy: rather than beginning with a specific candidate gene as a grouping factor and searching for differences in neuroimaging results, it begins with brain imaging as a phenotype and determine the SNPs that influence that phenotype. It allows for completely novel SNPs to be identified as playing a role in the disease phenotype. Six genes that are related to forebrain development and stress response are implicated in schizophrenia. The most statistically significant genes are involved in the development of cortex, particularly the forebrain and midline/callosal connections. These genes, for the most part not previously implicated in schizophrenia, do support schizophrenia being a neurodevelopmental disorder. Abnormal callosal morphometry is well described in schizophrenia. The CTXN3-SLC12A2 region, identified in the Potkin et al publication using GWAS, has been linked to schizophrenia in the

meta-analysis by Lewis et al,⁵ and it is on the boundary of the chromosome 5 region implicated in multiple cognitive measures in schizophrenia by Almasy et al (2008).⁶ Three of the identified genes have functions related to the hypothalamus-pituitary-adrenal (HPA) stress axis. DLPFC function is strongly influenced by prenatal (second trimester) and postnatal/adult stress,^{7,8} and HPA axis is overactivated in schizophrenia, particularly in paranoid schizophrenia.⁹

Exposure to stress exacerbates schizophrenic symptoms and causes marked DLPFC cortical dysfunction. Hains and Arnstein¹⁰ suggest that patients with serious mental illness have weaker endogenous regulation of stress pathways possibly related to DISC1 and RGS4. Cortisol released during stress inhibits brain COMT (an enzyme which degrades dopamine) in the cortex, leading to increased extracellular dopamine that can disrupt prefrontal cognitive functioning.¹¹⁻¹⁴ This example demonstrates how genetic vulnerability and stress could converge to disrupt DLPFC functioning, creating impaired working memory and other psychiatric symptoms. Such integrative approaches of combining cognitive, imaging, and genetic data offer enhanced explanatory power in addressing the complexities of schizophrenia.

These publications indicate the power of multisite neuroimaging; a single study can answer multiple questions regarding the breadth of psychiatric dysfunction within a clinical population. While improved methods are still being developed, multisite methods are now developed to the point where they can be used when the research questions require large samples. The data used in all these articles are available to the research public for further analysis and exploration in the BIRN Data Repository (www.nbirn.net).

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