Archival Report

Biological Psychiatry

In Search of Multimodal Neuroimaging Biomarkers of Cognitive Deficits in Schizophrenia

Jing Sui, Godfrey D. Pearlson, Yuhui Du, Qingbao Yu, Thomas R. Jones, Jiayu Chen, Tianzi Jiang, Juan Bustillo, and Vince D. Calhoun

ABSTRACT

BACKGROUND: The cognitive deficits of schizophrenia are largely resistant to current treatments and thus are a lifelong illness burden. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) provides a reliable and valid assessment of cognition across major cognitive domains; however, the multimodal brain alterations specifically associated with MCCB in schizophrenia have not been examined.

METHODS: The interrelationships between MCCB and the abnormalities seen in three types of neuroimaging-derived maps—fractional amplitude of low-frequency fluctuations (fALFF) from resting-state functional magnetic resonance imaging (MRI), gray matter (GM) density from structural MRI, and fractional anisotropy from diffusion MRI—were investigated by using multiset canonical correlation analysis in data from 47 schizophrenia patients treated with antipsychotic medications and 50 age-matched healthy control subjects.

RESULTS: One multimodal component (canonical variant 8) was identified as both group differentiating and significantly correlated with the MCCB composite. It demonstrated 1) increased cognitive performance associated with higher fALFF (intensity of regional spontaneous brain activity) and higher GM volumes in thalamus, striatum, hippocampus, and the mid-occipital region, with co-occurring fractional anisotropy changes in superior longitudinal fascicules, anterior thalamic radiation, and forceps major; 2) higher fALFF but lower GM volume in dorsolateral prefrontal cortex related to worse cognition in schizophrenia; and 3) distinct domains of MCCB might exhibit dissociable multimodal signatures, e.g., increased fALFF in inferior parietal lobule particularly correlated with decreased social cognition. Medication dose did not relate to these findings in schizophrenia.

CONCLUSIONS: Our results suggest linked functional and structural deficits in distributed cortico-striato-thalamic circuits may be closely related to MCCB-measured cognitive impairments in schizophrenia.

Keywords: Diffusion magnetic resonance imaging (dMRI), Functional magnetic resonance imaging (fMRI), Gray matter, MATRICS Consensus Cognitive Battery (MCCB), Multimodal fusion, Schizophrenia

http://dx.doi.org/10.1016/j.biopsych.2015.02.017

Interview-based assessments of cognition subsume multiple domains, including attention, working memory, language processing, problem solving, and decision making. Cognitive impairments are recognized as core functional deficits of schizophrenia (SZ) and are a key reason that schizophrenia patients do not successfully re-enter the community (1,2). Unlike positive symptoms, which may be suppressed by medications, cognitive dysfunction remains in the majority of schizophrenia patients with resulting suboptimal community functioning.

Launched by the National Institute of Mental Health, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) is recognized as a valuable tool for comprehensive cognitive function evaluation of schizophrenia in the context of clinical trials. The MCCB includes 10 neurophysiologic tests clustered in 7 cognitive domains (1), including speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning/problem solving, and social cognition. Despite its widespread use, the neural networks underlying MCCB performance in schizophrenia have been examined in only a few single-modality brain imaging studies (3–5), presenting inconsistent results. Only one study examined MCCB correlates of fused neuroimaging data (magnetoencephalography and diffusion tensor imaging) by joint independent component analysis (6). A posterior visual processing network was related to reduced magnetoencephalography amplitude, reduced fractional anisotropy (FA), and poorer MCCB composite scores in schizophrenia, suggesting the advantage of this fused approach. Currently, National Institute of Mental Health emphasizes the importance of target engagement in clinical trials (7). Understanding the brain network organization related to MCCB performance may allow imaging assessments to be

 ISSN: 0006-3223

engaged early in clinical trials, hence, accelerating the development of new therapeutic approaches to enhance cognition.

This is the first study to combine functional magnetic resonance imaging (fMRI), structural MRI (sMRI), and diffusion MRI (dMRI) with MCCB to generate a full perspective of neuroimaging targets of cognitive dysfunction in schizophrenia patients. Nowadays, collecting these three types of widely used MRI data from the same subject on one scanner has become a common practice that can provide comprehensive brain measures of blood flow, gray matter (GM) volume, and white matter (WM) integrity. By taking advantage of the three-way MRI cross-information and the MCCB in a fusion analysis, we may reveal important covariation that may only partially be detected by a single modality.

METHODS AND MATERIALS

The study was approved by the Institutional Review Board of University of New Mexico.

Participants

Forty-seven schizophrenia patients and 50 age-matched healthy control subjects (HC) participated in this study. Demographic data for the subjects are provided in Table 1. Schizophrenia patients were recruited from the University of New Mexico Hospital and the Albuquerque Veterans Administration Medical Center. Healthy control subjects were recruited from the community through local advertisement. All subjects were screened and excluded if they had a diagnosis of central neurological disorder or active substance use disorder (6-month minimum before enrollment, except for nicotine). In addition, healthy control subjects were excluded if they had first-degree relatives with any psychotic disorder. Patients met criteria for schizophrenia defined by the DSM-IV-TR based on the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition interview (8). All patients were clinically stable on the same antipsychotic medications >4 weeks before the scan. Please see Table S1 in Supplement 1 for more information about medication and substance use history. Clinical assessment was performed within 1 week of scanning using the Positive and Negative Syndrome Scale (PANSS) (9). PANSS raters achieved good interrater reliabilities (positive symptom intraclass correlation coefficient = .86 and negative symptom intraclass correlation coefficient = .64). Informed consent was obtained from all subjects according to institutional guidelines required by the Institutional Review Board. Subjects were paid for their participation.

The MCCB

The MCCB (10) was administered within 1 week of imaging. Raw measurement scores were converted to normalized T-scores, resulting in seven domain T-scores and a composite T-score via the MCCB scoring program. As shown in Table 1, all MCCB scores were significantly lower in SZ and all domain scores were significantly correlated with the composite. No correlation was found between MCCB composite and medication dose in SZ. The domain of speed of processing had the highest correlation (r = .91), consistent with the reports that MCCB composite is usually dominated by the domain of speed of processing (11,12), which proved to be the best single predictor of overall cognitive performance (13). Additionally, as expected (14,15), negative PANSS scores had a significant anticorrelation with the MCCB composite ($r = -.48$, $p = .0008$).

Imaging Parameters

All subjects were scanned by fMRI, sMRI, and dMRI, which were collected on a 3-Tesla Siemens Trio scanner with a 12-channel radio frequency coil (Mind Research Network, Albuquerque, New Mexico).

fMRI. Resting-state scans were a minimum of 5 minutes, 4 seconds in duration (152 volumes). Subjects were instructed to keep their eyes open during the scan and stare passively at

Table 1. Demographics and the MCCB Scores of the Subjects

Measure		HC	SZ	p	r
Number		50	47		
Age		36.7 ± 12.6	35.3 ± 12.6	.6	.04
Gender		20F / 30M	6F / 41M	.01	.17
Olanzapine Equivalent		NA	13.5 ± 9.4		−.09
MCCB	Composite	49.8 ± 10.5	31.3 ± 15.7	1.3E-09	1
	Speed of processing	51.9 ± 9.0	35.3 ± 13.7	1.5E-09	.91
	Attention/vigilance	48.3 ± 9.9	36.0 ± 15.1	1.4E-05	.86
	Working memory	46.8 ± 11.4	37.1 ± 14.5	5.3E-04	.83
	Verbal learning	47.4 ± 8.9	38.0 ± 8.6	8.4E-07	.8
	Visual learning	49.3 ± 9.3	36.6 ± 12.6	1.5E-07	.79
	Reasoning/problem solving	54.2 ± 9.9	46.1 ± 11.7	5.1E-04	.64
	Social cognition	50.8 + 11.1	40.5 ± 13.0	8.3E-05	.65
PANSS	Negative	NA	15.1 ± 5.4		−.48
	Positive	NA	15.4 ± 5.9		−.10

Olanzapine equivalent = olanzapine total (standardized current dose of antipsychotic medication). p denotes the significance value of two-sample t test performed between control subjects and schizophrenia patients for all measures, except gender (used chi-squared test). r is the correlation value between MCCB composite and other measures.

HC, healthy control subjects; F, female; M, male; MCCB, MATRICS Consensus Cognitive Battery; NA, not applicable; PANSS, Positive and Negative Syndrome Scale; SZ, schizophrenia.