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Cortical Structural Abnormalities in Deficit Versus Nondeficit Schizophrenia

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Abstract

Objective—To examine the structural integrity of the dorsolateral prefrontal-basal ganglia-thalamocortical circuit in people with the deficit form of schizophrenia.

Method—A three-dimensional structural MRI sequence was used to conduct morphometric assessments of cortical and subcortical regions in deficit and nondeficit outpatients with schizophrenia and healthy controls.

Results—The superior prefrontal and superior and middle temporal gyral gray matter volumes were significantly smaller in the deficit versus the nondeficit group and normal control groups. There were no significant group differences in examined subcortical structures.

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Conflict of Interest

Drs. Fischer, Keller, and Pearlson, Mr. Meyer, and Mr. Francis report no conflicts.

Contributors

Drs. Buchanan, Arango, Kirkpatrick, Carpenter, and Pearlson designed the study and wrote the protocol. Dr. Buchanan was responsible for supervising the MRI morphometric assessments and Mr. Francis had primary responsibility for conducting these assessments. Dr. McMahon and Mr. Meyer managed the statistical analysis. Drs. Buchanan, Fischer, Keller, and McMahon interpreted the data. Drs. Fischer and Keller managed the literature search and Dr. Fischer wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Conclusion—People with deficit schizophrenia are characterized by selective reductions in the prefrontal and temporal cortex.

Keywords

schizophrenia; deficit syndrome; frontal lobe; temporal lobe; structural MRI

1. Introduction

Primary, enduring negative symptoms define a subtype of schizophrenia with a characteristic epidemiology, illness course, and clinical correlates (Kirkpatrick et al, 2001). Behavioral and functional neuroimaging studies (Buchanan et al, 1990, 1994, 1997; Lahti et al, 2001; Tamminga et al, 1992) have led us to hypothesize that the dorsolateral prefrontal-basal ganglia-thalamocortical (DLPFC) circuit (Alexander et al, 1990) is involved in deficit schizophrenia pathology.

We previously examined DLPFC circuit integrity by comparing prefrontal cortex and caudate volumes in deficit, nondeficit, and healthy comparison groups (Buchanan et al, 1993). We found that the nondeficit group had smaller prefrontal volumes compared to deficit and control groups, with the difference due to decreased white matter. There were no other significant schizophrenia group differences. A limitation of this earlier study was the inability to focus on specific cortical components of the circuit. Since then, we have developed a reliable procedure for segmenting cortical regions into component gyri (Buchanan et al, 2004; Rademacher et al, 1993).

The present study examined the structural integrity of cortical and subcortical DLPFC circuit components in deficit and nondeficit people with schizophrenia and a healthy comparison group. We hypothesized that we would find smaller volume of one or more components of the circuit specific to the deficit group, while there would be no deficit-specific volume differences in non-circuit regions.

2. Methods

2.1 Participants

Participants were outpatients, aged 21–51 years old, with DSMIV-TR schizophrenia or schizoaffective disorder (American Psychiatric Association, 2000). The Schedule for the Deficit Syndrome (Kirkpatrick et al, 1989) was used to subtype participants into deficit and nondeficit groups. The Brief Psychiatric Rating Scale (BPRS) total score and positive symptom items and the modified Scale for the Assessment of Negative Symptoms (SANS) total score were used to assess global psychopathology and positive and negative symptoms, respectively.

Schizophrenia groups were matched on age, gender, proportion on each type of antipsychotic (FGA, second generation (SGA), or clozapine), and duration of illness. Healthy comparison participants were recruited from the community and matched to schizophrenia participants on age and gender. Potential participants were excluded for a history of neurological disorder, mental retardation, head injury with loss of consciousness > 30 minutes, or diagnosis of DSM-IV substance abuse or dependence (except nicotine) within the last 12 months. Healthy comparison participants were also excluded if they had a history of any DSM-IV Axis I diagnosis.

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The University of Maryland School of Medicine IRB approved the protocol and informed consent procedures. Written documentation of informed consent and capacity to provide consent was obtained from all participants prior to study participation.

2.2 MRI Procedures

MRIs were performed on a 1.5-Tesla Signa GE Scanner (General Electric, Milwaukee, WI). Brains were evaluated in the coronal plane using a spoiled gradient recall acquisition in the steady-state three-dimensional imaging sequence (TR=35msec; TE=5msec; flip angle=45 degrees; number of excitations=1; field of view=24cm; matrix size: 256 by 256; slice thickness=1.5mm without skips). The image processing and procedures for measuring the cortical regions of interest are described in detail elsewhere (Barta et al, 1997; Buchanan et al, 1998; Buchanan et al, 2004). The cortical regions of interest are illustrated in Buchanan et al (2004).

We measured the gray matter volumes of the following cortical and subcortical DLPFC circuit components: the dorsolateral prefrontal cortex (middle frontal gyrus), inferior parietal cortex (angular and supramarginal gyri), thalamus, and caudate. Non-circuit control regions were other prefrontal cortex (orbital frontal, inferior frontal, superior frontal gyri), temporal cortex (superior and middle temporal gyri), and the amygdala-hippocampuc complex (AHC). Inter-rater reliability for volume calculations ranged from 0.86–0.99.

2.3 Statistical Analyses

A mixed analysis of covariance model for repeated measures, with volume as the within subject repeated measure, was used to examine group differences in circuit and non-circuit brain regions: Volume = diagnostic group + age + hemisphere + sex + (diagnosis × hemisphere) + (sex × hemisphere). In view of the limited number of female subjects, three- and four-way interaction terms were not included. Groups were not different on either TCV or TBV (see Table 1), so these measures were not included in the model. Separate models were run for each gray matter ROI in the volumes included or not in the circuit we hypothesized to distinguish deficit and non-deficit patients. Within the two sets of circuit and non-circuit ROIs, the Benjamini-Hochberg method was used to control for multiple testing of the main effect of group (Benjamini and Hochberg, 1995). Post hoc pairwise tests for differences among the three groups were conducted in ROIs in which the main effect of group was significant after correction for multiple testing.

3. Results

Demographic and clinical characteristics are presented in Table 1.

3.1 Deficit versus Nondeficit versus Healthy Comparison Group

3.1.1 Circuit Volumes (see Table 2)—Although the deficit group generally had smaller gray matter volumes, there were no significant effects of diagnosis for any cortical or subcortical circuit component.

3.1.2 Non-circuit Volumes (see Tables 2 and 3)—There was a significant main effect of diagnostic group for the superior frontal gyrus, the middle temporal gyrus, and the AHC; and a trend for the superior temporal gyrus.

The superior frontal and superior and middle temporal gyral gray matter volume findings were unique to the deficit group. All volumes were smaller in the deficit group compared to the nondeficit and healthy comparison groups. There was no difference between the nondeficit and healthy comparison groups in these volumes. The effect on AHC volume was

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a general schizophrenia finding; both patient group volumes were smaller than the healthy comparison group, but not different from each other.

4. Discussion

In contrast to our a priori hypothesis, we found little evidence for altered DLPFC circuit component volumes in people with deficit schizophrenia. Instead, we found that people with deficit schizophrenia were differentiated from nondeficit schizophrenia and healthy comparison groups by smaller superior frontal and superior and middle temporal gyral volumes. These smaller volumes were observed in the absence of significant group differences in TBV or TCV, which suggests these abnormalities are not merely a function of overall decreased brain volume, but are specific to these cortical regions.

The finding of smaller temporal gyral volumes in people with deficit schizophrenia is counter to our a priori hypothesis. However, several neuropsychological studies have found that people with deficit schizophrenia do as poorly (or worse) on tests involving temporal cortex as they do on those tests sensitive to frontal or parietal lobe function (Cohen et al, 2007). Functional neuroimaging studies have also shown diminished blood flow and metabolism in the temporal region of people with deficit schizophrenia compared to both healthy controls and nondeficit participants (Gonul et al, 2003; Heckers et al, 1999).

Moreover, other structural MRI studies have reported temporal lobe abnormalities in deficit schizophrenia. In an ROI study, in contrast to the nondeficit and healthy comparison groups, the deficit group had increased left temporal lobe CSF volume (Turetsky et al, 1995). There were no deficit/nondeficit frontal lobe volume differences. Using VBM, Sigmundsson et al (2001) found decreased gray and white matter signal intensity in the left superior temporal gyrus and medial temporal lobe in deficit schizophrenia versus a healthy comparison group. However, they did not include a nondeficit group for comparison. In a second VBM study, Galderisi et al (2008) found that temporal lobe signal intensity was decreased in both schizophrenia groups compared to controls, with greater decrease in right temporal lobe signal intensity in the deficit versus the nondeficit group. The schizophrenia groups did not differ on frontal lobe signal intensity. Finally, Cascella et al (2010) recently reported a VBM study in which bilaterally decreased superior frontal and superior temporal gyri signal intensity distinguished deficit from nondeficit schizophrenia.

There are several limitations to this study. First, in light of selecting the temporal cortex as a comparison region, we did not anticipate the need to examine the planum temporale; which would have been interesting given our temporal cortical findings. In addition, although our method of assessing cortical volume is generally sound, the potential for slight inaccuracies increases with atrophy (Buchanan et al, 2004). Finally, although the proportion of participants exposed to FGAs, SGAs, and clozapine were not different between schizophrenia groups, we did not control for lifetime antipsychotic dose exposure. In primate models, exposure to clinical levels of antipsychotics results in decreased cortical brain weights (Dorph-Petersen et al, 2005), which may also be the case in humans for some volumetric measurements (Ho et al, 2011). While unlikely, it is possible the deficit group was exposed to higher lifetime antipsychotic dosing, accounting for observed volume differences.

In summary, we found deficit symptoms to be uniquely associated with smaller superior frontal and middle temporal gray matter volumes. In light of the hypothesized functions of these cortical regions, the results suggest that future studies should examine whether there is selective involvement of the neural circuits that underlie decision-making (Paulus et al,

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2001), language (Martin, 2003), and theory of mind (Carrington and Bailey, 2009) in people with the deficit form of schizophrenia.

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Table 1

Sample Characteristics.

		Deficit Schizophrenia (N=20)	Nondeficit Schizophrenia (N=36)	Healthy Comparison Group (N=28)
Age at MRI (Years) [Mean (SD)]		40.1 (7.2)	38.4 (7.9)	36.0 (6.6)
Age Range (Years)		23–51	21–50	26–48
Male (%)		17 (85.0)	31 (86.1)	23 (82.1)
Non-White (%)		4 (20.0)	8 (22.2)	6 (21.4)
Education (Years)*		11.4 (2.5)	13.9 (1.9)+	14.2 (1.7)
Schizoaffective Diagnosis (%)		0	3 (8)	--
Duration of Illness (Years) [Mean (SE)]		18.0 (1.9)	19.3 (1.4)	--
BPRS Total Score [Mean (SE)]		34.1 (1.8)	33.4 (1.6)	--
BPRS Positive Symptom Item Score [Mean (SE)]		9.8 (1.1)	9.5 (0.7)	--
SANS Total Score [Mean (SE)]**		38.7 (2.8)	23.8 (4.4)	--
Medication Status				
	FGAs (%)	9 (45.0)	15 (41.7)	--
	Non-Clozapine SGAs (%)	4 (20.0)	10 (27.8)	--
	Clozapine (%)	7 (35.0)	11 (30.6)	--
Right Handed (%)		20 (100.0)	32 (88.9)	27 (96.4)
Volume Comparisons (mL) [Mean (SE)]***				
Total Cranial Volume (TCV)		1430.3 (47.0)	1455.4 (36.0)	1460.7 (36.4)
Total Brain Volume (TBV)		1299.2 (43.9)	1331.1 (33.6)	1339.2 (34.0)
Total Ventricular Volume		16.5 (2.8)	14.2 (2.1)	10.8 (2.1)
Total CSF Volume		114.6 (10.4)	110.1 (7.9)	110.6 (8.0)

BPRS=Brief Psychiatric Rating Scale; SANS=Scale for the Assessment of Negative Symptoms;

FGA: First Generation Antipsychotic; SGA: Second Generation Antipsychotic

SD: Standard Deviation; SE: Standard Error

*: The deficit group had significantly less education than the nondeficit ($t(52) = 4.33$, $p<0.0001$) and healthy comparison ($t(46) = 4.75$, $p=0.0001$) groups.

**: Significant group difference for SANS; $t_{50}=2.46$, $p=0.02$.

***: The main effect of diagnosis was not significant for TCV ($F_{2,77} = 0.14$, $p=0.87$), TBV ($F_{2,77}=0.28$, $p=0.76$), total ventricular volume ($F_{2,77}=1.45$, $p=0.24$), or total CSF volume ($F_{2,77}=0.07$, $p=0.94$).

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Table 2

Comparison of DLPFC Circuit versus Non-circuit Volumes by Diagnosis.*

Region	Deficit Schizophrenia			Nondeficit Schizophrenia			Healthy Comparison Group			Group Effect (p-value)	False Discovery Rate Critical Value**
	n	Volume	SE	n	Volume	SE	n	Volume	SE		
DLPFC Circuit Regions											
Middle Frontal Gyrus Gray Matter	20	11.40	1.15	35	13.55	0.92	28	13.42	0.95	0.20	0.01
Supramarginal Gyrus Gray Matter (Inferior Parietal)	20	5.34	0.37	36	5.99	0.29	28	5.54	0.30	0.23	0.02
Angular Gyrus Gray Matter (Inferior Parietal)	19	4.50	0.32	36	4.72	0.25	28	4.45	0.26	0.65	0.05
Thalamus	20	4.13	0.27	36	4.45	0.22	28	4.57	0.23	0.38	0.04
Caudate	13	4.37	0.27	32	4.78	0.18	24	4.83	0.19	0.25	0.03
Non-DLPFC Circuit Regions											
Superior Frontal Gyrus Gray Matter	20	19.47	1.01	35	22.04	0.80	28	22.72	0.83	0.019	0.025
Inferior Frontal Gray Matter	20	7.28	0.61	35	8.28	0.49	28	8.85	0.51	0.09	0.04
Orbital Frontal Gray Matter	20	11.91	0.45	35	12.37	0.36	28	12.72	0.37	0.31	0.05
Superior Temporal Gyrus Gray Matter	20	13.28	0.64	36	14.91	0.51	28	15.12	0.53	0.0336	0.0333
Amygdala-Hippocampal Complex	20	6.04	0.18	35	6.29	0.15	28	6.77	0.15	0.002	0.017
Middle Temporal Gyrus Gray Matter	20	7.42	0.45	36	9.33	0.36	28	9.28	0.38	0.0005	0.008

Dorsolateral Prefrontal-Basal Ganglia-Thalamocortical: DLPFC

SE: Standard Error

*All volumes in mL.

**Benjamini-Hochberg stepwise testing procedure used to keep overall false discovery rate for circuit and non-circuit regions at $p<0.05$.

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Table 3

Comparison of Region Volumes by Deficit, Nondeficit, and Healthy Comparison Group.*

Brain Region	Deficit versus Healthy Comparison					Deficit versus Nondeficit					Nondeficit versus Healthy Comparison				
	Difference	SE	t	df	p	Difference	SE	t	df	p	Difference	SE	t	df	p
Superior Frontal Gyrus Gray Matter	−3.25	1.17	2.77	78.1	0.007	−2.57	1.10	2.34	78	0.02	−0.68	1.0	0.68	78	0.50
Superior Temporal Gyrus Gray Matter	−1.84	0.75	2.44	79.0	0.02	−1.63	0.70	2.33	79.0	0.02	−0.21	0.64	0.32	79.0	0.75
Middle Temporal Gyrus Gray Matter	−1.86	0.53	3.50	79.1	0.0008	−1.90	0.49	3.86	78.6	0.0002	0.05	0.45	−0.11	78.9	0.91
Amygdala-Hippocampal Complex	−0.73	0.21	3.54	78.4	0.0007	−0.24	0.19	1.27	78.1	0.21	−0.48	0.18	2.73	78.3	0.008

SE: Standard Error

df: Degrees of Freedom (calculated by Kenward-Rogers method).

*All volumes in mL.