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Subcortical structure alterations impact language processing in individuals with schizophrenia and those at high genetic risk

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ABSTRACT

Objective: Cortical structural and functional anomalies have been found to associate with language impairments in both schizophrenia patients and genetic high risk individuals for developing schizophrenia. However, subcortical structures that contribute to language processing haven't been well studied in this population, and thus became the main objective of this study.
Method: We examined structural MRI data from 20 patients with schizophrenia, 21 individuals at genetic high risk, and 48 controls. Surface shape and volume differences of 6 subcortical structures that are involved in language processing, including nuclei pallidum, putamen, caudate, amygdala, thalamus, and hippocampus from both hemispheres, were compared between groups. Performance scores of language-associated cognitive tests were obtained to identify relationships of subcortical structures to language-related behaviors.
Results: Significantly reduced volumes of both the left and right side caudate nuclei, thalami and right side amygdala were shown in patients when compared with controls. Very interestingly, the high risk group demonstrated significantly increased correlations between volumes of left side pallidum nucleus and bilateral thalami and language-related cognitive test scores when compared to controls.
Conclusions: This study furthers our understanding of subcortical structural alterations in schizophrenia and high risk individuals, and suggests the contribution of subcortical structures to the language impairments that may serve as an early sign for impending development of schizophrenia.

1. Introduction

Schizophrenia is a complicated and debilitating mental disorder characterized by altered behaviors, emotions, perceptions, and cognition. Impaired language function is one of the central features of this severe disorder. The anatomical circuit for language processing is a highly distributed multi-level bidirectional network involving multiple cortical and subcortical structures. In this circuit, bilateral superior temporal gyri and occipital cortex serve as auditory and visual input centers (McNealy et al., 2006). The supramarginal gyrus is responsible for phonological encoding in word production, and the angular gyrus for memory of visual word forms (Poeppel and Hickok, 2004). These two sites interface with widely distributed conceptual knowledge systems located primarily at the junction of the left temporal, occipital, and parietal lobes, i.e. inferior temporal region (Wernicke's area), fusiform and lingual gyri. The sound or visual-based system transfers the input information to the conceptual knowledge systems, and then reaches the frontal motor systems (Broca's area) via an auditory–motor interface system in the inferior parietal lobe. Besides these key cortical sites, subcortical structures are frequently involved in the language processing pathways. Particularly, the thalamus, which has extensive white matter connections to cerebral cortices and the striatum, plays the unique role in filtering the visual and/or auditory input information and passing needed information to the conceptual knowledge systems; whereas the nuclei of striatum, including caudate, putamen and pallidum, connect with thalamus and widespread cortical regions and involve in cognitive control of motor patterns during language processing (McFarland and Haber, 2002a). In addition, the hippocampus and amygdala work together for memory formation that is critical in language processing (Mcdonald and White, 2013). While extensive studies have reported structural and functional anomalies in cortical regions that contribute to aberrant language processing in patients with schizophrenia (Zhang et al., 2015; Catani et al., 2011), the role of the subcortical structures

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within these circuits that contribute to language impairment in this disorder is not yet well known.

Schizophrenia has significant and complex genetic heritability (Modinos et al., 2013). Early disturbances in brain pathways can later progress to chronic schizophrenia, indicating the benefits of studying individuals at high genetic risk, for evidence of developmental changes in brain structures that contribute to the onset of the disorder (DeLisi et al., 2002). Our previous neuroimaging and clinical studies have specifically demonstrated functional and structural alterations of cortical areas involved in the language-processing pathways in the genetic high-risk subjects for developing schizophrenia (Li et al., 2007a; Li et al., 2012a,b). While these previous studies have consistently highlighted that cortical gray matter and white matter structural and functional abnormalities significantly contribute to the disorganized language observed within schizophrenia and present early before onset of the disorder, there is less information regarding how the subcortical structures, which are essential components of the complete language circuit, may also be implicated in the atypical language processes in patients with schizophrenia or even early at the high-risk stage.

Very recently, there has been more evidence to support the existence of subcortical structural defects in people at high risk for developing schizophrenia. One study of genetic high risk relatives of schizophrenia patients revealed alterations in the hippocampus, pallidum, and putamen (Dougherty et al., 2012). Disrupted normal pattern of asymmetry has been identified in the amygdala–hippocampus connectivity, striatum, and thalamus of patients with schizophrenia and their high risk siblings, compared to control subjects (Qiu et al., 2009). The current study further explores subcortical abnormalities in individuals with schizophrenia and those at genetic high risk, to clarify their potential roles within the cortical–subcortical–cortical circuits that contribute to disrupted language processing, which is associated with the auditory hallucinations and thought disorder that are hallmark features of this diagnosis. A total of 6 subcortical regions of interest (ROIs) were investigated in individuals with schizophrenia, individuals at genetic high risk, and healthy controls, including the left and right side nuclei of caudate, pallidum, putamen, amygdala, hippocampus, and thalamus. Selection of these subcortical regions was based on their theoretical roles in the language processing circuits that have been reviewed earlier in this section. Volumetric and vertex-based shape analyses were performed. Associations between these structural measures and language-related behavioral measures were conducted. We hypothesized that both subjects with schizophrenia and those at high risk would have distinct subcortical structural defects that underlie language processing defects, as compared to healthy controls.

2. Methods

2.1. Subjects

Data from a total of 89 subjects were included in this study. These data were from 3 independent clinical groups (20 patients with schizophrenia, 21 individuals at genetic high risk for developing schizophrenia, and 48 healthy controls). Each patient was interviewed using the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) and was diagnosed with DSM-IV criteria. Evaluations were made based on interviews, information collected from family members, and medical records, as appropriate. Individuals in the control group did not have personal or family history of any psychotic disorder, psychiatric hospitalization, or suicide in any first or second-degree relatives, and were not found to have any evidence of a psychotic illness (schizophrenia, bipolar disorder or psychosis not otherwise specified) upon evaluation. Subjects in the high-risk group were 16–30 years old, which is within the peak age range of risk for developing schizophrenia (Li et al., 2007b) and originated from families in which at least one first-degree relative (parent or sibling) had a diagnosis of schizophrenia or schizoaffective disorder. Although none of the high risk group subjects had a history of psychosis, 4 had a history of at least one episode of major depression. Controls were age and sex matched to high-risk subjects. Neither the normal controls nor the high-risk participants were ever treated with medication for psychotic symptoms. All patients with schizophrenia were taking conventional or atypical antipsychotic medications.

Individuals with schizophrenia and those at high-risk were recruited by advertisements in newspapers and newsletters distributed by the National Alliance on Mental Illness (NAMI), or from families who had previously participated in past genetic studies of schizophrenia (DeLisi et al., 2002). Control subjects were independently solicited from the community by public advertisements. This study received Institutional Review Board Approval for human subject research at the Nathan S. Kline Institute for Psychiatric Research, a New York State Institution, and at New York University Langone School of Medicine, where this study was performed. Every participant provided written informed consent after a careful explanation of the study and its procedures.

2.2. Language-related cognitive tests

To characterize the general and language-related cognitive capacity of each subject, information was aggregated from a series of cognitive tests: 1) Full-scale, Verbal, and Performance IQ scores (FSIQ, VIQ, and PIQ, respectively) from the age-appropriate Wechsler test were used to measure general cognitive ability (Wechsler, 2004); 2) Verbal Comprehension Index (WAIS-VCI) was used to assess verbal capacity; 3) Peabody Picture Vocabulary Test, 3rd Edition (PPVT-II) measured receptive language capacity (Dunn and Dunn, 1997); 4) Wide Range Achievement Test, 3rd Edition (WRAT)-reading subtest evaluated word decoding and academic skills (Wilkinson, 1993); 5) Boston Naming Test (BNT) detected difficulties in word retrieval (Kaplan et al., 1983); 6) Woodcock Johnson Tests of Achievement, 3rd Edition (WJTA) evaluated reading comprehension (Woodcock et al., 2000); and 7) California Verbal Learning Test (CVLT) determined verbal memory capacity (Delis et al., 1987). Any subject with an IQ less than 85 was excluded from the study. The Edinburgh Handedness Inventory was used to test handedness (Oldfield, 1971). Group comparisons of demographic, medical, and language-related behavioral characteristics are shown in Table 1.

2.3. MRI data acquisition and processing in individuals

The MRI data were acquired on a 1.5 T Siemens Vision scanner (Erlangen Germany). The high-resolution 3D T1-weighted magnetization

Table 1
Subject demographics analyzed by one-way ANOVA.

	NC ($n = 48$)	HR ($n = 21$)	SCH ($n = 20$)	d.f.	p-Value
Age (mean ± SD)	22.0 ± 5.1	21.1 ± 5.5	37.7 ± 10.3	2	0.000
Age (range)	16–32	16–30	20–55		
Male/female (Chi-sq.)	24/24	7/14	13/7	2	0.176
Left/right handed	3/45	3/18	2/18	–	–
Education (years)	14.8 ± 3.0	12.6 ± 2.8	14.5 ± 2.2	2	0.634
Mother's education	13.8 ± 3.5	14.5 ± 2.5	12.5 ± 2.2	2	0.695
Father's education	15.1 ± 2.1	15.0 ± 2.2	14.5 ± 3.3	2	0.942
WAIS-VCI	113.2 ± 17.4	108.1 ± 14.6	105.5 ± 14.3	2	0.882
PPVT-III	102.5 ± 12.9	101.3 ± 12.2	102.5 ± 16.6	2	0.873
WRAT	104.1 ± 13.1	105.9 ± 9.1	106.6 ± 11.9	2	0.631
WJTA	102.4 ± 14.2	104.5 ± 11.1	103.5 ± 13.3	2	0.670
BNT	103.6 ± 15.7	103.1 ± 16.6	101.5 ± 12.1	2	0.714
CVLT	104.7 ± 12.9	103.9 ± 12.5	105.7 ± 18.7	2	0.760

NC: normal control group; HR: high-risk group; SCH: schizophrenia group; d.f.: degrees of freedom; WAIS-VCI: Wechsler Adult Intelligence Scale-Verbal Comprehension Index; PPVT-III: Peabody Picture Vocabulary Test, Third Edition; WRAT: Wide Range Achievement Test; WJTA: Woodcock Johnson Tests of Achievement, Third Edition; BNT: Boston Naming Test; CVLT: California Verbal Learning Test.