Reduced anterior cingulate gray matter volume and thickness in subjects with deficit schizophrenia

Mizuho Takayanagi [a,b], Jacqueline Wentz [c], Yoichiro Takayanagi [d], David J. Schretlen [a], Elvan Ceyhan [e], Lei Wang [f], Michio Suzuki [b], Akira Sawa [a], Patrick E Barta [c], J. Tilak Ratnanather [c], Nicola G. Cascella [g,*]

[a] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[b] Department of Neuropsychiatry, University of Toyama, Toyama, Japan
[c] Center for Imaging Science and Institute for Computational Medicine, The Whitaker Biomedical Engineering Institute, Johns Hopkins University, Baltimore, MD, USA
[d] Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
[e] Department of Mathematics, Koc University, Istanbul, Turkey
[f] Department of Psychiatry and Behavioral Sciences, Northwestern University School of Medicine, Chicago, IL, USA
[g] Neuropsychiatry Program, Sheppard Enoch Pratt Hospital, Baltimore, MD, USA

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ABSTRACT

Background: Patients with deficit schizophrenia (D-SZ) differ from patients with the non-deficit form of schizophrenia (ND-SZ) in several aspects such as risk factors, neurobiological correlates, treatment response and clinical outcome. It has been debated if brain morphology could differentiate D-SZ from ND-SZ. Anterior cingulate gyrus (ACG) region regulates cognitive and emotional processing and past studies reported structural changes in this region in patients with SZ.
Methods: 1.5-T 3D MRI scans were obtained from 18 D-SZ patients, 30 ND-SZ patients and 82 healthy controls (HCs). We used FreeSurfer-initalized labeled cortical distance mapping (FSLCDM) to measure ACG gray matter volume, cortical thickness, and area of the gray/white interface. Furthermore, cortical thickness was compared among the 3 groups using the pooled labeled cortical distance mapping (LCDM) method.
Results: The ACG cortex of the D-SZ group was thinner than the ND-SZ group. Pooled LCDM demonstrated that the ACG cortex was bilaterally thinner in both the ND-SZ group and the D-SZ group compared with the control group. The right ACG gray matter volume was significantly reduced in D-SZ patients as compared with healthy controls ($p = 0.005$
Conclusion: Our data suggest that qualitative, categorical differences in neuroanatomy may distinguish between deficit and non-deficit subtypes of schizophrenia.

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1. Introduction

Since Kraepelin, the observed clinical heterogeneity of schizophrenia has been the source of considerable controversy. The deficit syndrome of schizophrenia (D-SZ) has been proposed as a clinical subtype defined by severe primary negative symptoms that endure as trait-like features even during periods of clinical stability (Carpenter et al., 1988). By definition, primary negative symptoms are not attributable to secondary causes such as depression, medication side-effects, mental retardation or social deprivation. Patients with D-SZ differ from patients with the non-deficit form of schizophrenia (ND-SZ) in terms of risk factors (Messias et al., 2004), neurobiological correlates (Lahti et al., 2001; Quarantelli et al., 2002), treatment response (Kirkpatrick et al., 2001), and long-term clinical outcome (Tek et al., 2001). Patients with D-SZ

also demonstrate cognitive deficits relative to healthy adults and patients with ND-SZ (Wagman et al., 1987; Cascella et al., 2008).

In a previous neuroimaging study using magnetic resonance imaging (MRI), we investigated the differences in regional gray-matter volume between D-SZ with ND-SZ by using voxel-based morphometry (VBM) and found that patients with D-SZ showed decreased gray matter volume in brain areas including the anterior cingulate gyrus (ACG) (Cascella et al., 2010) which is part of the limbic lobe and whose main function is regulation of cognitive and emotional processing (Bush et al., 2000). This is consistent with several structural neuroimaging studies of the ACG in SZ that have shown reduced bilateral gray matter (GM) volume (Suzuki et al., 2002; Yamasue et al., 2004; Fujiwara et al., 2007).

However results have not been unanimous (Ohnuma et al., 1997; Kopelman et al., 2005). A more specific measurement of ACG pathology in SZ has been reported by Yucel et al. (2002a, 2002b) who examined the sulcal–gyral morphology of the ACG, focusing on the presence or absence of a paracingulate sulcus (PCS) and continuity of the cingulate sulcus (CS). They found that SZ patients were less likely to manifest a

well-developed PCS/CS in the left hemisphere, resulting in a lack of "normal" leftward asymmetry. Bilateral volume reduction in Brodmann area 32 was observed in 27 schizophrenia subjects with prominent negative symptoms compared with 27 control subjects (Sigmundsson et al., 2001). Also a more recent study reported that right hemispheric ACG volume reduction in SZ patients compared to healthy controls was most pronounced in SZ patients with more negative symptoms (Preuss et al., 2010). Similar findings have been reported recently in SZ patients in their early stages of the disease (Aston et al., 2012).

In another previous study, individuals with SZ showed smaller ACG gray matter volume and thickness, but not surface area, than healthy controls using labeled cortical distance mapping (LCDM) (Wang et al., 2007). It was also found that thinning of the left ACG correlated with a longer duration of illness and a greater severity of psychotic symptoms.

LCDM is a powerful tool in quantifying such morphometric differences and characterizes the morphometry of the laminar cortical mantle of cortical structures. Specifically, LCDM data are distances of labeled gray matter (GM) voxels with respect to the gray/white matter cortical surface and thus are local measures characterizing the morphometry of the cortical mantle (Ceyhan et al., 2011). LCDMs have been used to quantify cortical thickness in the cingulate in subjects with Alzheimer's (Miller et al., 2003) and schizophrenia (Wang et al., 2007), in the ventral medial prefrontal cortex in subjects with major depressive disorder (Ceyhan et al., 2011), and in the planum temporale in subjects with schizophrenia (Qiu et al., 2008).

It is therefore opportune to apply the new methodology of LCDM to confirm and expand on previously reported ACG structural abnormality in the D-SZ subgroup adding thickness and surface area to the analysis. Specifically we employ a recently developed automated LCDM pipeline by integrating data from FreeSurfer (Fischl, 2012) with LCDM to examine the gray matter volume, thickness and surface area of the ACG in D-SZ and ND-SZ patients.

2. Methods and materials

2.1. Participants

Forty-eight adults (35 males, 13 females) with schizophrenia, diagnosed according to criteria of the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) (American Psychiatric Association, 1994) participated in the study. Of these, 18 were recruited for a study of apathy in schizophrenia and traumatic brain injury and constitute the D-SZ group (the Apathy study), 30 were recruited for a study of structural neuroimaging and cognition in psychosis and represent the ND-SZ group (the Psychosis study). All the patients in both studies were recruited from outpatient clinics, inpatient services, and psychiatric day hospitals affiliated with the Johns Hopkins University and Hospital. Patients were excluded if they had any untreated major medical condition like diabetes or high blood pressure or had had traumatic brain injury with loss of consciousness for more than 1 h or had a diagnosis of substance abuse for the previous 6 months or dependence for the previous 12 months. The HC group consisted of 82 healthy adult participants in a study of normal aging, brain imaging, and cognition (the ABC study). Participants in the ABC study were recruited from the Baltimore metropolitan region primarily via random digit dialing, although a few were recruited via telephone calls to randomly selected listings from the Baltimore metropolitan area residential telephone directory. ABC study participants who reported any history of dementia, stroke, transient ischemic attack, traumatic brain injury with >1 loss of consciousness, Parkinson's disease, multiple sclerosis, severe heart disease, complicated diabetes, bipolar disorder, schizophrenia, current major depression, current alcohol/drug abuse or dependence were excluded from the present analysis.

Although all the study subjects were from our previous published research (Cascella et al., 2010) we were unable to process some images

(one D-SZ patients, one ND-SZ patients, 8 HCs) with Freesurfer and LCDM due to the quality of the raw images.

All three studies (Psychosis, Apathy, and ABC) were approved by the Johns Hopkins Medicine Institutional Review Board and all participants provided written informed consent.

2.2. Procedure

Diagnostic and clinical assessments of patients recruited for the Psychosis study included the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994), Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS) (Andreasen and Olsen, 1982), and the Scale to Assess Unawareness of Mental Disorders-Abridged (SUMD-A) (Amador et al., 1994), all of which were administered by a study psychiatrist or psychologist. Patients recruited for the Apathy study underwent a Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV) (First et al., 1997) rather than the DIGS, but they also received SANS, SAPS, and SUMD. Prior to making a diagnosis, the study clinician also reviewed any available medical and psychiatric records. The designation of deficit syndrome schizophrenia was based on the Schedule for the Deficit Syndrome (SDS), a semi-structured interview with known reliability Kirkpatrick et al. (1989) by a study psychiatrists (N.G.C.) trained for reliability at the Maryland Psychiatric Research Center (kappa = .79). Collateral information was obtained whenever possible.

Each HC group participant also underwent diagnostic and clinical assessments by a study psychiatrist or psychologist. These included the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) interview (Wing et al., 1996), review of medical history, physical and neurological examinations, laboratory blood studies, anatomic brain magnetic resonance imaging (MRI), and cognitive testing.

Neuropsychological assessment of all study participants included a battery of tests designed to cover a broad range of cognitive abilities. Testing required about 2 h and yielded 18 individual measures. Results of the cognitive assessment have been reported elsewhere (Cascella et al., 2008). However, premorbid IQ was assessed using the Hopkins Adult Reading Test (HART) (Schretlen et al., 2009) and is reported.

2.3. MRI data acquisition

Brain imaging was acquired on the same single 1.5 T GE Sigma scanner (General Electric, Milwaukee, WI) to assure continuity of scan parameters. Participants were scanned from 2000 to 2004. Images were acquired with a 3D volumetric radiofrequency spoiled gradient echo (SPGR) series with the following scan parameters: repetition time = 35 ms, echo time = 5 ms, flip angle = 45, matrix size = 256 × 256, field of view = 240 mm. This sequence produced 124 contiguous, T1-weighted images (slice thickness = 1.5 mm). There was no major upgrade of the scanner during the period of brain imaging acquisition.

2.4. FreeSurfer-initalized labeled cortical distance mapping (FSLCDM)

The FSLCDM pipeline provides measures for cortical thickness, volume, and surface area of multiple cortical regions in the brain. The pipeline has two steps: first FreeSurfer (FS) generates the gray/white cortical surface and parcellates the brain into regions of interest (ROIs) and then labeled cortical distance mapping (LCDM) segments the cortical ROI and computes the distance of each gray matter voxel from the FS surface.

FreeSurfer (FS) initiates the FSLCDM Pipeline by generating the GM/WM surface and parcellating the brain MRI image into ROIs. FS reconstructs the cortical surface defined by the GM/WM boundary in 3-D MRI volume (Dale et al., 1999; Fischl and Dale, 2000). Region labels are assigned to each point on the cortical surface based on a