Abnormal cortical folding patterns within Broca's area in schizophrenia: Evidence from structural MRI

Jonathan J. Wisco [a,*], Gina Kuperberg [a,b,c], Dara Manoach [a,b], Brian T. Quinn [a],
Evelina Busa [a], Bruce Fischl [a,d,e], Stephan Heckers [a,b], A. Gregory Sorensen [a,d]

[a] MGH/MIT/HMS Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Building 149 13th Street, Room 2301,
Charlestown, MA 02129, United States
[b] Department of Psychiatry, Massachusetts General Hospital, Building 149 13th Street, Room 2301, Charlestown, MA 02129, United States
[c] Department of Psychology, Tufts University, 490 Boston Avenue, Medford, MA 02155, United States
[d] MIT/HST, Massachusetts Institute of Technology, 77 Massachusetts Avenue, E25-519, Cambridge, MA 02139, United States
[e] CSAIL, Massachusetts Institute of Technology, The Stata Center, Building 32, 32 Vassar Street, Cambridge, MA 02139, United States

Abstract

We compared cortical folding patterns between patients with schizophrenia and demographically-matched healthy controls in prefrontal and temporal regions of interest. Using the Freesurfer (http://surfer.nmr.mgh.harvard.edu) cortical surface-based reconstruction methodology, we indirectly ascertained cortical displacement and convolution, together, by measuring the degree of metric distortion required to optimally register cortical folding patterns to an average template. An area within the pars triangularis of the left inferior frontal gyrus (Broca's area) showed significantly reduced metric distortion in the patient group relative to the control group ($p = 0.0352$). We discuss these findings in relation to the neurodevelopmental hypothesis and language dysfunction in schizophrenia.
© 2007 Elsevier B.V. All rights reserved.

1. Introduction

During normal cortical development, neurons migrate from the ventricular zone to the cortical plate and begin to establish intrinsic and extrinsic connections around gestational week 20 (Chi et al., 1977; Marin-Padilla, 1992). This occurs with precise timing and is dependent upon a delicate balance of genetic regulation (Rakic, 1995). The connections formed during the pre-natal period eventually experience a dramatic period of plasticity in the pre-adolescent years during which pruning occurs (Lewis, 1997). Van Essen hypothesized that, as the brain grows and expands, the strength of

* Corresponding author. Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, Room 52-060 CHS, Los Angeles, CA. 90095-1732, United States. Tel.: +1 310 825 7880; fax: +1 310 825 3058.

E-mail addresses: jjwisco@mednet.ucla.edu (J.J. Wisco),
kuperber@nmr.mgh.harvard.edu (G. Kuperberg),
dara@nmr.mgh.harvard.edu (D. Manoach),
btquinn@nmr.mgh.harvard.edu (B.T. Quinn),
evelina@nmr.mgh.harvard.edu (E. Busa),
fischl@nmr.mgh.harvard.edu (B. Fischl),
stephan.heckers@Vanderbilt.Edu (S. Heckers),
sorensen@nmr.mgh.harvard.edu (A.G. Sorensen).

connectivity between neighboring areas of cerebral cortex determines its adult folding patterns such that strongly connected areas form gyri and weakly connected areas form sulci (Van Essen, 1997).

Schizophrenia is a devastating psychiatric illness characterized by positive and negative symptoms as well as severe cognitive impairments across multiple domains including language, memory and executive function. Abnormal cortical development has been thought to be part of the etiology of schizophrenia (Murray and Fearon, 1999; Weinberger, 1987, 1996). Although the pathophysiology of the disease is not yet understood, it has been hypothesized that abnormal structural and/or functional connectivity may lead to its symptoms and cognitive impairments (Elvevag and Weinberger, 2001; Friston, 2005, 1996, 1998, 1999; Friston and Frith, 1995; Weinberger, 1987). Given Van Essen's hypothesis, it is possible that maldevelopment of intrinsic or extrinsic connections of the cerebral cortex in schizophrenia might manifest as abnormalities of cortical folding patterns in adult patients.

Cortical folding abnormalities in schizophrenia measured using the gyrification index (GI) methodology (Zilles et al., 1988) have been reported in post-mortem (Vogeley et al., 2000) and MRI studies (Harris et al., 2004a,b; Kulynych et al., 1997; Sallet et al., 2003). Since the GI measures the ratio of inner and outer cortical surface contours, these studies were limited to analyses of brain slices in different lobes. Cortical folding abnormalities of asymmetry, complexity and variability in the frontal, temporal and parietal lobes of schizophrenia patients have been reported in MRI studies by Narr and colleagues (Narr et al., 2001, 2004). Using cortical surface matching based on major sulcus landmarks, Narr and colleagues found greater variability and deviations of gyral complexity asymmetry in the frontal areas and significant gyral asymmetries in the temporal and parietal regions of schizophrenia patients. All these studies motivated the present study to examine cortical folding within specific, functionally relevant areas of cortex.

We used the Freesurfer cortical surface-based reconstruction methodology (Dale and Sereno, 1993; Dale et al., 1999; Fischl et al., 2001, 1999a,b; Segonne et al., 2004, 2005) to examine cortical folding displacement and convolution, together, in patients with schizophrenia compared to healthy demographically-matched controls. The entire cortical surface of each individual participant was unfolded and the degree of cortical folding was examined within three selected prefrontal and temporal anatomical cortical ROI's: (1) the left inferior frontal gyrus [Broca's area, comprised of the pars orbitalis (pOr), pars triangularis (pTr) and pars opercularis (pOp)], and the corresponding regions in the right hemisphere, (2) the right and left dorsolateral prefrontal cortices (DLPFC) and (3) the right and left superior temporal gyri (STG). These cortical regions were selected on the basis of previous morphometric studies that have demonstrated reduced cortical thickness (Kuperberg et al., 2003) and volume (Shenton et al., 2001) in these regions in patients relative to controls, and on the basis of previous fMRI studies reporting that they show abnormal functional modulation and/or functional connectivity in patients relative to controls (Callicott et al., 2000; Jennings et al., 1998; Kuperberg et al., 2006b; Manoach et al., 2000, 1999; Shenton et al., 1992).

The degree of cortical folding was operationalized as the degree of displacement (linear and/or rotational shift) and convolution (complexity of gyrification) of the cortical surface relative to an average template. The template was independently created from the cortical surfaces of a third group of 40 healthy participants (Desikan et al., 2006; Duvernoy, 1991; Ono et al., 1990). Displacement and convolution, together, were indirectly measured from the metric distortion as calculated by the Jacobian energy functional (Fischl et al., 1999a,b) required to align the cortical surface of an individual to the template. We expected cortical surfaces for all individuals to undergo some metric distortion as each unique surface was mapped onto the template, and hypothesized that the degree of metric distortion would be greater in schizophrenia patients than control subjects within each of the *a priori* ROI's.

2. Experimental methods

2.1. Participants

Written informed consent was obtained from all subjects before participation according to the established guidelines of the Massachusetts General Hospital Institutional Review Board and the Health Insurance Portability and Accountability Act (HIPAA) guidelines.

Twenty-five healthy volunteers (20 male, 5 female) with no history of neurological or psychiatric disorder were recruited by advertisement and 26 patients (22 male, 4 female) diagnosed with schizophrenia according to DSM-IV criteria (American Psychiatric Association, 1990) and on a stable regimen of antipsychotic medication for at least 6 months were recruited from the Erich Lindemann Mental Health Center (Boston, MA). Handedness was measured using the modified Edinburgh Handedness Inventory (Oldfield, 1971; White and Ashton, 1976). Patients and controls were gender, age and handedness matched (see Table 1).

Table 1
Subject demographics

Parameter	Controls (n=25)[a]	Patients (n=26)[b]
Age (years)	45.68 (1.19)	45.69 (1.32)
Age of onset (years)		24.25 (2.22)
Duration of illness (years)		20.00 (2.28)
Gender	20 M, 5 F	22 M, 4 F
Handedness [c]	23 R, 2 L	21 R, 5 L
Race/ethnicity	22 C, 1 AA, 1 AsA, 1 M	17 C, 8 AA, 1 AI
Psychiatric rating [d]		
PANSS Positive		13.22 (1.19)
PANSS Negative		17.44 (1.67)
PANSS General		25.22 (1.45)
PANSS Global		55.89 (3.81)
Medications		
CPZ Equivalent		608.80 (75.91)
Anticholinergic		1/26
Anti-anxiety		5/26
Anti-depression		9/26
Mood stabilizer		2/26
Other		7/26

Subjects were gender, age and handedness matched. Data are expressed as mean (SEM) unless otherwise indicated. Abbreviations: males (M), females (F), right-handed (R), left-handed (L), Caucasian (C), African American (AA), Asian American (AsA), American Indian (AI), Mixed (M), Chlorpromazine (CPZ).

[a] Four subjects who did not complete the study are excluded from this count.
[b] One subject who did not complete the study is excluded from this count.
[c] Measured using the Edinburgh Handedness Inventory.
[d] Data available from 18 (16 M, 2F) schizophrenic patients.

Exclusion criteria included neurological disease or damage, head trauma with documented cognitive impairment or loss of consciousness greater than 5 min, medical disorders that could (American Psychiatric Association, 1990) impair neurocognitive function, a history of substance abuse within three months prior to participation and specific exclusions for MRI.

2.2. MRI acquisition

We acquired two data sets of T1-weighted MPRAGE images as part of a larger set of structural data that were acquired during a 1.5 h scan session. The MPRAGE protocol was run in a Siemens 3T Trio scanner (Siemens Medical Solutions, Erlangen, Germany) using an 8-channel phased-array head coil: TR/TE/TI=2530/3.45/1100 ms; flip angle=7°; FOV=256 mm; $1.3 \times 1.0 \times 1.3$ voxels; 128 slices in the sagittal plane. Images covered the entire brain. Motion artifact was monitored throughout the scan session. The protocol for any image data set that exhibited excessive motion was re-run after verbally informing the participants.

2.3. Image reconstruction

Individual cortical surfaces were reconstructed using the Freesurfer analyses tools (http://surfer.nmr.mgh. harvard.edu) developed at the Martinos Center for Biomedical Imaging as described in detail previously (Dale and Sereno, 1993; Dale et al., 1999; Fischl et al., 2001, 1999a,b; Segonne et al., 2004, 2005). First, image intensity variations due to magnetic field inhomogeneities were normalized. Second, extra-cerebral voxels were removed, essentially "skull-stripping" the brain. Third, the resulting intensity normalized, skull-stripped brain images were segmented to classify voxels into gray and white matter regions. Fourth, cutting planes were computed to separate the cerebral hemispheres from each other and from the brainstem and cerebellum. Finally, the resulting hemisphere volumes were covered with a triangular tessellation and deformed to produce a representation of the gray/white matter interface for each subject. Any geometric inaccuracies were corrected manually and the reconstruction procedure was repeated until an accurate surface was achieved. The gray/white matter interface surface was inflated and transformed into a spherical representation (Fig. 1).

2.4. Measuring metric distortion

Each individual subject's spheres were non-linearly registered to an average template sphere created from 40 independent control subjects (see example in
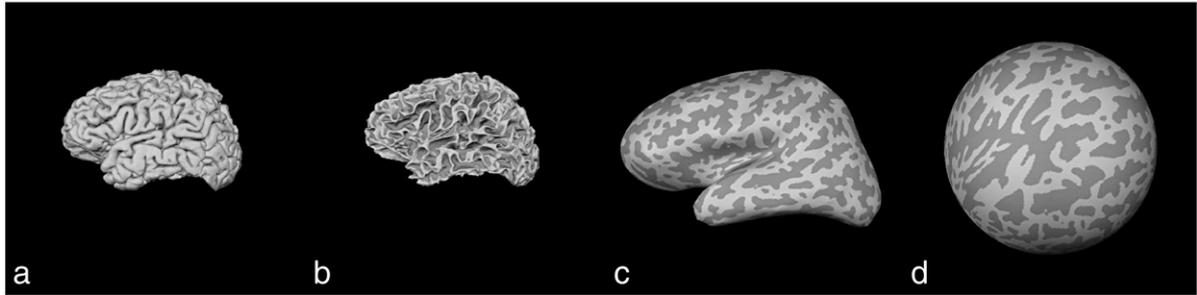
Fig. 1. Cortical reconstruction. A given subject brain represented here by a 3D pial surface reconstruction (a) was transformed into gray matter/white matter interface surface (b), inflated (c) and transformed again into a spherical surface (d). Gyri and sulci are represented in light gray and dark gray colors, respectively.

Fig. 2) (Fischl et al., 1999a). A spherical coordinate system based on the average template was translated back to the subject spheres such that every coordinate corresponded across all subjects, and thus every participant's brain was registered into a common coordinate system.

In order to achieve the registration of individual spheres into the common coordinate system, the triangular
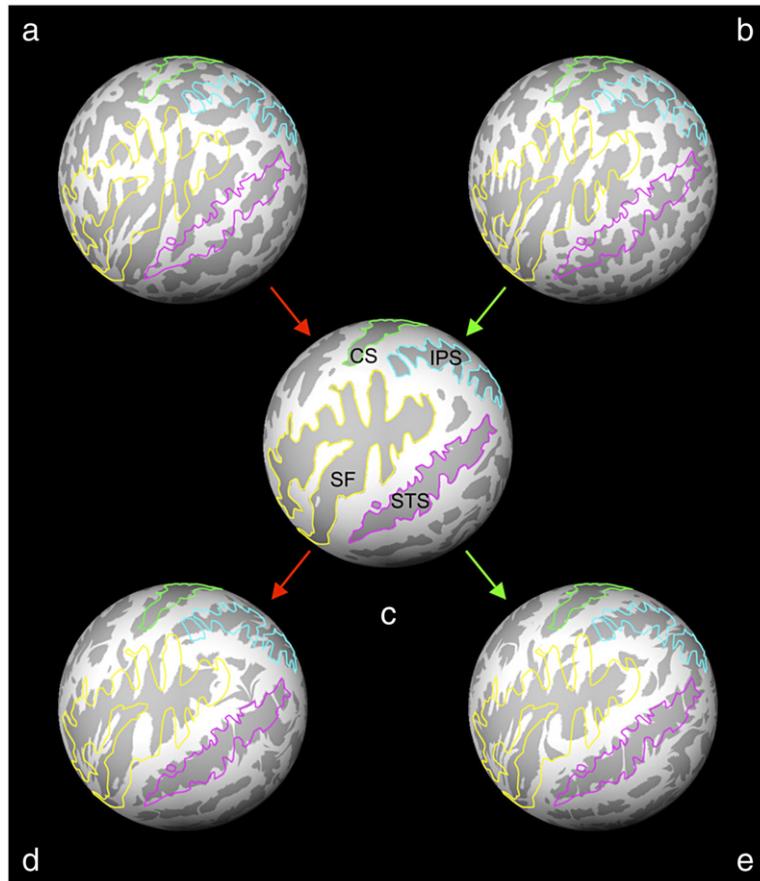

Fig. 2. Spherical registration and metric distortion. Spheres (a, d) and (b, e) are reconstructed brain surfaces from a control subject and a schizophrenia patient, respectively. A subject sphere was registered to the average subject template sphere (c) using a non-linear warping algorithm. The metric distortion required to correctly align gyri (light gray) and sulci (dark gray) was an indirect reflection of the cortical folding distortions and convolutions between a subject sphere and the template average. Outlines of the central sulcus (CS, light green), intraparietal sulcus (IPS, light blue), Sylvian fissure (SF, yellow) and superior temporal sulcus (STS, magenta) based on the average subject template sphere (c) are overlaid on the subject spheres before and after registration to illustrate the process.

tessellation used to represent the gray/white matter interface and its spherical representation was necessarily deformed. The deformation of a particular tessellation vertex was its metric distortion, which was calculated using the following general equation:

$$\text{Metric distortion} = \frac{k * \text{area of a triangle on registered sphere}}{\text{area of triangle on original gray/white interface surface}}$$

$$\text{Where } k = \frac{\text{total surface area of original gray/white interface surface}}{\text{total surface area of individual sphere}}$$

We measured the metric distortion required to achieve optimal spherical registration of gyri and sulci (at each tesselation vertex) across individual cortical surfaces (Fischl et al., 1999b). We restricted statistical analysis within three ROI's that were generated on each subject's gray/white matter interface surface during the Freesurfer reconstruction stream (see Fig. 3). [These ROI's were validated previously (Desikan et al., 2006; Duvernoy, 1991; Ono et al., 1990)]. The ROI's included: (1) The inferior frontal gyri [pars orbitalis (pOr), pars triangularis (pTr) and pars opercularis (pOp) gyri, comprising Broca's area on the left] operationally defined as the three adjacent gyri rostral to the precentral gyrus (Desikan et al., 2006; Duvernoy, 1991; Ono et al., 1990); (2) bilateral dorsolateral prefrontal cortices (DLPFC), operationally defined as the middle third of the middle frontal gyrus (Rajkowska and Goldman-Rakic, 1995); (3) bilateral superior temporal gyri (STG) operationally defined as the gyrus surrounded by the Sylvian fissure, superior temporal fissure and supra-marginal gyrus (Desikan et al., 2006; Duvernoy, 1991; Ono et al., 1990).

2.5. Statistical analysis of metric distortion

We used a General Linear Model (GLM) to calculate cohort differences in metric distortion at each tesselation vertex within the *a priori* ROI's (inferior frontal gyrus, DLPFC, STG) of both hemispheres. Monte Carlo permutation cluster analyses were then performed to correct for multiple comparisons using a cluster threshold of 0.0500. Finally, the mean metric distortion was calculated in any clusters that survived multiple comparisons analysis.

3. Results

In the left hemisphere, clusters that were significant ($p < 0.05$) before correction for multiple comparisons were located in pars triangularis (pTr) (maxima $p = 0.0030$) and pars operularis (pOp) (maxima $p_1 = 0.0039$, $p_2 = 0.0481$) (Table 2). No clusters were detected in the pars orbitalis (pOr), the left dorsolateral prefrontal cortex (L-DLPFC) or left superior temporal gyrus (L-STG). The only cluster surviving correction for
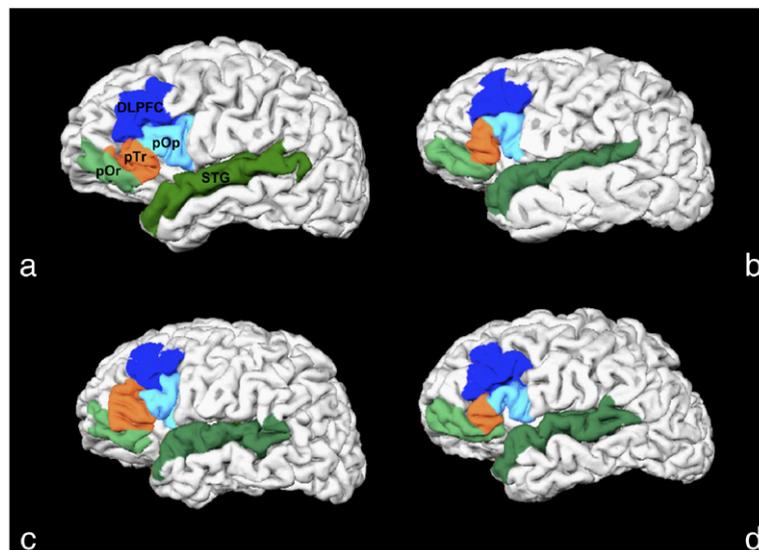

Fig. 3. Cortical folding variability in Broca's area (pOr, pTr, pOp), dorsolateral prefrontal cortex (DLPFC) and superior temporal gyrus (STG). This illustrates the individual cortical folding variability of these ROI's between two control subjects (a, b) and two schizophrenia patients (c, d) in a pial surface reconstruction of brain image volumes. In the spherical registration of these subjects to an average subject template, the metric distortion required for optimal alignment is a reflection individual cortical displacement and convolution.

Table 2
Clusters of significant metric distortion between schizophrenia patients and control subjects

a priori ROI	Distortion direction	Cluster size (mm²)	X	Talairach Coordinates Y	Z	Maxima *p*-value	Clusterwise *p*-value
Left inferior frontal gyrus							
Pars orbitalis				No clusters			
Pars triangularis	**Sz>C**	**630.18**	**−52.3**	**28.2**	**6.7**	**0.0030**	**0.0352**
Pars opercularis	Sz>C	243.49	−52.5	26.2	8.3	0.0039	0.1114
	Sz>C	0.58	−42.5	24.5	9.0	0.0481	0.3819
Right inferior frontal gyrus							
Pars orbitalis	C>Sz	328.41	31.1	47.6	−9.5	0.0071	0.0526
Pars triangularis	Sz>C	405.54	54.8	26.0	11.9	0.0041	0.0534
Pars opercularis	Sz>C	278.30	54.8	25.9	12.9	0.0042	0.0860

Maxima *p*-values for General Linear Model (GLM) analysis prior to Monte Carlo permutation correction for multiple comparisons correction are listed with corresponding clusterwise *p*-values after correction. Only the cluster located in the left pars triangularis (pTr) was found to be significant after multiple comparisons correction (bold).

multiple comparisons was located in pTr (630.18 mm², clusterwise *p*=0.0352). Metric distortion in this cluster was greater in schizophrenia patients relative to control subjects (Fig. 4). Within the pTr cluster, we found the mean (SD) metric distortion in schizophrenia patients was 1.579 (0.269) and in control subjects was 1.377 (0.225).

In the right hemisphere, clusters that were significant before multiple comparisons correction were located in pOr (maxima *p*=0.0071), pTr (maxima *p*=0.0041) and pOp (maxima *p*=0.0042) (Table 2). No clusters were found in the R-DLPFC or the R-STG. None of the clusters in the right hemisphere survived correction for multiple comparisons.

4. Discussion

4.1. Cortical development and schizophrenia

Previous studies have shown regional cortical folding abnormalities of gyrification (Harris et al., 2004a,b; Kulynych et al., 1997; Sallet et al., 2003; Vogeley et al.,
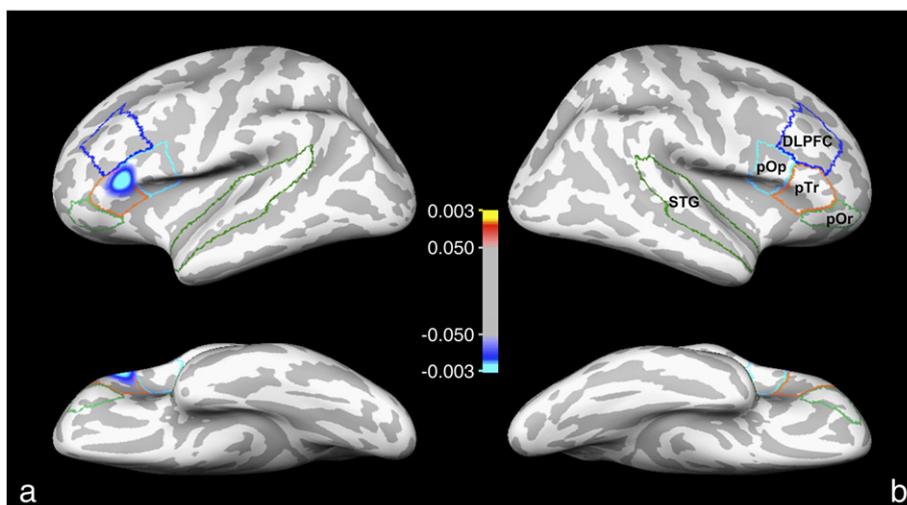

Fig. 4. Composite surface representation of statistically significant clusters of metric distortion in the (a) left and (b) right hemispheres that survived multiple comparisons correction in the pars orbitals (pOr), pars triangulars (pTr), pars opercularis (pOp), dorsolateral prefrontal cortex (DLPFC) and superior temporal gyrus (STG) ROI's. One blue-cyan cluster in the left pTr survived multiple comparisons correction. Statistical analysis was performed using a General Linear Model (GLM) and corrected for multiple comparisons using the Monte Carlo permutation method. Color bar represents statistical significance for the maxima *p*-value of the coordinate vertices located within the significant clusters of metric distortion: control subjects>schizophrenia patients (0.1<*p*<0.003, red/yellow); schizophrenia patients>control subjects (0.1<*p*<0.003, blue/cyan). Refer to Table 2 for further details of the cluster in this figure and of the clusters that did not survive multiple comparisons correction.

2000), asymmetry, complexity and variability (Narr et al., 2001, 2004) in patients with schizophrenia. These studies used a variety of methods to compare the spatial distribution of entire gyri and sulci. Their results motivated the present study to measure metric distortion at each point on the tessellated surface of the left inferior frontal gyrus, dorsolateral prefrontal cortex (DLPFC) and superior temporal gyrus, thereby providing an analysis of folding abnormalities within these cortical areas.

We have thus demonstrated an area within the left pars triangularis (pTr) of Broca's area in which metric distortion was significantly greater in schizophrenia patients relative to healthy, demographically-matched control participants. In the spherical registration algorithm of the Freesurfer analysis tools, the energy functional to generate accurate alignment includes a term for minimizing metric distortion while optimally aligning sulci and gyri (Fischl et al., 1999a,b). The magnitude of metric distortion, therefore, is an indirect measurement of cortical displacement and convolution, together, relative to the average subject template.

The cerebral cortex undergoes marked changes in its intrinsic and extrinsic connectivity over the life span (Chi et al., 1977; Lewis, 1997; Marin-Padilla, 1992; Rakic, 1995). Broca's area, specifically, is known to undergo substantial plasticity from birth to adulthood (Amunts et al., 2003; Etchepareborda and Lopez-Lazaro, 2005). The genetic process controlling cortical development may contribute to the onset and expression of schizophrenia (Woolf, 1997; Wyatt, 1996).

Volume measurement has been used as another index for assessing the integrity of gray matter and white matter. Bartzokis and colleagues made an interesting observation of white matter volume increase with concomitant gray matter volume decrease between the second and fourth decades of life in the frontal lobes of normal aging subjects (Bartzokis et al., 2001). However, within the same age range, they found an absence of white matter volume expansion accompanying gray matter volume reduction in the frontal lobes of patients with schizophrenia (Bartzokis et al., 2003). These studies together suggested that normal white matter myelination with increasing age is abnormal in patients with schizophrenia. White matter atrophy in the frontal lobes has been noted in other recent studies (Sanfilipo et al., 2000; Wible et al., 2001), but the discrepancy may be due to not taking the normal aging process into account.

Volume changes due to normal aging and the disease process of schizophrenia may affect the relative geometric surface patterns of sulci and gyri. Although Kuperberg and colleagues showed cortical thinning in specific areas of the frontal lobe, including Broca's area (Kuperberg

et al., 2003), these changes in gray matter volume are unlikely to alter the relative position of sulci or gyri, which are more likely determined by the geometry of the underlying white matter (Van Essen, 1997). Aberrant white matter development between the second and fourth decades of life in schizophrenia, as observed by Bartzokis et al. (2003), would contribute most to abnormal cortical folding patterns. After the fourth decade, however, degeneration of white matter due to normal aging would contribute more to changes in cortical geometry. In this study, we measured metric distortion during the fourth decade of life (mean age of subjects and patients was approximately 45 years, see Table 1), which would be between the time gray matter and white matter development would be ending and normal aging degenerative processes would be beginning. Therefore, the results presented here may reflect the disease process of schizophrenia before degeneration of normal aging.

4.2. Functional significance of abnormalities in Broca's area

The precise functional significance of cortical folding abnormalities in Broca's area in schizophrenia is unclear. However, given that abnormal cortical folding may reflect abnormal structural and/or functional cortical connectivity, we can speculate on potential functional links between cortical folding abnormalities in this area and the symptoms and patterns of cognitive dysfunction that characterize the schizophrenia syndrome.

In the healthy brain, the left inferior prefrontal gyrus is a major component of the circuitry mediating both language comprehension and language output. Its precise role is debated but it has been implicated in aspects of semantic processing including semantic encoding (Demb et al., 1995; Kirchhoff et al., 2000; Wagner et al., 1998), semantic priming (Copland et al., 2003; Giesbrecht et al., 2004; Kotz et al., 2002; Kuperberg et al., 2006b; Matsumoto et al., 2005; Wheatley et al., 2005), controlled semantic retrieval (Wagner et al., 2001), and semantic selection (Fletcher et al., 2000; Moss et al., 2005; Thompson-Schill et al., 1997, 1999). Broca's area has also been implicated in phonological processing (Poldrack et al., 1999), aspects of syntactic processing (Caplan, 2001; Caplan et al., 2000), syntactic working memory (Fiebach et al., 2005) and, more generally, in other aspects of verbal working memory function (Barde and Thompson-Schill, 2002), and in speech output (Blank et al., 2002).

Schizophrenia has long been characterized as a disorder of thought, language and communication (Andreasen, 1979; Bleuler, 1911/1950). Many of its core symptoms including verbal hallucinations and positive thought

disorder with disorganized speech are characterized by language dysfunction (American Psychiatric Association, 1990). Cognitively, language deficits have been identified in children at risk for schizophrenia (Cannon et al., 2002; Fuller et al., 2002; Ott et al., 2001) as well as in patients in their first episode of psychosis (Fuller et al., 2002; Hoff et al., 1999). Numerous neuropsychological and psycho-linguistic studies have established that patients with schizophrenia show selective language abnormalities as they monitor the source of verbal input (Ditman and Kuperberg, 2005; Johns et al., 2001), explicitly or implicitly retrieve information from semantic memory [e.g. (Goldberg et al., 1998; Minzenberg et al., 2002)], select the appropriate meaning of semantically ambiguous words (Sitnikova et al., 2002; Titone et al., 2000), detect linguistic anomalies within sentences (Kuperberg et al., 2006a,b, 1998, 2000) and parse syntactically complex sentences (Condray et al., 1996) [for reviews, see (Kuperberg and Caplan, 2003; Kuperberg and Goldberg, 2006)]. Functional imaging studies report both abnormal increases and decreases in the recruitment of the left inferior prefrontal gyrus in schizophrenia during semantic tasks including encoding (Kubicki et al., 2003; Ragland et al., 2004), retrieval (Weiss et al., 2003) and priming (Kuperberg et al., 2007), although abnormal function in this region is not usually seen in isolation, but rather in association with abnormal modulation of other language regions including superior, inferior and medial temporal cortices.

It is possible that localized abnormalities in folding within Broca's area reflect abnormal cortical connectivity in this region and that this, in turn, leads to widespread cortical dysfunction during language processing in schizophrenia and to the clinical language disturbances that characterize this disorder. However, the current sample size was relatively small and, at uncorrected thresholds, other regions including the inferior parietal lobule and frontopolar region (not reported here) also showed abnormal folding. Future studies with larger samples will determine the degree to which cortical folding abnormalities are localized or generalized across the cortical ribbon, and whether these abnormalities predict the severity of specific symptoms or specific cognitive deficits in schizophrenia.

4.3. Caveats

The present study included 26 patients and 25 demographically-matched healthy controls, a sample size that would be adequate for statistical analysis of gross morphological changes. However, we measured cohort differences in metric distortion at several thousand tessellation vertices, even within *a priori* ROI's. Table 2 illustrates the stringent statistical analysis performed to avoid false-positive results. The most plausible solution leading to the discovery of more clusters of significant metric distortion that might be expected in other areas of the cortex responsible for language would be to add many more subjects.

The sample of patients for this study was limited to chronic, medicated patients. The present study cannot account for whether medication might also contribute to the metric distortions associated with the disease. An opportunity to measure metric distortion in non-medicated patients would be valuable to pursue.

References

American Psychiatric Association, 1990. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Rev ed. American Psychiatric Press, Washington, DC.

Amunts, K., Schleicher, A., Ditterich, A., Zilles, K., 2003. Broca's region: cytoarchitectonic asymmetry and developmental changes. J. Comp. Neurol. 465, 72–89.

Andreasen, N.C., 1979. Thought, language and communication disorders: I. Clinical assessment, definition of terms, and evaluation of their reliability. Arch. Gen. Psychiatry 36, 1315–1321.

Barde, L.H., Thompson-Schill, S.L., 2002. Models of functional organization of the lateral prefrontal cortex in verbal working memory: evidence in favor of the process model. J. Cogn. Neurosci. 14, 1054–1063.

Bartzokis, G., Beckson, M., Lu, P.H., Nuechterlein, K.H., Edwards, N., Mintz, J., 2001. Age-related changes in frontal and temporal lobe volumes in men: a magnetic resonance imaging study. Arch. Gen. Psychiatry 58, 461–465.

Bartzokis, G., Nuechterlein, K.H., Lu, P.H., Gitlin, M., Rogers, S., Mintz, J., 2003. Dysregulated brain development in adult men with schizophrenia: a magnetic resonance imaging study. Biol. Psychiatry 53, 412–421.

Blank, S.C., Scott, S.K., Murphy, K., Warburton, E., Wise, R.J., 2002. Speech production: Wernicke, Broca and beyond. Brain 125, 1829–1838.

Bleuler, E., 1911/1950. Dementia Praecox, or The Group of Schizophrenias. International Universities Press, New York.

Callicott, J.H., Bertolino, A., Mattay, V.S., Langheim, F.J., Duyn, J., Coppola, R., Goldberg, T.E., Weinberger, D.R., 2000. Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. Cereb. Cortex 10, 1078–1092.

Cannon, M., Caspi, A., Moffitt, T.E., Harrington, H., Taylor, A., Murray, R.M., Poulton, R., 2002. Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. Arch. Gen. Psychiatry 59, 449–456.

Caplan, D., 2001. Positron emission tomographic studies of syntactic processing. In: Shapiro, L., Grodzinsky, Y., Shapiro, D. (Eds.), The Neurology of Language. Academic Press.

Caplan, D., Alpert, N., Waters, G., Olivieri, A., 2000. Activation of Broca's area by syntactic processing under conditions of concurrent articulation. Hum. Brain Mapp. 9, 65–71.

Chi, J.G., Dooling, E.C., Gilles, F.H., 1977. Gyral development of the human brain. Ann. Neurol. 1, 86–93.

Condray, R., Steinhauer, S.R., van Kammen, D.P., Kasparek, A., 1996. Working memory capacity predicts language comprehension in schizophrenic patients. Schizophr. Res. 20, 1–13.

Copland, D.A., de Zubicaray, G.I., McMahon, K., Wilson, S.J., Eastburn, M., Chenery, H.J., 2003. Brain activity during automatic semantic priming revealed by event-related functional magnetic resonance imaging. NeuroImage 20, 302–310.

Dale, A., Sereno, M., 1993. Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction. J. Cogn. Neurosci. 5, 162–176.

Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. NeuroImage 9, 179–194.

Demb, J.B., Desmond, J.E., Wagner, A.D., Vaidya, C.J., Glover, G.H., Gabrieli, J.D., 1995. Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. Neuroscience 15, 5870–5878.

Desikan, R.S., Segonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage 31, 968–980.

Ditman, T., Kuperberg, G.R., 2005. A source-monitoring account of auditory verbal hallucinations in patients with schizophrenia. Harv. Rev. Psychiatry 13, 280–299.

Duvernoy, H., 1991. The Human Brain. Springer–Verlag, Vienna.

Elvevag, B., Weinberger, D.R., 2001. The Neuropsychology of Schizophrenia and its Relationship to the Neurodevelopmental Model. The MIT Press, Cambridge, MA.

Etchepareborda, M.C., Lopez-Lazaro, M.J., 2005. Cytoarchitectural structure of the areas of language. Rev. Neurol. S103–S106.

Fiebach, C.J., Schlesewsky, M., Lohmann, G., von Cramon, D.Y., Friederici, A.D., 2005. Revisiting the role of Broca's area in sentence processing: syntactic integration versus syntactic working memory. Hum. Brain Mapp. 24, 79–91.

Fischl, B., Sereno, M.I., Dale, A.M., 1999a. Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. NeuroImage 9, 195–207.

Fischl, B., Sereno, M.I., Tootell, R.B., Dale, A.M., 1999b. High-resolution intersubject averaging and a coordinate system for the cortical surface. Hum. Brain Mapp. 8, 272–284.

Fischl, B., Liu, A., Dale, A.M., 2001. Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. IEEE Trans. Med. Imag. 20, 70–80.

Fletcher, P.C., Shallice, T., Dolan, R.J., 2000. "Sculpting the response space" — an account of left prefrontal activation at encoding. NeuroImage 12, 404–417.

Friston, K.J., 1996. Theoretical neurobiology and schizophrenia. Br. Med. Bull. 52, 644–655.

Friston, K.J., 1998. The disconnection hypothesis. Schizophr. Res. 30, 115–125.

Friston, K.J., 1999. Schizophrenia and the disconnection hypothesis. Acta Psychiatr. Scand., Suppl. 395, 68–79.

Friston, K., 2005. Disconnection and cognitive dysmetria in schizophrenia. Am. J. Psychiatry 162, 429–432.

Friston, K.J., Frith, C.D., 1995. Schizophrenia: a disconnection syndrome? Clin. Neurosci. 3, 89–97.

Fuller, R., Nopoulos, P., Arndt, S., O'Leary, D., Ho, B.C., Andreasen, N.C., 2002. Longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia through examination of standardized scholastic test performance. Am. J. Psychiatry 159, 1183–1189.

Giesbrecht, B., Camblin, C.C., Swaab, T.Y., 2004. Separable effects of semantic priming and imageability on word processing in human cortex. Cereb. Cortex 14, 521–529.

Goldberg, T.E., Aloia, M.S., Gourovitch, M.L., Missar, D., Pickar, D., Weinberger, D.R., 1998. Cognitive substrates of thought disorder, I: the semantic system. Am. J. Psychiatry 155, 1671–1676.

Harris, J.M., Whalley, H., Yates, S., Miller, P., Johnstone, E.C., Lawrie, S.M., 2004a. Abnormal cortical folding in high-risk individuals: a predictor of the development of schizophrenia? Biol. Psychiatry 56, 182–189.

Harris, J.M., Yates, S., Miller, P., Best, J.J., Johnstone, E.C., Lawrie, S.M., 2004b. Gyrification in first-episode schizophrenia: a morphometric study. Biol. Psychiatry 55, 141–147.

Hoff, A.L., Sakuma, M., Wieneke, M., Horon, R., Kushner, M., DeLisi, L.E., 1999. Longitudinal neuropsychological follow-up study of patients with first-episode schizophrenia. Am. J. Psychiatry 156, 1336–1341.

Jennings, J.M., McIntosh, A.R., Kapur, S., Zipursky, R.B., Houle, S., 1998. Functional network differences in schizophrenia: a rCBF study of semantic processing. NeuroReport 9, 1697–1700.

Johns, L.C., Rossell, S., Frith, C., Ahmad, F., Hemsley, D., Kuipers, E., McGuire, P.K., 2001. Verbal self-monitoring and auditory verbal hallucinations in patients with schizophrenia. Psychol. Med. 31, 705–715.

Kirchhoff, B.A., Wagner, A.D., Maril, A., Stern, C.E., 2000. Prefrontal–temporal circuitry for episodic encoding and subsequent memory. J. Neurosci. 20, 6173–6180.

Kotz, S.A., Cappa, S.F., von Cramon, D.Y., Friederici, A.D., 2002. Modulation of the lexical-semantic network by auditory semantic

priming: an event-related functional MRI study. NeuroImage 17, 1761–1772.

Kubicki, M., McCarley, R.W., Nestor, P.G., Huh, T., Kikinis, R., Shenton, M.E., Wible, C.G., 2003. An fMRI study of semantic processing in men with schizophrenia. NeuroImage 20, 1923–1933.

Kulynych, J.J., Luevano, L.F., Jones, D.W., Weinberger, D.R., 1997. Cortical abnormality in schizophrenia: an in vivo application of the gyrification index. Biol. Psychiatry 41, 995–999.

Kuperberg, G., Caplan, D., 2003. Language dysfunction in schizophrenia. In: Schiffer, R.B., Rao, S.M., Fogel, B.S. (Eds.), Neuropsychiatry. Lippincott Williams and Wilkins, Philadelphia, pp. 444–466.

Kuperberg, G.R., Goldberg, T., 2006. Insights into semantics and language in schizophrenia. In: Wood, S., Allen, N., Pantelis, C. (Eds.), Handbook of Neuropsychology of Mental Illness. Cambridge University Press.

Kuperberg, G.R., McGuire, P.K., David, A., 1998. Reduced sensitivity to linguistic context in schizophrenic thought disorder: evidence from online monitoring for words in linguistically-anomalous sentences. J. Abnorm. Psychol. 107, 423–434.

Kuperberg, G.R., McGuire, P.K., David, A.S., 2000. Sensitivity to linguistic anomalies in spoken sentences: a case study approach to understanding thought disorder in schizophrenia. Psychol. Med. 30, 345–357.

Kuperberg, G.R., Broome, M.R., McGuire, P.K., David, A.S., Eddy, M., Ozawa, F., Goff, D., West, W.C., Williams, S.C., van der Kouwe, A.J., Salat, D.H., Dale, A.M., Fischl, B., 2003. Regionally localized thinning of the cerebral cortex in schizophrenia. Arch. Gen. Psychiatry 60, 878–888.

Kuperberg, G.R., Kreher, D.A., Goff, D., McGuire, P., David, A., 2006a. Building up linguistic context in schizophrenia: Evidence from self-paced reading. Neuropsychology 442–452.

Kuperberg, G.R., Sitnikova, T., Goff, D., Holcomb, P.J., 2006b. Making sense of sentences in schizophrenia: electrophysiological evidence for abnormal interactions between semantic and syntactic processing. J. Abnorm. Psychol. 115, 243–256.

Kuperberg, G., Deckersbach, T., Holt, D., Goff, D., West, W.C., 2007. Increased temporal and prefrontal activity to semantic associations in schizophrenia. Arch. Gen. Psychiatry 138–151.

Lewis, D.A., 1997. Development of the prefrontal cortex during adolescence: insights into vulnerable neural circuits in schizophrenia. Neuropsychopharmacology 16, 385–398.

Manoach, D.S., Press, D.Z., Thangaraj, V., Searl, M.M., Goff, D.C., Halpern, E., Saper, C.B., Warach, S., 1999. Schizophrenic subjects activate dorsolateral prefrontal cortex during a working memory task, as measured by fMRI. Biol. Psychiatry 45, 1128–1137.

Manoach, D.S., Gollub, R.L., Benson, E.S., Searl, M.M., Goff, D.C., Halpern, E., Saper, C.B., Rauch, S.L., 2000. Schizophrenic subjects show aberrant fMRI activation of dorsolateral prefrontal cortex and basal ganglia during working memory performance. Biol. Psychiatry 48, 99–109.

Marin-Padilla, M., 1992. Ontogenesis of the pyramidal cell of the mammalian neocortex and developmental cytoarchitectonics: a unifying theory. J. Comp. Neurol. 321, 223–240.

Matsumoto, A., Iidaka, T., Haneda, K., Okada, T., Sadato, N., 2005. Linking semantic priming effect in functional MRI and event-related potentials. NeuroImage 24, 624–634.

Minzenberg, M.J., Ober, B.A., Vinogradov, S., 2002. Semantic priming in schizophrenia: a review and synthesis. J. Int. Neuropsychol. Soc. 8, 699–720.

Moss, H.E., Abdallah, S., Fletcher, P., Bright, P., Pilgrim, L., Acres, K., Tyler, L.K., 2005. Selecting among competing alternatives: selection and retrieval in the left inferior frontal gyrus. Cereb. Cortex 15, 1723–1735.

Murray, R.M., Fearon, P., 1999. The developmental 'risk factor' model of schizophrenia. J. Psychiatry Res. 33, 497–499.

Narr, K., Thompson, P., Sharma, T., Moussai, J., Zoumalan, C., Rayman, J., Toga, A., 2001. Three-dimensional mapping of gyral shape and cortical surface asymmetries in schizophrenia: gender effects. Am. J. Psychiatry 158, 244–255.

Narr, K.L., Bilder, R.M., Kim, S., Thompson, P.M., Szeszko, P., Robinson, D., Luders, E., Toga, A.W., 2004. Abnormal gyral complexity in first-episode schizophrenia. Biol. Psychiatry 55, 859–867.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Ono, M., Kubik, S., Abernathey, C.D., 1990. Atlas of the Cerebral Sulci. Thieme Medical Publishers, New York.

Ott, S.L., Allen, J., Erlenmeyer-Kimling, L., 2001. The New York high-risk project: observations on the rating of early manifestations of schizophrenia. Am. J. Med. Genet. 105, 25–27.

Poldrack, R.A., Wagner, A.D., Prull, M.W., Desmond, J.E., Glover, G.H., Gabrieli, J.D., 1999. Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. NeuroImage 10, 15–35.

Ragland, J.D., Gur, R.C., Valdez, J., Turetsky, B.I., Elliott, M., Kohler, C., Siegel, S., Kanes, S., Gur, R.E., 2004. Event-related fMRI of frontotemporal activity during word encoding and recognition in schizophrenia. J. Abnorm. Psychol. 161, 1004–1015.

Rajkowska, G., Goldman-Rakic, P.S., 1995. Cytoarchitectonic definition of prefrontal areas in the normal human cortex: I. Remapping of areas 9 and 46 using quantitative criteria. Cereb. Cortex 5, 307–322.

Rakic, P., 1995. A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during evolution. Trends Neurosci. 18, 383–388.

Sallet, P.C., Elkis, H., Alves, T.M., Oliveira, J.R., Sassi, E., Campi de Castro, C., Busatto, G.F., Gattaz, W.F., 2003. Reduced cortical folding in schizophrenia: an MRI morphometric study. Am. J. Psychiatry 160, 1606–1613.

Sanfilipo, M., Lafargue, T., Rusinek, H., Arena, L., Loneragan, C., Lautin, A., Feiner, D., Rotrosen, J., Wolkin, A., 2000. Volumetric measure of the frontal and temporal lobe regions in schizophrenia: relationship to negative symptoms. Arch. Gen. Psychiatry 57, 471–480.

Segonne, F., Dale, A.M., Busa, E., Glessner, M., Salat, D., Hahn, H.K., Fischl, B., 2004. A hybrid approach to the skull stripping problem in MRI. NeuroImage 22, 1060–1075.

Segonne, F., Grimson, E., Fischl, B., 2005. Genetic algorithm for the topology correction of cortical surfaces. IPMI 393–405.

Shenton, M.E., Kikinis, R., Jolesz, F.A., Pollak, S.D., LeMay, M., Wible, C.G., Hokama, H., Martin, J., Metcalf, D., Coleman, M., et al., 1992. Abnormalities of the left temporal lobe and thought disorder in schizophrenia. A quantitative magnetic resonance imaging study. N. Engl. J. Med. 327, 604–612.

Shenton, M.E., Dickey, C.C., Frumin, M., McCarley, R.W., 2001. A review of MRI findings in schizophrenia. Schizophr. Res. 49, 1–52.

Sitnikova, T., Salisbury, D.F., Kuperberg, G., Holcomb, P.I., 2002. Electrophysiological insights into language processing in schizophrenia. Psychophysiology 39, 851–860.

Thompson-Schill, S.L., D'Esposito, M., Aguirre, G.K., Farah, M.J., 1997. Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. Proc. Natl. Acad. Sci. U. S. A. 94, 14792–14797.

Thompson-Schill, S.L., D'Esposito, M., Kan, I.P., 1999. Effects of repetition and competition on activity in left prefrontal cortex during word generation. Neuron 23, 513–522.

Titone, D., Levy, D.L., Holzman, P.S., 2000. Contextual insensitivity in schizophrenic language processing: evidence from lexical ambiguity. J. Abnorm. Psychol. 109, 761–767.

Van Essen, D.C., 1997. A tension-based theory of morphogenesis and compact wiring in the central nervous system. Nature 385, 313–318.

Vogeley, K., Schneider-Axmann, T., Pfeiffer, U., Tepest, R., Bayer, T.A., Bogerts, B., Honer, W.G., Falkai, P., 2000. Disturbed gyrification of the prefrontal region in male schizophrenic patients: a morphometric postmortem study. Am. J. Psychiatry 157, 34–39.

Wagner, A.D., Schacter, D.L., Rotte, M., Koutstaal, W., Maril, A., Dale, A., Rosen, B., Buckner, R.L., 1998. Building memories: remembering and forgetting verbal experiences as predicted by brain activity. Science 281, 1188–1191.

Wagner, A.D., Pare-Blagoev, E.J., Clark, J., Poldrack, R.A., 2001. Recovering meaning: left prefrontal cortex guides controlled semantic retrieval. Neuron 31, 329–338.

Weinberger, D.R., 1987. Implications of normal brain development for the pathogenesis of schizophrenia. Arch. Gen. Psychiatry 44, 660–669.

Weinberger, D.R., 1996. On the plausibility of "the neurodevelopmental hypothesis" of schizophrenia. Neuropsychopharmacology 14, 1S–11S.

Weiss, A.P., Schacter, D.L., Goff, D., Rauch, S.L., Alpert, N.M., Fischman, A.J., Heckers, S., 2003. Impaired hippocampal recruitment during normal modulation of memory performance in schizophrenia. Biol. Psychiatry 53, 48–55.

Wheatley, T., Weisberg, J., Beauchamp, M.S., Martin, A., 2005. Automatic priming of semantically related words reduces activity in the fusiform gyrus. J. Cogn. Neurosci. 17, 1871–1885.

White, K., Ashton, R., 1976. Handedness assessment inventory. Neuropsychologia 14, 261–264.

Wible, C.G., Anderson, J., Shenton, M.E., Kricun, A., Hirayasu, Y., Tanaka, S., Levitt, J.J., O'Donnell, B.F., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2001. Prefrontal cortex, negative symptoms, and schizophrenia: an MRI study. Psychiatry Res. 108, 65–78.

Woolf, C.M., 1997. Does the genotype for schizophrenia often remain unexpressed because of canalization and stochastic events during development? Psychol. Med. 27, 659–668.

Wyatt, R.J., 1996. Neurodevelopmental abnormalities and schizophrenia. A family affair. Arch. Gen. Psychiatry 53, 11–15.

Zilles, K., Armstrong, E., Schleicher, A., Kretschmann, H.J., 1988. The human pattern of gyrification in the cerebral cortex. Anat. Embryol. (Berl) 179, 173–179.