Schizophrenia Research xxx (2009) xxx-xxx



Contents lists available at ScienceDirect

Schizophrenia Research



journal homepage: www.elsevier.com/locate/schres

Increased diffusivity in superior temporal gyrus in patients with schizophrenia: A Diffusion Tensor Imaging study

KangUk Lee ^{a,b,c,*}, Takeshi Yoshida ^{b,e}, Marek Kubicki ^{a,b}, Sylvain Bouix ^{a,b}, Carl-Fredrik Westin ^d, Gordon Kindlmann ^d, Margaret Niznikiewicz ^b, Adam Cohen ^a, Robert W. McCarley ^b, Martha E. Shenton ^{a,b}

^a Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, 1249 Boylston Street, Boston, MA 02215 USA ^b Clinical Neuroscience Division, Laboratory of Neuroscience, VA Boston Healthcare, Brockton Campus Psychiatry 116A, 940 Belmont St. Brockton MA 02301 USA

^c Department of Psychiatry, Kangwon National University College of Medicine, 17-1 Hyoja-dong, Chunchon, Kangwon-do, South Korea

^d Laboratory of Mathematics in Imaging, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, 323 Thorn Building, Boston, MA 02115 USA ^e Department of Psychiatry, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359-8513 Japan

ARTICLE INFO

Article history: Received 29 October 2007 Received in revised form 12 November 2008 Accepted 15 November 2008 Available online xxxx

Keywords: Schizophrenia Superior temporal gyrus Diffusion Tensor Imaging Mean diffusivity Fractional anisotropy Auditory hallucination

ABSTRACT

Background: Superior temporal gyrus (STG) volume reduction is one of the most consistent findings in schizophrenia. The goal of this study was to conduct the first Diffusion Tensor Imaging (DTI) study to investigate altered structural integrity in STG gray and white matter in patients with chronic schizophrenia compared with healthy controls.

Methods: Magnetic resonance imaging (MRI) and DTI were acquired in 21 male patients with schizophrenia and 22 age-, handedness-, and parental social economic status-matched male comparison subjects. After manual segmentation of gray and white matter, mean diffusivity and fractional anisotropy were measured within STG. Correlational analyses were also conducted to test possible associations between DTI and clinical measures, including positive and negative symptoms of schizophrenia.

Results: Compared with controls, patients demonstrated reduced volume, bilaterally, in STG gray matter but not in white matter. For DTI measures, patients showed increased mean diffusivity, bilaterally, in STG gray matter, and in left STG white matter. In addition, mean diffusivity in left STG white matter showed statistically significant correlations with auditory hallucinations and attentional impairments in patients.

Conclusions: These findings suggest a disruption of tissue integrity in STG gray and white matter in schizophrenia. In addition, increased water diffusivity in left-side STG, which was associated with auditory hallucinations and attentional impairments, suggests the possibility of a disconnection among auditory/language processing regions in schizophrenia.

© 2008 Elsevier B.V. All rights reserved.

1. Introduction

Superior temporal gyrus (STG) is a brain region that it is thought to be a substrate of both auditory and language pro-

cessing (Galaburda et al., 1978), domains often impaired in schizophrenia. Indeed, converging findings suggest volume reductions in STG in schizophrenia using magnetic resonance imaging (MRI) (e.g., McCarley et al., 1999; Pearlson, 1997; Shenton et al., 2001). Of further note, thought disorder (Barta et al., 1997; Shenton et al., 1992) and auditory hallucinations (Barta et al., 1990; Gaser et al., 2004; Sumich et al., 2005), hallmark symptoms in schizophrenia, have been associated with left STG volume reduction. Such left-sided abnormalities are also observed at first episode of schizophrenia, but not at

^{*} Corresponding author. Department of Psychiatry, Kangwon National University Hospital, 17-1 Hyoja-dong, Chunchon, Kangwon-do, 200-947, South Korea. Tel.: +82 33 258 2471, +82 10 3006 0923 (mobile); fax: +82 33 256 3344.

E-mail address: kuleemd@kangwon.ac.kr (K. Lee).

^{0920-9964/\$ –} see front matter S 2008 Elsevier B.V. All rights reserved. doi:10.1016/j.schres.2008.11.024

first episode of bipolar disorder (Hirayasu et al., 1998), further suggesting the possible specificity of these findings to schizophrenia. Superior temporal gyrus (STG) volume reduction is, in fact, one of the most consistent findings in schizophrenia when gray and white matter are evaluated separately (Shenton et al., 2001).

Structural abnormalities observed in MRI studies of schizophrenia have also ignited a renewed interest in postmortem investigations. Here, numerous investigations have shown neuropathological abnormalities in schizophrenia such as reduced neuronal size, changes in neuronal or glial cell densities, aberrant clustering of neurons, fewer dendritic arborizations, and reduction of interneurons and their synaptic projections (Harrison, 1999; Harrison and Weinberger, 2005). Of note here, reduced neuropil and neuronal size, rather than a loss of neurons, have been proposed as one reason for decreased cortical volume in schizophrenia (Selemon and Goldman-Rakic, 1999). Additionally, there are a small number of studies that have investigated changes in dendritic spine density, neuronal cell volume, and axon terminal density in STG (Garey et al., 1998; Sweet et al., 2007; Sweet et al., 2003). Cytoarchitectural changes in STG, however, have not been as thoroughly investigated as MRI studies of STG, and thus while cytoarchitectural changes in STG are promising, they need to be investigating further to determine their importance with respect to the pathophysiology of schizophrenia.

Diffusion Tensor Imaging (DTI), a relatively new imaging technique, may, however, add to our understanding of STG abnormalities in schizophrenia. This method relies on the motion of water molecules to provide structural information about underlying cytoarchitectural changes, in vivo (e.g., Pierpaoli et al., 1996). Here, the structural environment of the brain influences water diffusion, such that the interaction of various tissue components, including cell membranes, macromolecules, myelin sheaths, and nerve fibers restrict the motion of water molecules. DTI is thus useful in evaluating the integrity of brain tissue where diffusion is anisotropic, or restricted in one direction more than in other directions (as in case of white matter, where water is restricted in directions that are parallel to the axons), as well as in tissues where diffusion is isotropic, or equally restricted in all directions (as in cerebrospinal fluid, and less so, for gray matter, where water is not restricted in mobility).

To date, white matter investigations using DTI have been applied to schizophrenia, where both changes in integrity of large white matter regions (Buchsbaum et al., 1998; Foong et al., 2000), as well as in small, organized white matter structures (Burns et al., 2003; Hubl et al., 2004; Kubicki et al., 2003; Wang et al., 2004) have been detected.

Gray matter has received far less attention in DTI research. One reason for this is that diffusion in gray matter is much less anisotropic than in white matter, thus standard techniques used to analyze the principal direction of diffusion, or the degree of anisotropy, become less meaningful. However, very recent investigations demonstrate the utility of DTI for the analysis of gray matter regions in schizophrenia as well in multiple sclerosis and in other conditions (Kalus et al., 2005; Munoz Maniega et al., 2004; Oreja-Guevara et al., 2005). Moreover, measures such as diffusivity, a measure of diffusion in all directions, may be more meaningful in gray matter than measures of anisotropy, such as fractional anisotropy, since the latter is a better indicator of anisotropic diffusion, which is an excellent measure of white matter integrity.

The current study investigates possible alterations in the structural integrity of STG gray and white matter in schizophrenia using quantitative analyses of the diffusion tensor, using both fractional anisotropy (FA), a measure of anisotropic diffusion, or the magnitude of the diffusion ascribed to FA. while mean diffusivity measures the average diffusion of water within tissues, in all directions. Thus altered tissue integrity may be reflected by either decreased FA or increased mean diffusivity. Accordingly, we will test the hypothesis that mean diffusivity is increased and fractional anisotropy is decreased in STG gray and white matter in schizophrenia. Additionally, correlations between DTI and clinical measures, including positive and negative symptoms, as well as demographic variables such as duration of illness, will be investigated in an exploratory manner, although we predict that auditory/language processing measures, particularly auditory hallucinations and formal thought disorder, will be associated with STG abnormalities.

2. Methods and materials

2.1. Subjects

Twenty-one male patients with chronic schizophrenia were recruited from the Veteran's Administration (VA) Boston Healthcare System, Brockton, MA. In addition, 22 normal male subjects, group-matched to patients on age, handedness, and parental socioeconomic status, were recruited from the community. We note that while there was some overlap in the patients and controls between this study and two previous diffusion studies of uncinate fasciculus (UF; Kubicki et al., 2002) and cingulum bundle (CB; Kubicki et al., 2003), we decided not to include UF and CB data for comparison in the current study, since these earlier studies used slightly different methods of analysis and our main focus in the current study was on STG.

Inclusion criteria are described in a previous study (Hirayasu et al., 1998). Briefly, all subjects were right-handed, between 18 and 55 years, with no history of neurological illness, electroconvulsant therapy, and no substance dependence history over the last 5 years. Diagnoses were based on the Structured Clinical Interview for DSM-IV-TR (SCID) (First MB et al., 2001), in conjunction with a review of hospital course, and the patients' medical records. All of the patients had longer than 2 years of illness duration. The study was approved by the local IRB (VA Boston Healthcare System), Harvard Medical School and Partners Healthcare System), and subjects provided written informed consent prior to study participation.

2.2. Clinical and cognitive measurements

Socioeconomic status (SES) of subjects and of their parents was assessed using the Hollingshead two-factor index (Hollingshead, 1965). Handedness was evaluated using a modified Edinburgh inventory (Oldfield, 1971). Intelligence was measured using the Wechsler Adult Intelligence Scale (WAIS-III). The Scale for the Assessment of Positive Symptoms

(SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) were used to evaluate positive and negative symptoms in schizophrenia (Andreasen, 1984).

2.3. MRI acquisition and data processing

2.3.1. Acquisition of structural MRI and segmentation

MR images were acquired using a 1.5-T GE scanner (GE Medical Systems, Milwaukee). The acquisition protocol included two MRI pulse sequences. The first resulted in contiguous spoiled gradient-recalled acquisition (SPGR) with the following parameters; TR=35 ms, TE=5 ms, FA 45°, FOV 24 cm², NEX=1.0, matrix=256×256 (192 phase-encoding steps). The voxel dimensions were $0.9375 \times 0.9375 \times 1.5$ mm. The second acquisition sequence produced an axial series of contiguous double-echo (proton density and T2-weighted) images (TR=3000 ms, TE=30 ms and 80 ms, 24 cm² field of view, interleaved acquisitions with 3.0 mm slice thickness). The voxel dimensions were $0.9375 \times 0.9375 \times 3.0$ mm. This latter pulse sequence was used to measure the volume of total intracranial contents (ICC).

Gray and white matter of STG were segmented manually by one rater (T.Y.) who was blind to the diagnosis. Established procedures were used based on our previous report (Hirayasu et al., 2000). After delineating gray matter, the boundary of STG white matter was delineated by connecting a straight line between two open ends of the ROI of gray matter (see Fig. 1). Three raters, blind to diagnosis, independently created the ROI on five subjects to test the interrater reliability (intraclass correlation coefficients for left and right STG were 0.988 and 0.987 for gray matter, 0.996 and 0.999 for white matter).

2.3.2. Diffusion Tensor Imaging

DTI data were acquired using line scan diffusion imaging (LSDI), a protocol implemented on conventional MR scanners (Maier et al., 1998). MR diffusion scans were performed on a 1.5 T GE scanner, which permits maximum gradient amplitudes of 40 mT/m. Coronal LSDI scans were acquired perpendicular to both the AC-PC line and interhemispheric fissure. For each line, six images with high (1000 s/mm²) diffusion-weighting along six non-collinear directions and two images with low (5 s/mm²) diffusion-weighting were collected. The following scan parameters were used: FOV 220×165 mm²; scan matrix 128×128 (image matrix 256×256); slice thickness 4 mm; interslice distance 1 mm; receiver bandwidth \pm 4 kHz; TE=64 ms; effective TR=2592 ms; scan time 60 s/slice. Mean diffusivity (Dm), and fractional anisotropy (FA) were calculated.

To calculate the mean regional Dm and FA in STG, ROI maps of the STG were transformed in the DTI space. For each subject, this transformation was estimated by registering the SPGR images to the B0 maps of the DTI using a mutual information rigid body coregistration algorithm (Wells et al., 1996). ROI maps of STG were then realigned and resampled to the B0 maps by applying the corresponding transformation matrix. To test the reliability of this coregistration method, measurements of Dm and FA in STG were repeated three times in five cases. The intraclass correlation coefficients were 0.984 (right gray matter), 0.988 (left gray matter), 0.999 (right white matter), 0.993 (left white matter) for Dm, and 0.947 (right gray matter), 0.998 (left gray matter), 0.990 (right white matter), 0.953 (left white matter) for FA.

Motion-related artifact maps (Maier et al., 1998) were also constructed and the number of lines missing in the raw



Fig. 1. ROI maps of superior temporal gyrus superimposed on fractional anisotropy maps in one normal comparison subject. The most anterior part of superior temporal gyrus begins at slice 1 and ends at slice 9. Fractional anisotropy in each voxel was calculated and scaled from 0 to 1. Segmented regions of interest are shown in different colors (right gray: green, right white: brown, left gray: purple, left white: pink). Note also the result of whole brain segmentation by expectation–maximization algorithm (gray matter: blue, white matter: light yellow).

Table 1

Demographic characteristics for patients with chronic schizophrenia (SZ) and normal comparison (NC) subjects

| | SZ | NC | Two sample <i>t</i> -test (2-tailed) | | | |
|--|------------------|-------------------|--------------------------------------|----|---------|--|
| | (n=21) | (n=22) | t | df | р | |
| Age (yr) | 40.3±8.61 (41) | 40.4±9.00 (41) | 0.011 | 41 | 0.991 | |
| Socioeconomic status (SES) ^a | 4.05±1.24(5) | 2.35±1.09(2) | -4.639 ^b | 41 | < 0.001 | |
| Parental SES ^a | 2.63±1.21(3) | 2.91±1.37(2) | 0.680 | 41 | 0.501 | |
| Education (yr) | 12.3±1.91 (12) | 15.4±1.84 (16) | 5.207 ^b | 41 | < 0.001 | |
| Handedness | 0.78±0.24 (0.87) | 0.82±0.16 (0.87) | 0.648 | 41 | 0.520 | |
| WAIS-III IQ | 89.5±11.02 (90) | 110.6±14.17 (109) | 5.115 ^b | 41 | < 0.001 | |
| Duration of illness | 17.85±9.04 (21) | - | | - | | |
| Age at onset | 21.48±4.40(21) | - | | - | | |

Mean±SD (Median).

WAIS-III IQ, Intelligence Quotient by the third edition of the Wechsler Adult Intelligence Scale.

^a Higher numbers represent lower SES.

^b p < 0.01.

LSDI data due to subjects' motion within the segmented ROI of STG was calculated. There was no significant diference in the number of lines between groups. Nonetheless, all voxels within the missing lines were removed for further analyses.

2.4. Statistics

Two sample *t*-tests were used to compare demographic characteristics and WAIS-III IQ between groups. Repeated measures two-way ANOVA, with group as a between-subject factor and hemisphere (right, left) as a within-subject factor, was used to test for group differences in mean gray and white matter volumes, mean D*m*, and mean FA in STG.

For correlation analyses between DTI measures and other measures, the presence of a normal distribution for each variable was first tested using both a Kolmogorov–Smirnov test and a Shapiro–Wilk test. Pearson's *r* was used as a correlation measure if the variable passed both tests, otherwise Spearman's rho was used. For correlation analyses between DTI and clinical measures, the sum of each item score of symptom types on the SAPS (Hallucinations, Delusions, Bizarre Behavior, and Positive Formal Thought Disorder) was used. For SAPS-Hallucinations score, we extracted three items (Auditory Hallucinations, Voices Commenting, and Voices Conversing) to create an additional score, SAPS-Auditory Hallucinations. As with the SAPS, the sum of each item score of symptom types on the SANS (Affective Flattening or Blunting, Alogia, Avolition–Apathy, Anhedonia–Asociality, Attention) was used for correlation analyses.

3. Results

3.1. Demographic data

There were no significant differences in age, handedness, or parental SES between groups. Patients diagnosed with schizophrenia showed lower SES, education level, and total IQ than controls. Mean age at onset and mean duration of illness were 21.5 years (SD; 4.40) and 17.9 years (SD; 9.04), respectively (see Table 1). All patients were receiving antipsychotic medication: 5 were taking typical antipsychotics, 15 atypical, and 1 both. Mean dose in chlorpromazine equivalence was 418.2 mg/d (SD; 307.9).

3.2. Relative volume of gray and white matter of STG

Relative STG gray matter volume in patients was decreased compared with normal controls, where a repeated measures two-way ANOVA showed a statistically significant main effect for group (F=6.801, df=1,41, p=0.013). Further post-hoc contrasts using Bonferroni correction (2-tailed) revealed significant differences in STG gray matter volume between groups for both left (F=6.362, df=1, p=0.016) and right (F=4.962, df=1, p=0.031) hemispheres. For relative STG white matter volume, there was no main effect of group observed (F=0.049, df=1,41, p=0.827) (see Table 2).

3.3. DTI measures

Descriptive statistics for the DTI measures and results of the repeated-measures two-way ANOVA are summarized in Table 3. For STG gray matter, Dm was increased in patients compared with controls (F=12.447, df=1,41, p=0.001). There was no differences between groups for FA (F=1.407, df=1,41, p=0.242). Further post-hoc contrasts using Bonferroni correction (2-tailed) revealed significant differences in gray matter Dm between groups for left (F=7.772, df=1, p=0.008) and

Table 2

Superior temporal gyrus relative gray and white matter volumes in patients with schizophrenia and normal comparison subjects

| RV (%) of superior temporal gyrus ^a | SZ subjects (n=21) | | NC subjects | NC subjects (n=22) | | Main effect of group | | Group×hemisphere | |
|---|--------------------|-------|-------------|--------------------|--------------------|----------------------|---------|------------------|--|
| | Mean | SD | Mean | SD | F(1,41) | р | F(1,41) | р | |
| Gray matter | | | | | | | | | |
| Right | 0.644 | 0.075 | 0.696 | 0.077 | 6.801 ^b | 0.013 | 0.070 | 0.793 | |
| Left | 0.575 | 0.079 | 0.632 | 0.069 | | | | | |
| White matter | | | | | | | | | |
| Right | 0.337 | 0.046 | 0.337 | 0.047 | 0.049 | 0.827 | 0.094 | 0.761 | |
| Left | 0.306 | 0.029 | 0.302 | 0.042 | | | | | |

Repeated measures two-way ANOVA with group as a between-subject factor and hemisphere (right, left) as a within-subject factor. ^a Relative volume (RV)=[absolute volume]/[volume of intracranial contents]×100.

^b p<0.05.

K. Lee et al. / Schizophrenia Research xxx (2009) xxx-xxx

Table 3

DTI measurements in superior temporal gyrus in patients with chronic schizophrenia and normal comparison subjects

| DTI measures | SZ subjects | SZ subjects $(n=21)$ | | NC subjects (n=22) | | Main effect of group | | Group×hemisphere | |
|-------------------|-------------|----------------------|-------|--------------------|----------|----------------------|---------|------------------|--|
| | Mean | SD | Mean | SD | F(1,41) | р | F(1,41) | р | |
| Gray matter | | | | | | | | | |
| $Dm (\mu m^2/ms)$ | | | | | | | | | |
| Right | 0.886 | 0.042 | 0.841 | 0.030 | 12.447** | 0.001 | 0.113 | 0.738 | |
| Left | 0.909 | 0.064 | 0.859 | 0.051 | | | | | |
| FA | | | | | | | | | |
| Right | 0.232 | 0.016 | 0.240 | 0.028 | 1.407 | 0.242 | 0.054 | 0.818 | |
| Left | 0.228 | 0.016 | 0.235 | 0.025 | | | | | |
| White matter | | | | | | | | | |
| $Dm (\mu m^2/ms)$ | | | | | | | | | |
| Right | 0.750 | 0.028 | 0.744 | 0.026 | 2.214 | 0.144 | 5.119* | 0.029 | |
| Left | 0.767 | 0.025 | 0.751 | 0.023 | | | | | |
| FA | | | | | | | | | |
| Right | 0.351 | 0.029 | 0.357 | 0.028 | 1.963 | 0.169 | 1.405 | 0.243 | |
| Left | 0.336 | 0.027 | 0.351 | 0.025 | | | | | |

Repeated measures two-way ANOVA with group as a between-subject factor and hemisphere (right, left) as a within-subject factor.

⁺*p*<0.05, ⁺⁺*p*<0.01.

right (F=16.527, df=1, p<0.001) hemispheres. When group comparisons were repeated after controlling for possible confounding effects of volume, group differences in Dm for STG gray matter were still significant for left (F=4.073, df=1, p=0.050) and right (F=12.130, df=1, p=0.001) hemispheres. In addition, correlational analyses between Dm and relative volumes of STG gray matter showed no significance for either right or left hemisphere in either patients or controls.

For STG white matter, there was no main effect for group, for either Dm (F=2.214, df=1,41, p=0.144) or FA (F=1.963, df=1,41, p=0.169). However, a significant group-by-hemisphere interaction was observed for Dm (F=5.119, df=1,41, p=0.029). In post-hoc contrasts using Bonferroni correction (2-tailed), Dm for left STG white matter was increased in patients compared to controls (F=4.789, df=1, p=0.034), while right hemisphere showed no significant difference (F=0.566, df=1, p=0.456). Group differences in Dm for left STG white matter remained significant (F=4.783, df=1, p=0.035) after controlling for volume; there was no significant correlation between Dm and relative volume for STG white matter.

3.4. Correlation analyses between DTI measures and clinical measures

Duration of illness was positively correlated with Dm for left and right STG gray matter (left, rho=0.728, p<0.001; right, rho=0.590, p=0.008). Furthermore, using partial correlation coefficients adjusted for age, these findings remained significant for left (r=0.549, p=0.015) and right (r=0.466, p=0.045) STG gray matter. Neither age at onset nor intelligence score were correlated with any of the DTI measures. In correlation analyses between DTI measures and SAPS scores, a positive correlation was observed between Dm in left STG white matter and SAPS-Auditory Hallucination score (rho=0.465, p=0.039). Further analyses for each subitem showed that Dm in left STG white matter was positively correlated with "Voices Commenting" score (rho=0.542, p=0.017) and "Voices Conversing" score (rho=0.635, p=0.004; see Fig. 2). Using Bonferroni correction for the 8 correlations, with statistical significance at p < 0.0063, the "Voices Conversing" score remained statistically significant. In



Fig. 2. Scatter plots for correlations between hallucination scores on SAPS and mean diffusivity of left STG white matter in patients with schizophrenia (*n*=21): (a) SAPS-Auditory Hallucination (rho=0.465, *p*=0.039); (b) "Voice Commenting" score (rho=0.542, *p*=0.017); (c) "Voice Conversing" score (rho=0.635, *p*=0.004).

correlation analyses between DTI measures and SANS scores, increased Dm in the left STG white matter was positively associated with high score of SANS-Attention score (rho=0.547, p=0.010). In further analyses for sub-items, Dm in left STG white matter was positively correlated with "Social Inattentiveness" score (rho=0.495, p=0.031) and "Global Rating of Attention" score (rho=0.519, p=0.019). None of the SANS score remained significant after Bonferroni correction for multiple correlations.

In correlation analyses between DTI measures in STG and chlorpromazine equivalent antipsychotics dose, increased Dm was associated with a higher dose of antipsychotics use in left (r=0.502, p=0.028), but not in right gray matter (r=0.377, p=0.111). Neither Dm in STG white matter nor FA in STG gray or white matter showed a significant correlation with antipsychotics dose.

4. Discussion

The most novel and intriguing findings of this study are the detection of increased *Dm*, bilaterally, in STG *gray matter*, and increased *Dm* in *left* STG *white matter*, in patients with schizophrenia, compared with healthy controls. In addition, mean diffusivity in left STG white matter showed significant correlations with auditory hallucinations, most particularly "Voices Conversing", in schizophrenia. This is the first study, to the best of our knowledge, to use DTI to investigate STG gray and white matter in patients with schizophrenia, a brain region that has figured prominently in volume studies of schizophrenia (see review in Shenton et al., 2001).

4.1. Diffusion anisotropy in gray matter

In general, diffusion anisotropy in *gray matter* is much lower than in white matter because the cell membranes comprising neuronal processes are not orientated along a preferential direction. Therefore trace, or mean diffusivity, may be a more appropriate and sensitive indicator of gray matter integrity than an anisotropy index such as fractional anisotropy. This is also why we included a measure of mean diffusivity (Dm) in this study, and it is also likely the main reason for the significant finding for Dm group differences, but the lack of significant FA group differences in STG gray matter in our study.

Since increased diffusivity in gray matter is likely largely the effect of increased unoccupied intercellular space, and since this increase is not due to a change in neuronal cell density, increased diffusivity in STG gray matter, while speculative, might be the result of reduced cortical neuropil, which includes axonal, dendritic, and glial processes (branchings) embedding neuronal cell bodies.

4.2. Changes in neuropil in the temporal region

Of note here, although most investigations have generally focused on prefrontal regions, there are several studies that suggest changes in neuropil in the temporal region. One study reports reduced dendritic spine density in the temporal region, including BA 22 (Garey et al., 1998). There is also a series of investigations that report decreased pyramidal cell somal volume in BA41 and BA42, which the authors suggest likely the result of a reduction in dendritic arborization and hence reduced neuropil volume of dendrites and associated synaptic structures (Sweet et al., 2004; Sweet et al., 2003). Furthermore, Sweet et al. (2007) have recently reported more direct evidence of reduced neuropil in their study, where the density of axon terminal was lower in patients with schizophrenia than in control subjects.

4.3. Gray matter and white matter volume in schizophrenia

We also replicated previous findings of STG gray matter volume reduction in patients with schizophrenia. It is notable that there was no significant correlation between volumes and Dm in STG gray matter. In addition, group differences in Dm in STG gray matter was still significant after controlling for volume.

In contrast to STG gray matter, we failed to find differences in STG white matter volume between patients and control groups. This finding is consistent with at least one study in the literature which evaluated the volume of both STG gray and white matter and reported no volume differences in STG white matter (Hajek et al., 1997). We did, nonetheless, observe an increase of Dm in left STG white matter in patients with schizophrenia. This is of particular note because while white matter abnormalities have been demonstrated by decreases in anisotropy indices in major white matter tracts such as internal capsule, corpus callosum (Buchsbaum et al., 1998; Foong et al., 2000), and in small, organized white matter structures such as uncinate fasciculus, arcuate fasciculus or cingulum bundle (Burns et al., 2003; Hubl et al., 2004; Kubicki et al., 2003; Wang et al., 2004), abnormalities in STG white matter have not been specifically investigated. Our finding of increased diffusivity in left STG white matter could reflect loss of organization in white matter fiber tracts such as loss of myelin, axonal fibers, and/or increased extracellular space in this region. Moreover, Dm in STG white matter might be a more appropriate measure than an anisotropy index such as FA because this region is composed of multiple directional nerve fibers, and numerous fiber-crossings exist within this anatomically complicated white matter region.

4.4. Correlations between Dm in STG white matter and clinical and cognitive abnormalities

In correlation analyses, Dm in STG white matter, on the left, showed an association with auditory hallucinations. This finding is consistent with evidence for altered STG being associated with auditory hallucination in structural MRI (Barta et al., 1990; Gaser et al., 2004; Sumich et al., 2005), functional MRI (Dierks et al., 1999; Lennox et al., 2000), and electrophysiological studies (Youn et al., 2003). In addition, attentional impairment was positively correlated with increased diffusivity in left STG white matter. Although this finding is consistent with the previous observation of decreased white matter volume in left temporal regions in patients with prominent negative symptoms (Sigmundsson et al., 2001), it is still not clear whether left STG white matter abnormalities are associated with negative symptoms because there are several studies using PET (Potkin et al., 2002; Thoma et al., 2005), that have shown correlations between negative symptoms and functional impairment in the right temporal lobe. Of further note, Dm in

STG gray matter showed a positive correlation with duration of illness, suggesting a possible progressive deterioration of STG tissue integrity. This is consistent with the finding of progressive volume reduction of STG in patients with schizophrenia (Kasai et al., 2003). Importantly, however, this can only be addressed by conducting a longitudinal study to provide direct evidence for progressive cytoarchitectural changes in schizophrenia.

4.5. Possible limitations of the study

Several methodological issues in this study need to be mentioned. First, because our study focused on males, generalizations can not be made to females as they have not been evaluated separately. Second, STG is not a unitary structure but is composed of several functionally distinctive subdivisions characterized by different cytoarchitectonic features (Sweet et al., 2005). A further study using higher resolution DTI data will be required for subregional analyses. Finally, all patients were medicated with antipsychotics, which might affect DTI measures. However, correlational analyses between DTI measures and dose of antipsychotics showed inconsistent results in that only Dm in left STG gray matter showed a statistically significant correlation. There is a study by our group which reports no significant correlations between FA and medication (Kubicki et al., 2002), and another study which reports a positive correlation between FA and antipsychotic medication (Minami et al., 2003). Of further note, a recent study reported no difference in axon terminal density between haloperidol-treated and control monkeys (Sweet et al., 2007). Thus while our mean diffusivity finding for left STG gray matter is not likely attributable to antipsychotic medication, possible confounds with medication need to be considered.

5. Conclusions

In conclusion, our findings of increased diffusivity in STG gray and white matter provide evidence for alteration of structural integrity in this brain region in schizophrenia. Moreover, the finding of increased diffusivity in STG gray matter, while speculative, may reflect a reduction of neuropil in gray matter (e.g., similar reductions in neuropil in prefrontal cortex have been reported (Selemon and Goldman-Rakic, 1999)). Importantly, and less speculative with respect to our findings, significant correlations between mean diffusivity and auditory hallucination and attentional impairment in left STG white matter suggest the possibility of a disconnection among auditory/language processing regions in schizophrenia.

Acknowledgements

The authors would like to thank Nancy Maxwell for administrative support; Takeshi Yoshida for his assistance in the segmentation and in the statistical analyses; Marek Kubicki and Martha Shenton for their assistance with the design of the study and for reviewing multiple versions of the manuscript; Sylvain Bouix, Carl-Fredrik Westin and Gordon Kindlmann for their technical assistance; Adam Cohen for his support as research assistant; Margaret Niznikiewicz for her assistance in the characterization of the subject sample; and Robert McCarley for his support in providing subjects and for reviewing parts of the manuscript. Additionally, we gratefully acknowledge the support of the National Institute of Health (K05 MH070047 and R01 MH 50740 to MES, R01 MH 40799 to RWM and R01 MH 074794 to CFW, P50 MH 080272 to RWM, MES), the Department of Veterans Affairs Merit Awards (MES, RWM), and the VA Schizophrenia Center Grant (RWM, MES). This work is also part of the National Alliance for Medical Image Computing (NA-MIC), funded by the National Institutes of Health through the NIH Roadmap for Medical Research, U54 EB005149 (MK, MES).

References

Andreasen, N.C., 1984. Scale for the Assessment of Positive Symptoms (SAPS). University of Iowa College of Medicine, Department of Psychiatry, Iowa.

- Barta, P.E., Pearlson, G.D., Powers, R.E., Richards, S.S., Tune, L.E., 1990. Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. Am. J. Psychiatry 147, 1457–1462.
- Barta, P.E., Pearlson, G.D., Brill 2nd, L.B., Royall, R., McGilchrist, I.K., Pulver, A.E., Powers, R.E., Casanova, M.F., Tien, A.Y., Frangou, S., Petty, R.G., 1997. Planum temporale asymmetry reversal in schizophrenia: replication and relationship to gray matter abnormalities. Am. J. Psychiatry 154, 661–667.
- Buchsbaum, M.S., Tang, C.Y., Peled, S., Gudbjartsson, H., Lu, D., Hazlett, E.A., Downhill, J., Haznedar, M., Fallon, J.H., Atlas, S.W., 1998. MRI white matter diffusion anisotropy and PET metabolic rate in schizophrenia. Neuroreport 9, 425–430.
- Burns, J., Job, D., Bastin, M.E., Whalley, H., Macgillivray, T., Johnstone, E.C., Lawrie, S.M., 2003. Structural disconnectivity in schizophrenia: a diffusion tensor magnetic resonance imaging study. Br. J. Psychiatry 182, 439–443.
- Dierks, T., Linden, D.E., Jandl, M., Formisano, E., Goebel, R., Lanfermann, H., Singer, W., 1999. Activation of Heschl's gyrus during auditory hallucinations. Neuron 22, 615–621.
- First MB, S.R., Gibbon, M., Williams, J.B., 2001. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version. Biometrics Research Department, New York State Psychiatric Institue, New York.
- Foong, J., Maier, M., Clark, C.A., Barker, G.J., Miller, D.H., Ron, M.A., 2000. Neuropathological abnormalities of the corpus callosum in schizophrenia: a diffusion tensor imaging study. J. Neurol. Neurosurg. Psychiatry 68, 242–244.
- Galaburda, A.M., Sanides, F., Geschwind, N., 1978. Human brain. Cytoarchitectonic left-right asymmetries in the temporal speech region. Arch. Neurol. 35, 812–817.
- Garey, L.J., Ong, W.Y., Patel, T.S., Kanani, M., Davis, A., Mortimer, A.M., Barnes, T.R., Hirsch, S.R., 1998. Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. J. Neurol. Neurosurg. Psychiatry 65, 446–453.
- Gaser, C., Nenadic, I., Volz, H.P., Buchel, C., Sauer, H., 2004. Neuroanatomy of "hearing voices": a frontotemporal brain structural abnormality associated with auditory hallucinations in schizophrenia. Cereb. Cortex 14, 91–96.
- Hajek, M., Huonker, R., Boehle, C., Volz, H.P., Nowak, H., Sauer, H., 1997. Abnormalities of auditory evoked magnetic fields and structural changes in the left hemisphere of male schizophrenics—a magnetoencephalographic magnetic resonance imaging study. Biol. Psychiatry 42, 609–616.
- Harrison, P.J., 1999. The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain 122 (Pt 4), 593–624.
- Harrison, P.J., Weinberger, D.R., 2005. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol. Psychiatry 10, 40–68 image 45.
- Hirayasu, Y., Shenton, M.E., Salisbury, D.F., Dickey, C.C., Fischer, I.A., Mazzoni, P., Kisler, T., Arakaki, H., Kwon, J.S., Anderson, J.E., et al., 1998. Lower left temporal lobe MRI volumes in patients with first-episode schizophrenia compared with psychotic patients with first-episode affective disorder and normal subjects. Am. J. Psychiatry 155, 1384–1391.
- Hirayasu, Y., Shenton, M.E., Salisbury, D.F., McCarley, R.W., 2000. Hippocampal and superior temporal gyrus volume in first-episode schizophrenia. Arch. Gen. Psychiatry 57, 618–619.
- Hollingshead, A., 1965. Two Factor Index of Social Position. Yale University Press, New Haven, Connecticut.
- Hubl, D., Koenig, T., Strik, W., Federspiel, A., Kreis, R., Boesch, C., Maier, S.E., Schroth, G., Lovblad, K., Dierks, T., 2004. Pathways that make voices: white matter changes in auditory hallucinations. Arch. Gen. Psychiatry 61, 658–668.
- Kalus, P., Slotboom, J., Gallinat, J., Federspiel, A., Gralla, J., Remonda, L., Strik, W.K., Schroth, G., Kiefer, C., 2005. New evidence for involvement of the

<u>ARTICLE IN PRESS</u>

K. Lee et al. / Schizophrenia Research xxx (2009) xxx-xxx

entorhinal region in schizophrenia: a combined MRI volumetric and DTI study. Neuroimage 24, 1122–1129.

- Kasai, K., Shenton, M.E., Salisbury, D.F., Hirayasu, Y., Lee, C.U., Ciszewski, A.A., Yurgelun-Todd, D., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2003. Progressive decrease of left posterior superior temporal gyrus gray matter volume in patients with first-episode schizophrenia. Am. J. Psychiatry 160 (1), 156–164.
- Kubicki, M., Westin, C.F., Maier, S.E., Frumin, M., Nestor, P.G., Salisbury, D.F., Kikinis, R., Jolesz, F.A., McCarley, R.W., Shenton, M.E., 2002. Uncinate fasciculus findings in schizophrenia: a magnetic resonance diffusion tensor imaging study. Am. J. Psychiatry 159, 813–820.
- Kubicki, M., Westin, C.F., Nestor, P.G., Wible, C.G., Frumin, M., Maier, S.E., Kikinis, R., Jolesz, F.A., McCarley, R.W., Shenton, M.E., 2003. Cingulate fasciculus integrity disruption in schizophrenia: a magnetic resonance diffusion tensor imaging study. Biol. Psychiatry 54, 1171–1180.
- Lennox, B.R., Park, S.B., Medley, I., Morris, P.G., Jones, P.B., 2000. The functional anatomy of auditory hallucinations in schizophrenia. Psychiatry Res. 100, 13–20.
- Maier, S.E., Gudbjartsson, H., Patz, S., Hsu, L., Lovblad, K.O., Edelman, R.R., Warach, S., Jolesz, F.A., 1998. Line scan diffusion imaging: characterization in healthy subjects and stroke patients. AJR Am. J. Roentgenol. 171, 85–93.
- McCarley, R.W., Wible, C.G., Frumin, M., Hirayasu, Y., Levitt, J.J., Fischer, I.A., Shenton, M.E., 1999. MRI anatomy of schizophrenia. Biol. Psychiatry 45, 1099–1119.
- Minami, T., Nobuhara, K., Okugawa, G., Takase, K., Yoshida, T., Sawada, S., Ha-Kawa, S., Ikeda, K., Kinoshita, T., 2003. Diffusion tensor magnetic resonance imaging of disruption of regional white matter in schizophrenia. Neuropsychobiology 47, 141–145.
- Munoz Maniega, S., Bastin, M.E., Armitage, P.A., Farrall, A.J., Carpenter, T.K., Hand, P.J., Cvoro, V., Rivers, C.S., Wardlaw, J.M., 2004. Temporal evolution of water diffusion parameters is different in grey and white matter in human ischaemic stroke. J. Neurol. Neurosurg. Psychiatry 75, 1714–1718.
- Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.
- Oreja-Guevara, C., Rovaris, M., Iannucci, G., Valsasina, P., Caputo, D., Cavarretta, R., Sormani, M.P., Ferrante, P., Comi, G., Filippi, M., 2005. Progressive gray matter damage in patients with relapsing-remitting multiple sclerosis: a longitudinal diffusion tensor magnetic resonance imaging study. Arch. Neurol. 62, 578–584.
- Pearlson, G.D., 1997. Superior temporal gyrus and planum temporale in schizophrenia: a selective review. Prog. Neuropsychopharmacol. Biol. Psychiatry 21, 1203–1229.
- Pierpaoli, C., Jezzard, P., Basser, P.J., Barnett, A., Di Chiro, G., 1996. Diffusion tensor MR imaging of the human brain. Radiology 201, 637–648.
- Potkin, S.G., Alva, G., Fleming, K., Anand, R., Keator, D., Carreon, D., Doo, M., Jin, Y., Wu, J.C., Fallon, J.H., 2002. A PET study of the pathophysiology of

negative symptoms in schizophrenia. Positron emission tomography. Am. J. Psychiatry 159, 227–237.

- Selemon, L.D., Goldman-Rakic, P.S., 1999. The reduced neuropil hypothesis: a circuit based model of schizophrenia. Biol. Psychiatry 45, 17–25.
- 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.
- Sigmundsson, T., Suckling, J., Maier, M., Williams, S., Bullmore, E., Greenwood, K., Fukuda, R., Ron, M., Toone, B., 2001. Structural abnormalities in frontal, temporal, and limbic regions and interconnecting white matter tracts in schizophrenic patients with prominent negative symptoms. Am. J. Psychiatry 158, 234–243.
- Sumich, A., Chitnis, X.A., Fannon, D.G., O'Ceallaigh, S., Doku, V.C., Faldrowicz, A., Sharma, T., 2005. Unreality symptoms and volumetric measures of Heschl's gyrus and planum temporal in first-episode psychosis. Biol. Psychiatry 57, 947–950.
- Sweet, R.A., Pierri, J.N., Auh, S., Sampson, A.R., Lewis, D.A., 2003. Reduced pyramidal cell somal volume in auditory association cortex of subjects with schizophrenia. Neuropsychopharmacology 28, 599–609.
- Sweet, R.A., Bergen, S.E., Sun, Z., Sampson, A.R., Pierri, J.N., Lewis, D.A., 2004. Pyramidal cell size reduction in schizophrenia: evidence for involvement of auditory feedforward circuits. Biol. Psychiatry 55, 1128–1137.
- Sweet, R.A., Dorph-Petersen, K.A., Lewis, D.A., 2005. Mapping auditory core, lateral belt, and parabelt cortices in the human superior temporal gyrus. J. Comp. Neurol 491, 270–289.
- Sweet, R.A., Bergen, S.E., Sun, Z., Marcsisin, M.J., Sampson, A.R., Lewis, D.A., 2007. Anatomical evidence of impaired feedforward auditory processing in schizophrenia. Biol. Psychiatry 61, 854–864.
- Thoma, R.J., Hanlon, F.M., Moses, S.N., Ricker, D., Huang, M., Edgar, C., Irwin, J., Torres, F., Weisend, M.P., Adler, L.E., et al., 2005. M50 sensory gating predicts negative symptoms in schizophrenia. Schizophr. Res. 73, 311–318.
- Wang, F., Sun, Z., Cui, L., Du, X., Wang, X., Zhang, H., Cong, Z., Hong, N., Zhang, D., 2004. Anterior cingulum abnormalities in male patients with schizophrenia determined through diffusion tensor imaging. Am. J. Psychiatry 161, 573–575.
- Wells 3rd, W.M., Viola, P., Atsumi, H., Nakajima, S., Kikinis, R., 1996. Multimodal volume registration by maximization of mutual information. Med. Image. Anal. 1, 35–51.
- Youn, T., Park, H.J., Kim, J.J., Kim, M.S., Kwon, J.S., 2003. Altered hemispheric asymmetry and positive symptoms in schizophrenia: equivalent current dipole of auditory mismatch negativity. Schizophr. Res. 59, 253–260.

8