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Stochastic Tractography Study of Inferior Frontal Gyrus Anatomical Connectivity in Schizophrenia

Marek Kubicki[a,b], **Jorge L. Alvarado**[a], **Carl-Fredrik Westin**[c], **David F. Tate**[d,e], **Douglas Markant**[a], **Douglas P. Terry**[a], **Thomas J. Whitford**[a,f], **Julien De Siebenthal**[a], **Sylvain Bouix**[a], **Robert W. McCarley**[b], **Ron Kikinis**[g], and **Martha E. Shenton**[a,b,g]

[a] Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[b] Clinical Neuroscience Division, Laboratory of Neuroscience, Boston VA Healthcare System-Brockton Division, Department of Psychiatry, Harvard Medical School, Brockton, MA, USA

[c] Laboratory of Mathematics Imaging, MRI Division, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[d] Departments of Radiology and Psychiatry, Center for Neurological Imaging, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[e] Department of Neurology, Alzheimer's Disease Center, Boston University Medical Center, Boston, MA, USA

[f] Melbourne Neuropsychiatry Centre, University of Melbourne and Melbourne Health, Melbourne, VIC, Australia

[g] Surgical Planning Laboratory, MRI Division, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Abstract

Background—Abnormalities within language-related anatomical structures have been associated with clinical symptoms and with language and memory deficits in schizophrenia. Recent studies suggest disruptions in functional connectivity within the Inferior Frontal Gyrus (IFG) network in schizophrenia. However, due to technical challenges, anatomical connectivity abnormalities within this network and their involvement in clinical and cognitive deficits have not been studied.

Material and Methods—Diffusion and anatomical scans were obtained from 23 chronic schizophrenia patients and 23 matched controls. The IFG was automatically segmented, and its white matter connections extracted and measured with newly-developed stochastic tractography tools. Correlations between anatomical structures and measures of semantic processing were also performed.

Results—White Matter connections between the IFG and posterior brain regions followed two distinct pathways: dorsal and ventral. Both demonstrated left lateralization, but ventral pathway abnormalities were only found in schizophrenia. IFG volumes also showed left lateralization and

Corresponding Author: Marek Kubicki, MD, PhD; Psychiatry Neuroimaging Laboratory; 1249 Boylston Street, Boston, MA 02215; Tel: (617) 525-6234 Fax: (617) 525-6150, kubicki@bwh.harvard.edu.

abnormalities in schizophrenia. Further, despite similar laterality and abnormality patterns, IFG volumes and white matter connectivity were not correlated with each other in either group. Interestingly, measures of semantic processing correlated with white matter connectivity in schizophrenia and with gray matter volumes in controls. Finally, hallucinations were best predicted by both gray matter and white matter measures together.

Conclusions—Our results suggest abnormalities within the ventral IFG network in schizophrenia, with white matter abnormalities better predicting semantic deficits. The lack of a statistical relationship between coexisting gray and white matter deficits might suggest their different origin and the necessity for a multimodal approach in future schizophrenia studies.

Keywords

diffusion tensor imaging; schizophrenia; stochastic tractography; language network; inferior frontal gyrus; fractional anisotropy

1 Introduction

Fronto-temporal connectivity abnormalities have long been postulated as implicated in the etiology of schizophrenia (Kraepelin, 1919/1971; Wernicke, 1906). These ideas have been further fueled by relatively recent studies (McGuire and Frith, 1996; Weinberger et al., 1992) which have framed the disconnectivity hypothesis as explicitly functional in nature, reflecting disease-related abnormalities in communication and coordination of networks of neural regions (Friston and Frith, 1995). As further support for this hypothesis, fMRI studies in schizophrenia point to a reduction in correlated activation in frontal-temporal networks (e.g., Kubicki et al., 2003; Meyer-Lindenberg et al., 2005; Jeong et al., 2009; Lui et al., 2009). More recent studies, fueled in part by post mortem and genetic evidence of myelination abnormalities (e.g., Davis et al., 2003; Segal et al., 2007), are focused on anatomical disconnectivity in schizophrenia. Arguably the strongest evidence in favor of anatomical disconnectivity comes from studies that have used Diffusion Tensor Imaging (DTI), a method sensitive to white matter fiber tract integrity. Since the development of (DTI) (Basser et al., 1994), this method has become the tool of choice in studying brain connectivity in healthy subjects and its disruptions in various neuropsychological diseases.

The overwhelming advantages of DTI over other methods used to study connectivity (such as ERP, MEG, and animal post mortem tractography methods) include its wide availability, noninvasiveness, high spatial resolution, and the fact that it provides visualization capabilities heretofore not possible. Several studies, to date, have investigated white matter connections (tracts) between frontal and temporal cortices (including the Uncinate Fasciculus (UF), Cingulum Bundle (CB); Fornix, Inferior Occipito-Frontal Fasciculus (IOFF) and Arcuate Fasciculus (AF); for recent review of schizophrenia DTI literature, see Kubicki et al., 2007) in schizophrenia, but despite the potential statistical power of these experiments, results still remain inconclusive. Clinical and cognitive correlates of these connections also remain elusive.

Among the anatomical connections of interest in schizophrenia are those relevant to language processing. Of note here, cognitive deficits observed in schizophrenia are frequently associated with language and verbal memory impairments (e.g., Saykin et al., 1991; Saykin et al., 1994; Adams et al., 1993; Kareken et al., 1996; Nestor et al., 1997). Functional studies report abnormal activation in both frontal and temporal regions in schizophrenics during tasks that utilize linguistic stimuli (Heckers et al., 1998; Ragland et al., 2001; Stevens et al., 1998; Yurgelun-Todd et al., 1996). Additionally, hallmark clinical symptoms of schizophrenia, namely hallucinations, delusions, and thought disorder, are also

strongly related to language production and semantic processing (Ceccherini-Nelli et al., 2007; Ford et al., 2002; Han et al., 2007; Lawrie et al., 2002), as well as linked with anatomical abnormalities within both frontal and temporal lobes. Based on these findings, several theories postulate language and its dysfunction as central to schizophrenia psychopathology (e.g., Crow, 1997; Ford et al., 2002). It has been demonstrated that distant brain regions do not work independently, but form functional "networks", where several different regions communicate while performing specific tasks. These networks are interconnected usually by more than one connection, and disruption of one specific tract does not necessary lead to functional deficits, since the other connection might be able play a compensatory role. The fronto-temporal connections involved in language/semantic network are no exception. Recent functional and anatomical studies suggest that two distinct "processing streams" provide communication between two regions that are crucial to speech processing (posterior temporal region of Wernicke and inferior frontal region of Broca). These processing streams, called ventral and dorsal (Duffau, 2008; Haroon et al., 2006; Saur et al., 2008) (see also Figure 1) both contain direct and indirect white matter tracts (AF being the direct dorsal connection, and IOFF forming the direct ventral connection). In addition to direct connections, several studies point to indirect connections between those two regions, that would involve intermediate connections with Geshwind area (Catani et al., 2005; 2007), as well as Uncinate and Inferior/Medial Longitudinal Fasciculi (Mandonnet et al., 2007). Thus anatomical evaluation of the integrity of language/semantic network and its clinical and cognitive correlates should involve modeling and measuring both gray matter volumes as well as white matter connections. When successful, such studies should help to reveal specific roles played by gray and white matter pathology, as well as their synergic effect on clinical and cognitive schizophrenia symptomatology. Thus far, however, studies that combine measurements of gray and white matter integrity within the functionally homogenous regions of the brain are rare likely due to the technical challenges.

More specifically, thus far, most DTI studies investigating specific white matter connections in the brain use the streamline (otherwise called principal diffusion direction) tractography method. This popular method estimates tracts by following the direction of maximal water diffusion of the white matter voxels. Unfortunately streamline tractography does not provide information about the confidence regarding the estimated fiber bundles, thus uncertainty of the generated tracks caused by increased imaging noise (such as diffusion signal within the gray matter) or complex fiber configurations (such as fiber crossings) are not taken into account. Streamline tractography is thus not an optimal tool for studying connectivity between gray matter regions. The stochastic tractography method, introduced recently (Björnemo et al., 2002), is a Bayesian approach that addresses the aforementioned shortcomings of streamline tractography by performing tractography under a probabilistic framework that accounts for uncertainty in diffusion tensor fields. This method uses probabilistic models of imaging noise and fiber architecture to infer the underlying fiber configuration, and, since it explicitly models uncertainty, and does not use any stopping criteria for generating tracts, the method is not limited to generating tracts in regions of low uncertainty/low FA. Consequently, stochastic tractography can track through fiber crossings and be initiated in gray matter, which makes it a perfect tool to model and measure the anatomy of specific functional networks. In addition, certainty of white matter connection measured along the tract can provide additional information regarding the strength of anatomical connectivity between two ROIs (as proposed also recently by Kreher et al., 2008).

In this study, we use stochastic tractography in order to model the direct connections involved in fronto-temporal language/semantic network as well as to detect abnormalities in its integrity and connectivity in schizophrenia. Since such a model should include both gray matter regions as well as white matter connections, we measure gray matter volumes of the

inferior frontal and superior temporal gyri, connections between those two regions (white matter), relationships (correlations) between gray and white matter measurements, and their association with clinical symptoms as well as neuropsychological tests related to semantic processing.

2 Material and Methods

2.1 Subjects

Twenty three patients with chronic schizophrenia were recruited from in-patient, day treatment, out-patient, and foster care programs at the VA Boston Healthcare System, Brockton, MA. DSM-IV diagnoses were based on SCID-P interviews, and information from patient medical records. Twenty three comparison subjects (group-matched to patients on age, sex, handedness (Edinburgh Handedness Inventory), and parental social economic-status (PSES)) were recruited through advertisements in local newspapers, and tested with SCID-NP interviews. All subjects were included in the study if they met the following criteria: ages between 18 and 55 years, no history of neurological illness, no alcohol or drug dependence in the last 5 years and no abuse in the past year, right handedness and an ability and desire to cooperate with the procedures confirmed by written informed consent. Normal comparison subjects were also screened to exclude first degree relative with an Axis I disorder. The study was approved by the local IRB committee at the VA and Brigham and Women's Hospital. All subjects signed informed consent forms prior to study participation. See Table 1 for demographic information.

2.2 Cognitive Testing Procedures

Each study participant was administered a full battery of neuropsychological tests assessing a broad range of cognitive function including attention, executive function, memory, mood, and language. For this particular manuscript, we focus on several tests of language and verbal memory including the vocabulary and comprehension subtests from the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III); verbal paired associates and auditory recognition subtests from the Wechsler Memory Scale-Third Edition (WMS-III); reading and spelling subtests from the Wide Range Achievement Test-Third Edition (WRAT-3); and several measures of language fluency (animal naming, names/fruits, and FAS). All tests were administered and scored according to standard protocols by trained, supervised testers. Age corrected scaled scores for WAIS-III, WMS-III subtests, WRAT-3 and fluency measures were used in the analyses.

2.3 MRI Protocol

DTI data was collected on a 3 Tesla GE Echospeed system (General Electric Medical Systems, Milwaukee, WI). Scans were acquired with an echo planar imaging (EPI) DTI Tensor sequence, and a double echo option to reduce eddy-current related distortions (Alexander et al., 1997; Heid, 2000). To reduce the impact of EPI spatial distortion, an 8 Channel coil and ASSETT (Array Spatial Sensitivity Encoding techniques, GE) with a SENSE-factor (speed-up) of 2 was used. A product GE sequence was modified in order to accommodate for higher spatial resolution required by this study (Spatial-Spectral Pulse was replaced by Fat-Sat suppression pulse, we also decreased echo spacing by 15% to accommodate for more slices per TR). 85 axial slices parallel to the AC-PC line covering the whole brain were acquired in 51 diffusion directions with b=900. Eight baseline scans with b=0 were also acquired. Scan parameters were as follows: TR 17000 ms, TE 78 ms, FOV 24 cm, 144×144 encoding steps, 1.7 mm slice thickness, producing isotropic 1.7×1.7×1.7mm voxels. Total scanning time for DTI sequence was 17 minutes. In addition to DTI scans, a structural MRI acquisition protocol was also used, which includes two MRI pulse sequences. The first results in contiguous spoiled gradient-recalled acquisition

(fastSPGR) with the following parameters; TR=7.4ms, TE=3ms, TI=600, 10 degree flip angle, 25.6cm^2 field of view, matrix=256×256. The voxel dimensions are 1×1×1 mm. The second- XETA (eXtended Echo Train Acquisition) produces a series of contiguous T2-weighted images (TR=2500ms, TE=80ms, 25.6 cm^2 field of view). Voxel dimensions are also 1×1×1 mm. This latter sequence is used as the additional channel of information for brain segmentation.

2.4 Image Processing

2.4.1 ROI—Left and right Inferior Frontal Gyri (IFG) ROIs were extracted using a semiautomatic segmentation method and FreeSurfer software, which is also part of the Slicer3 environment (www.slicer.org). The parcellation process is described elsewhere (Fischl et al., 2004), and has been demonstrated to be reliable and give identical group differences as manual ROI tracing in several large studies (Morey et al., 2009; Shen et al.). In addition to IFG, in order to extract AF and IOFF white matter paths interconnecting IFG with the posterior language areas (Duffau, 2008, and Figure 1), two additional sets of ROIs were also extracted: Superior Temporal Gyrus (STG), which was later used to extract fronto-temporal language connections from other IFG connections (containing both AF and IOFF), and Occipital Lobe (OL), which was used to separate only the IOFF (see Figure 2). After ROI extraction, anatomical scans, along with corresponding ROIs, were co-registered to DTI space using 3D Slicer demon nonlinear registration pipeline.

2.4.2 Stochastic Tractography Generation—Once ROIs were transferred into the DTI space, stochastic tractography was performed (using freely available module, part of 3D Slicer software) to generate white matter connections. Tracts were seeded first in the IFG, and filtered through STG (Figure 3). Because IFG-STG connections were following two distinct fiber paths (ventral and dorsal), in order to separate out only the IOFF, the same procedure was performed again, but this time tracts were filtered through the OL ROI (Figure 4). The following parameters were used for stochastic tractography generation: three thousand seeds were placed in each voxel (this was determined after parametric simulation, where standard deviations of mean FA were compared across 5 subjects for 10 different seeding densities, with seed densities above 3000 seeds per voxel, significant increase of computational load (and time necessary for finishing the analysis) was not accompanied by SD FA decrease). No stopping criteria for tractography were used. As the initial output of stochastic tractography, we obtained a map of probability of connection based on the number of tracts per voxel divided by the total number of tracts generated. The probability map was subsequently thresholded at 10% (which was found optimal to remove artifacts due to noise (Powell et al., 2006)) and mean FA within each tract created this way was calculated.

2.5 Data Analysis

Relative volumes of regions of interest as well as mean FA for each of the connections and the volumes of the probability cloud after 10% probability threshold were recorded and subjected to quantitative analysis. We used random effect ANOVAs separately for each tract and volume, where diagnosis served as a between subject dependent variable, and side as a within subject factor. Pearson correlations were used to investigate the relationship between subjects' ROI volumes and connectivity measures and their a) cognitive performance (quantified by their neuropsychological test scores, as described previously), and b) clinical profile (quantified by their scores on the PANNS subscales). Given their proposed relationship with semantic processing, linear regression analyses were used to predict patients' scores on the hallucinations and delusions subscales of the PANNS, with all ROI volumes and connectivity measures entered as predictor variables.

3 Results

3.1 Demographic Data

Groups did not differ in age at the time of scan ($P_{(1,44)}$=0.236, t=−1.20), in handedness ($P_{(1,44)}$=0.99, t=−0.002) nor in gender (all males). Schizophrenics, similar to our previous investigations, had fewer years of education and lower SES than controls, but had comparable PSES with controls ($P_{(1,44)}$=0.48, t=−0.71). In addition, premorbid intelligence, tested using WRAT reading raw scores, showed no group differences ($P_{(1,44)}$=0.21, t=1.28). Schizophrenics had a mean duration of illness of 16.2 years, and all were medicated at the time of scan, with a mean Chlorpromazine Equivalent (CPZ) equivalent of 454 mg per day. (Stoll, 2001)

3.2 Volumetric Analysis

Volumes of IFG demonstrated a group effect ($F_{(1,44)}$=6.91, p=0.012), no side effect ($F_{(1,44)}$=1.64, p=0.21), and side x group interaction ($F_{(1,44)}$=4.55, p=0.039). Post hoc t-tests revealed a volume decrease in schizophrenics on the left side ($P_{(1,44)}$=0.01, t=3.51). Volumes of STG demonstrated no group effect ($F_{(1,44)}$=0.85, p=0.36), no side x group interaction ($F_{(1,44)}$=0.20, p=0.89), and no side effect ($F_{(1,44)}$=0.21, p=0.65). Volumes of Occipital Lobe (OL) demonstrated no group effect ($F_{(1,44)}$=0.78, p=0.38), no side x group interaction ($F_{(1,44)}$=0.79, p=0.38), and a side effect ($F_{(1,44)}$=25.42, p<0.001). Post hoc paired sample t-tests revealed left greater than right asymmetry in both groups ($P_{(1,45)}$<0.001, t=5.05).

3.3 Connectivity Analysis

IFG to STG total connectivity demonstrated a non-significant trend group effect ($F_{(1,44)}$=3.55, P=0.066), no side x group interaction ($F_{(1,44)}$=0.56, p=0.46), and a side effect ($F_{(1,44)}$=7.00, p=0.011). Post hoc paired sample t-test revealed left greater than right asymmetry in both groups ($P_{(1,45)}$=0.011, t=2.66). IOFF connectivity demonstrated a significant group effect ($F_{(1,44)}$=4.31, p=0.044), no side x group interaction ($F_{(1,44)}$=0.38, p=0.85), and a side effect ($F_{(1,44)}$=6.14, p=0.017). Post hoc paired sample t-tests revealed left greater than right asymmetry in both groups ($P_{(1,45)}$=0.016, t=2.50), and independent t-tests revealed a significant FA decrease on the left ($P_{(1,44)}$=0.042, t=2.10), and non-significant differences on the right ($P_{(1,44)}$=0.068, t=1.87) in patients compared with controls. Additionally, since volumes of seeding ROIs were significantly different between groups, volumes of the probability clouds were compared between groups in order to ensure that the connectivity group differences were not driven by the gray matter ROI volume differences. There were no significant differences between groups in volumes of connectivity clouds either for total IFG to STG connectivity (left: $P_{(1,44)}$=0.250, t=1.17; right: $P_{(1,44)}$=0.189, t=1.34), or IOFF connectivity (left: $P_{(1,44)}$=0.110, t=1.65; right: $P_{(1,44)}$=0.484, t=0.71),

3.4 Correlations

We did not observe any correlations between ROI volumes and connectivity measures for any connection in either group. We also did not see any correlations between connectivity measures and medication in schizophrenia group. Connectivity measures, as well as ROI volumes, however, did demonstrate interesting correlations with clinical as well as cognitive measures related to semantic processing. In control subjects, significant correlations were apparent between several neuropsychological measures (including auditory immediate, auditory recognition delayed, verbal pair associates, auditory recognition delayed scaled, and fluency, see Table 2 for more details) and gray matter volumes. In contrast, schizophrenics demonstrated significant correlations between most of the same

neuropsychological measures and the connectivity metrics from the tractography (i.e.., as opposed to volumetric measures) (see Table 2 for more details and correlation coefficients). Finally, none of the anatomical measures separately correlated with the clinical symptoms of schizophrenia, as measured with the PANNS subscale. However, a linear regression model that included all of the measures- gray matter volumes of STG and IFG as well as connectivity between them- was significantly predictive of hallucinations ($F=4.44$; $P=0.010$), and close to significance for delusions ($F=2.42$; $P=0.081$).

4 Discussion

Our results demonstrate reduced integrity in several anatomical structures involved in semantic processing in schizophrenia. These structures include left IFG gray matter, as well as white matter connections traveling through the temporal stem and connecting the IFG and STG. Interestingly, while gray matter integrity correlated with several cognitive measures of semantic processing in healthy subjects, the same cognitive measures in schizophrenics correlated with white matter integrity rather than gray matter volumes. Also of interest, co-existing, but not correlated, measures of gray and white matter integrity disruptions in schizophrenia described together, but not separately, clinical symptoms such as auditory hallucinations and delusions.

Gray matter deficits alone within both the IFG and STG have been described in previous imaging studies involving first episode (Hirayasu et al., 1998; Kubicki et al., 2002) and chronic (Yamasue et al., 2004) subjects, as well as in post mortem studies (Vogeley et al., 1998) of patients with schizophrenia (see also review in McCarley et al., 1999 and Shenton et al., 2001). White matter abnormalities involving the Arcuate Fasciculus, which is still believed to be the major language pathway, have also been reported in DTI studies involving patients with schizophrenia (Douaud et al., 2007; Hubl et al., 2004; Kubicki et al., 2005). The majority of these studies, however, have been performed with analytic techniques involving a whole brain voxel based morphometry, a method demonstrated to be heavily sensitive to different imaging and post-processing parameters. In addition, even though a voxel based approach is capable of investigating all white matter structures at once, the nature of the analysis (voxel based rather than tract based) precludes the results from being specific to any single anatomical connection. Only a handful of studies have used streamline tractography as a method of extracting and measuring language related WM structures in schizophrenia (Ashtari et al., 2007; Jones et al., 2006; Phillips et al., 2009). While this method is much more anatomically specific, by being capable of measuring a single fiber tract, it is still limited to large fiber bundles, and cannot be initiated in gray matter, thus no true connections can be generated and measured. Because of these methodological limitations, results of previous investigations are still equivocal, and no clear, replicable evidence of neuropsychological correlates have been demonstrated.

Our approach to DTI analysis, where we used gray matter IFG region as seeding ROIs, and STG and OL as filtering ROIs (STG was used to define anatomical location of posterior language region following Haroon et al., 2006), enabled us to extract all fiber bundles directly participating in communication between these gray matter regions. This operation resulted in generating a “connectivity” path that traveled by two distinct pathways, confirming Duffau’s ventral and dorsal semantic processing streams theory (Duffau, 2008; Mandonnet et al., 2007). “Connectivity” maps obtained in our analysis are similar to known anatomy of the Arcuate Fasciculus (dorsal path) and Inferior Occipito-Frontal Fasciculus (ventral path). Since it has been demonstrated that these direct connections are crucial for language processing (lesions within the AF cause conduction aphasia, while stimulation of IOFF causes paraphasia), modeling volumetric abnormalities within the IFG and STG along with abnormalities within their anatomical connectivity, the latter generated using stochastic

tractography, can be used to characterize and to closely monitor disruptions in the semantic network in schizophrenia.

Gray as well as white matter asymmetries observed in our study within the semantic network confirm the dominant role of the left hemisphere in language generation and semantic processing (Binder et al., 1997; Geschwind and Levitsky, 1968; Glasser and Rilling, 2008; Josse et al., 2009). More specifically, our study reveals left>right asymmetry within the gray matter (IFG) and white matter IFG connections in healthy controls. A similar finding of left>right asymmetry expressed in both fMRI semantic related signal, as well as integrity of superior longitudinal fasciculus that connects language related frontal and temporal lobes, has been described in one study of 10 healthy controls subjects (Powell et al., 2006). This asymmetry pattern, further investigated using DTI and tractography in (Catani et al., 2005; 2007), was in later publication studied in relationship with cognitive performance of verbal recall. Results of this study indicated that lateralization, at least for language pathways involved in dorsal stream, even though present in more than half of the population, might not be optimal for specific cognitive functions (Catani et al., 2007). These asymmetries observed by us and by others in healthy controls, are not, however, entirely preserved in the schizophrenia population. More specifically, gray matter asymmetries are lost in schizophrenics (due to the excessive left sided gray matter reduction), while white matter asymmetries observed in controls are preserved also in schizophrenia (even though significant connectivity reductions are observed only on the left side). While loss of cortical brain asymmetry has been previously hypothesized to be related to neurodevelopmental changes (torque) and language deficits observed in schizophrenia (Crow, 1998), preserved WM asymmetries observed in our study might suggest distinct and a more locally and functionally specific nature of WM pathology.

Cognitive and clinical correlations with MRI data also reveal interesting relationships and further confirm the distinct nature and functional dissociations of white and gray matter deficits. Specifically, even though measures of semantic processing were correlated positively and significantly with volumes of gray matter regions in healthy subjects, the same measures did not correlate with volumes in schizophrenics, but rather with their white matter connectivity. This relationship might suggest that the white matter disruptions impact cognition more than volume reductions in schizophrenic patients. It also suggests (along with the fact that these two pathologies do not correlate with each other in our data) their different origin. One plausible explanation of such dichotomy is that while gray matter volume reductions observed in schizophrenia might be related to late neurodevelopmental abnormalities such as abnormal (excessive) synaptic pruning (Keshavan, 1999; Keshavan et al., 1994), white matter abnormalities observed in DTI studies could be related more to microstructural abnormalities affecting myelinated axons (Davis et al., 2003). If this was the case, the fact that these two pathologies together describe auditory hallucinations and delusions better than each of them separately is even more interesting. Speculating on the nature of these pathologies, one might hypothesize underlying neurodevelopmental gray matter abnormalities (torque theory - Crow, 1998) that might constitute a risk factor, and late myelinating white matter abnormalities (Benes, 2003; Benes et al., 1994) might be the added anomaly needed to trigger the clinical symptoms of schizophrenia (Bayer et al., 1999).

Our study is not free from limitations. We studied here only chronically ill male patients with schizophrenia, and medication and aging effects (even though groups were matched on age and medication did not correlate with any measures) might still play a role (especially in white matter pathology). Regarding gray matter findings, our results do not indicate abnormalities within the left STG in schizophrenia, even though the majority of previous ROI studies described such abnormalities (see Shenton et al., 2001). We used automatic free

surfer parcellation method, and although demonstrated previously to be as equally sensitive to group differences as manual ROI drawing methods (Shen et al., 2010), discrepancies between those two methods might still arise from differences in ROI definitions between manual and automatic segmentation. In addition, Heschl's gyrus, the most frequently reported STG region related to schizophrenia that contains the functional language area of Wernicke, might be a better candidate for our ROI masking. Such labels, however, appeared too small, and led to exclusions of many probabilistic connections between frontal and temporal ROIs, mostly due to the fact that gray, not white matter ROIs were used. Thus we elected to use larger, less functionally specific ROIs. Similar approach has been used by others (Haroon et al., 2006), where authors demonstrated that the entire STG can be successfully used to detect direct white matter connections related to language processing. As to white matter abnormalities described here, since the specificity of FA measurements to any particular micro or macrostructural pathology is not known, it is not clear if measures of FA are capable of measuring myelination related "connectivity" per se, or whether such measurements merely reflect differences in brain geometry (which was suggested recently by Buchsbaum et al., 2006 and by Gilmore et al., 2007). Further, since our study involved only strongly right handed subjects, it is possible that asymmetries and their abnormalities observed in our study might be related to handedness, and are specific only to right handed subjects. Future studies are thus needed to understand better the nature, anatomy, and time course of white matter abnormalities in schizophrenia. Our current results, however, strongly suggest that these studies should combine white as well as gray matter measures.

5 Conclusions

Using high resolution DTI data and stochastic tractography techniques, we were able to map anatomical connections between the IFG and STG, and to measure them in chronic schizophrenia. Our results suggest abnormalities within the ventral processing stream in schizophrenia, further suggesting that, while volume of gray matter structures may predict semantic abilities, white matter abnormalities better predict cognitive deficits in this domain in schizophrenia. Even though gray and white matter deficits coexist in schizophrenia, they do not seem to be related to each other, and only their combination explains clinical psychotic symptoms such as hallucinations and delusions. These findings further emphasize the importance of investigating functional networks rather than individual anatomical structures, as well as their role in the psychopathology of schizophrenia.

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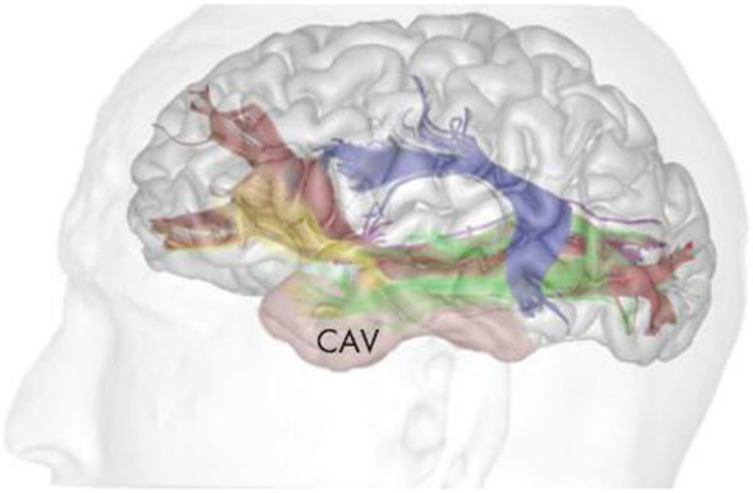

Figure 1.
Model of language networks proposed by Mandonnet (2007) and Duffau (2008), involving dorsal (arcuate fasciculus, blue) and ventral (IOFF, red) processing streams

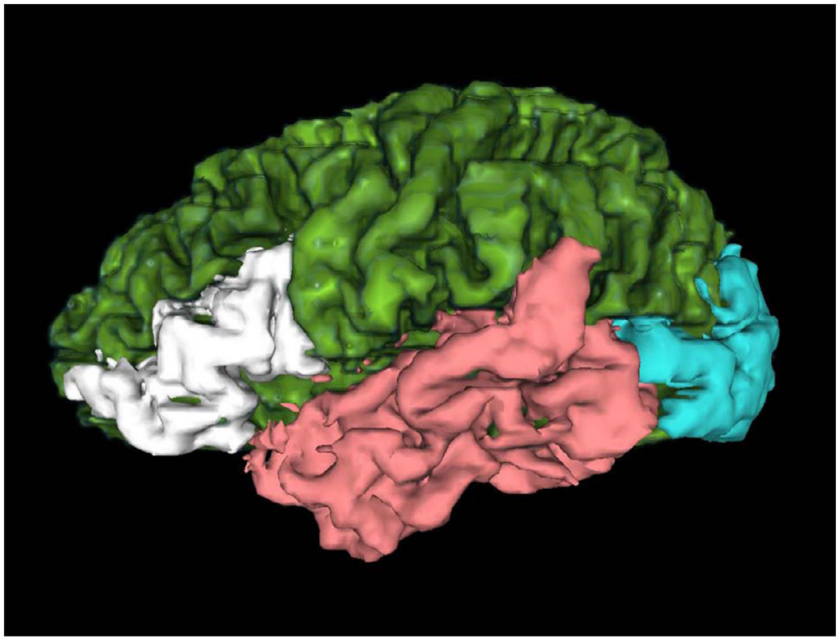

Figure 2.
Automatically extracted ROIs of the IFG (white), STG (pink), and the occipital lobe (teal).

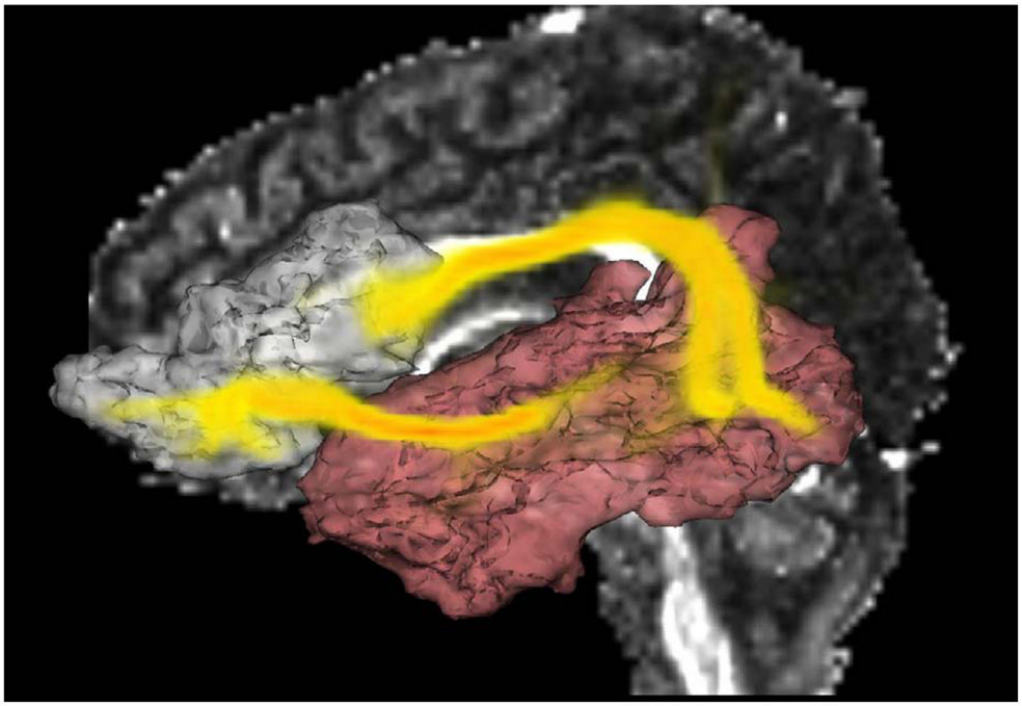

Figure 3.
Connections extracted by stochastic tractography between IFG (white) and STG (pink), overlaid on FA map.

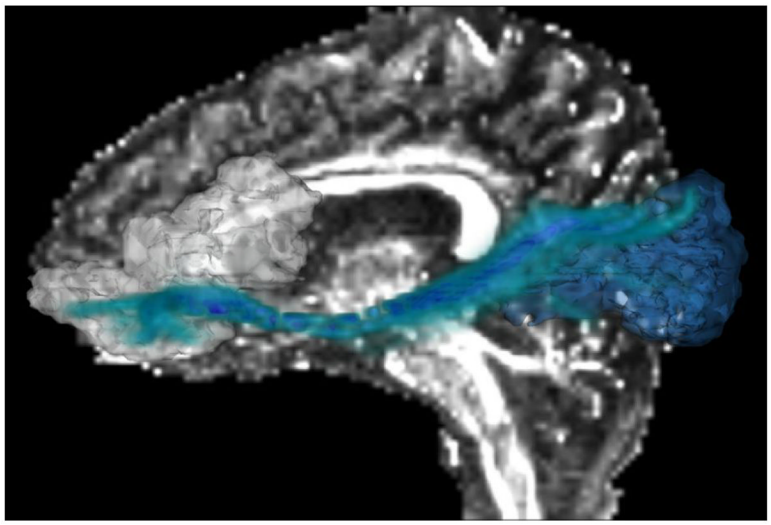

Figure 4.
Connections extracted by stochastic tractography between IFG and occipital lobe (blue), overlaid on FA map.

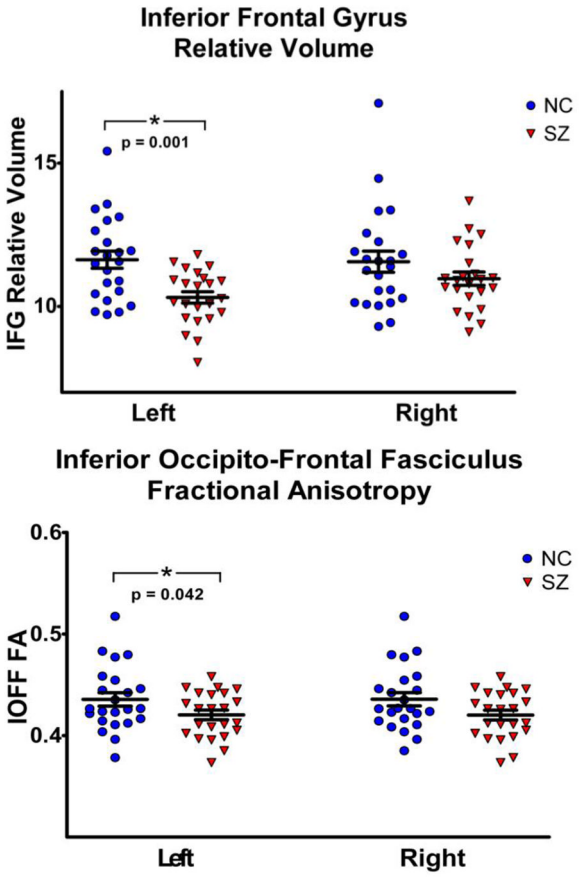

Figure 5.
Significant results of group comparison.