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Relationships between Diffusion Tensor Imaging and Resting State Functional Connectivity in Patients with Schizophrenia and Healthy Controls: A Preliminary Study

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Abstract: Schizophrenia is widely seen as a disorder of dysconnectivity. Neuroimaging studies have examined both structural and functional connectivity in the disorder, but these modalities have rarely been integrated directly. We scanned 29 patients with schizophrenia and 25 healthy control subjects and acquired resting state fMRI and diffusion tensor imaging. The Functional and Tractographic Connectivity Analysis Toolbox (FATCAT) was used to estimate functional and structural connectivity of the default mode network. Correlations between modalities were investigated, and multimodal connectivity scores (MCS) were created using principal components analysis. Nine of 28 possible region pairs showed consistent (>80%) tracts across participants. Correlations between modalities were found among those with schizophrenia for the prefrontal cortex, posterior cingulate, and lateral temporal lobes with frontal and parietal regions, consistent with frontotemporoparietal network involvement in the disorder. In patients, MCS values correlated with several aspects of the Positive and Negative Syndrome Scale, positively with those involving inwardly directed psychopathology, and negatively with those involving external psychopathology. In this preliminary sample, we found FATCAT to be a useful toolbox to directly integrate and examine connectivity between imaging modalities. A consideration of conjoint structural and functional connectivity can provide important information about the network mechanisms of schizophrenia.

Keywords: DTI; resting state; schizophrenia; FATCAT; tractography

1. Introduction

Schizophrenia (SZ) is increasingly thought to be a disorder of brain dysconnectivity [1,2]. This idea is supported by MRI studies showing reduced white matter organization using diffusion tensor imaging (DTI) and from other studies showing abnormal resting state functional connectivity (RSFC) in SZ compared to healthy controls. Many of these abnormalities are widespread throughout the brain, including between hemispheres, and are correlated with behavioral and psychophysiological deficits seen in the disorder, suggesting that they have clinical significance.

DTI [3] examines the self-diffusion of water. When boundaries to such diffusion are present, such as axonal membranes and myelin, this diffusion becomes directional...
(anisotropic). Fractional anisotropy (FA) is the most common measure of such anisotropy, and lower FA has typically been seen as indicative of less organized white matter. DTI has been extended to tractography [4–6], which can be used to estimate pathways of the brain based on the orientation of the diffusion tensor(s).

Studies have consistently observed abnormalities in FA associated with schizophrenia [7–10]. These abnormalities have been related to visual [11,12] and auditory [13] processing deficits, poor cognitive task performance [14], and psychiatric symptoms [15–17]. These abnormalities are present at first episode [18] and in those at high clinical risk [19–21], and show heritability [22]. Thus, white matter abnormalities are present in schizophrenia and have clinical relevance.

Abnormalities in RSFC in SZ have been demonstrated in numerous brain networks [23–26], including the limbic network, dorsal and ventral attention networks, and the default mode network (DMN). These network abnormalities have been related to many clinical phenomena, including symptomatology [27–30], cognition [31], sensory phenomena [32], and aggression or poor impulse control [33,34]. The DMN, in particular, is a set of regions including the medial prefrontal cortex, the posterior cingulate/precuneus, left and right hippocampal regions, and the left and right inferior parietal regions [35,36]. This network shows heightened activity and functional connectivity during rest and during self-referential mental activity [36] and is suppressed during cognitive challenges [37]. The DMN is abnormal in schizophrenia [38–40], and abnormalities in parts of the DMN are related to symptoms [41] and deficits [39] in the disorder. As with FA, RSFC abnormalities are seen in first episode schizophrenia [42–44] and those at risk [45]. They also show heritability [46].

It has been suggested that RSFC might be related to underlying white matter connectivity [47]. Thus, regions that show RSFC might be connected by fiber tracts, such that the low frequency fluctuations are mediated by physical brain tracts. If they are uncorrelated, the RSFC might be driven by a third region or the RSFC could be mediated by neurovascular coupling rather than structural connectivity. The reverse is also possible. In that case, there may be structural connectivity between regions that show RSFC in a frequency range that cannot be interrogated using BOLD fMRI.

The literature on direct relationships between structural and functional connectivity is limited. Uddin et al. [48] found preserved interhemispheric RSFC in a split-brain patient. In 2009, Greicius et al. [47] demonstrated tracts between brain regions that are nodes of the default mode network, suggesting coupling between functional and structural connectivity at a population level. Honey et al. [49] directly examined relationships between the two modalities. They found that in many cases, despite high RSFC, the measures were unrelated. They also found that indirect connections and interregional distance had some explanatory power regarding the RSFC. Other studies in healthy samples and populations with medical illness have used summary measures of structural-functional connectivity across the whole brain [50,51] or across neural networks (e.g., DMN, salience network) [52], rather than within ROI pairs comprising a network.

Very few studies have evaluated the correspondence between structural and RSFC in SZ. In a study comparing chronic and first episode patients with SZ, Kong et al. [53] found that coupling between RSFC and brain structure (in this case, gray matter volume) was higher in the former than the latter. Moreover, such coupling was lower in first episode patients than in healthy controls. Finally, coupling strength was positively correlated with PANSS negative system scores. Another study estimated a global metric of whole-brain structural-functional coupling, as well as intra- and interhemispheric connectivity metrics and estimates corresponding to fiber length (e.g., short, intermediate, and long fibers). Compared to healthy controls, offspring of parents diagnosed with SZ demonstrated increased structural-functional coupling in long-range fibers [54]. Further examination of structural and functional connectivity dynamics, particularly within networks implicated in SZ such as the DMN, could generate new insights into the network mechanisms of SZ.
Recently, general-use programs have been developed to simultaneously estimate RSFC and tractography between elements of brain networks. Among these is the Functional and Tractographic Connectivity Toolbox (FATCAT; [55]). A few articles using this method in psychiatric disorders have been published (e.g., prenatal alcohol exposure [56] and major depressive disorder [57]), but we are aware of none in SZ. Moreover, we are aware of no studies directly correlating structural and RSFC measures in the same region pairs within the DMN. An understanding of the structural basis of DMN RSFC abnormalities in SZ might prove informative about the neural basis of the disorder.

Here, we apply FATCAT to RSFC and DTI data for homologous region pairs (i.e., the same pairs of regions) in the DMN in a proof-of-concept study of patients with SZ and healthy comparison subjects. We hypothesized that RSFC would be correlated with diffusion tensor parameters differentially between groups and that in patients, structural-functional coupling would be related to psychiatric symptoms.

2. Materials and Methods

Subjects

Participants were 33 patients with schizophrenia or schizoaffective disorder, and 31 healthy comparison participants. Of the 64 participants, 3 showed excessive motion artifact in the RSFC data, and 7 showed excessive artifact in both the DTI and RSFC data. The final sample was 29 patients and 25 healthy comparison subjects. Diagnosis was confirmed by the SCID for DSM-IV-TR. None of the participants had substance use disorders within the past 6 months, and current abstinence was verified by urine toxicology screen for outpatients and healthy comparison participants. Inpatients were presumed to be abstinent. Informed consent was obtained from all subjects involved in the study, The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Nathan Kline Institute. Resting state data (processed differently than herein) have been previously published [32,34,58–63].

Psychiatric symptoms were rated using the Positive and Negative Syndrome Scale (PANSS; [64]), which was available for 21 patients. Scores were derived for the White et al. [65] 5 Factor Model, which included Positive, Negative, Dysphoric Mood, Activation, and Autistic Preoccupation scores, with higher scores reflecting greater severity.

MRI Acquisition

MRIs were acquired at the Center for Biomedical Imaging and Neuromodulation at the Nathan Kline Institute using a 3T Siemens TiM Trio (Erlangen, Germany). Resting state data were acquired using an echo-planar sequence (TR = 2000 ms, TE = 30 ms, matrix = 96x96, FOV = 240 mm, 34 3.5-mm slices NEX = 180, GRAPPA = 2). DTI was acquired using a twice-refocused spin echo sequence (TR = 9000 ms, TE = 84 ms, matrix = 128x128, FOV = 256mm, 72 2-mm slices, 30 diffusion weighted images (b = 800 s/mm²), 7 images with b = 0 s/mm², GRAPPA = 2; [66]). A T1-weighted anatomical image was acquired (MPRAGE; TR = 2500 ms, TE = 3.5ms, TI = 1200 ms, matrix = 256x256, FOV = 256 mm, 192 1-mm slices). A field map was acquired to correct distortion in the resting state data (TR = 500 ms, TE = 4.92/7.38 ms, matrix = 96x96, FOV = 240 mm, 34 3.5-mm slice).

Default Mode Network

The default mode network was extracted from the Yeo 7-network “liberal” template [67], downloaded from https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation_Yeo2011. This template was registered using an affine based nearest neighbor interpolation to the final resolution for all images. The network had 8 nodes (see inset Figure 1). These were isolated into separate regions using AFNI’s 3dClusterize command. For tractography, these nodes were inflated up to the gray matter/white matter boundary using an FA threshold of 0.2.

DTI
DTI were processed using FATCAT’s routines. First, images were converted to NIFTI format. Then slices and volumes with artifacts were automatically removed with 3dZipperZapper, which identifies intravolume intensity variations and/or signal dropouts that are typical with high degrees of motion. This resulted in the exclusion of 2 participants (referred to in Subjects above) who had fewer than 65% of volumes retained after this step. Data were eddy current and motion corrected and matched to a pseudo T2-weighted image that was created from the T1-weighted image and put into axial space by matching it to a T2-weighted standard image in ICBM 152 nonlinear symmetric atlas space (available at http://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152NLin2009) using TORTOISE, v. 3.14 [68]. A weighting mask was used to address issues of low signal in subcortical regions (available from the same website). TORTOISE’s outputs were in 1.5mm³ ICBM space.

Susceptibility-based distortions were then corrected using ANTs software [69]. In particular, the first $b=0$ image was registered to the imitation T2 image, which had been resampled to the 1.5mm³ resolution of the TORTOISE output. The transformation matrix was applied to the rest of the images in the DTI acquisition. Next, tensors were estimated using a nonlinear algorithm, along with eigenvalues, eigenvectors, and uncertainty distributions. Finally, tractography was computed using AFNI’s MINI protocol [70] with a resampling of 9 and an FA threshold of 0.2, using “AND” logic (i.e., tracts had to connect both ROIs) and a bundle size of ≥10 streamlines. For 9 of the 28 ROI pairs, at least 80% of subjects showed tracts meeting these criteria (see Table S2-S3). Pairwise tracts were computed within the network. For each tract, FA and number of streamlines (NS) were estimated. From these, a connectome was generated for each participant and for each parameter. Statistical outliers (25-75%ile IQR ± 1.5 SD) were then removed for each variable. FA and NS were extracted and used in further analysis.

RSFC

Resting state functional connectivity was examined using AFNI [71], FSL [72], and ANTS [69]. Prior to processing, the first 5 volumes were removed. Images were then motion-corrected, distortion-corrected using a field map, and smoothed with a 4mm Gaussian kernel using FSL. We then used FSL’s ICA AROMA program [73] to remove motion and other artifacts. For interscan registration, the mean smoothed image was affine registered to the 1.5mm³ resolution pseudo T2 image using ANTS, and the transformation matrix was applied to the denoised time series data, again using ANTS. The T1 image was segmented and used as regressors using AFNI’s anaticor algorithm [74]. White matter masks were eroded, and their time courses were extracted. Motion parameters from FSL were converted to AFNI’s format using code available at https://github.com/FCP-INDI/CPAC/blob/master/CPAC/func_preproc/func_preproc.py#L237-L256. Volumes with framewise displacement values of 0.5 were censored from the analyses, as was the preceding volume, with motion parameters and the white matter signal time course as additional nuisance covariates, and data were filtered at 0.01 to 0.1 Hz. Nuisance covariates were removed using 3dTproject.

From these images, the time series for each node of the DMN were extracted for use in RSFC computation. The resulting values were converted to Z-scores to improve normality of distributions, which we denoted as RSFC(Z). From this, a connectome was generated for each participant. Pairwise values were extracted for further analyses.

Multimodal Connectivity Scores (MCS)

For region pairs that showed correlations across modalities among participants with SZ or healthy controls, we entered the data into principal components analyses, separately for patients and controls, and separately for FA and NS DTI variates. We termed the first component scores as multimodal connectivity scores (MCS).

Statistical analyses
Group differences for FA, NS, and FC were examined across regions using MANO-VAs with follow-up t-tests. Because there were not tracts between every region pair for every subject, the number varied across elements of the DMN connectome, and thus, sample sizes are indicated for each correlation.

Parameter pairs that showed significant correlations in participants with SZ or healthy controls were examined for between-group differences in correlations. In addition, we examined the relationship between MCS and PANSS symptoms in correlational analysis. Tracts and RSFC(Z) were rendered in SUMA [75,76] for visualization.

3. Results

Demographics

Demographic data for patients and controls are shown in Table 1.

Table 1. Demographic data for the sample.

| Variable       | Patients | Controls | t/χ² | p   |
|----------------|----------|----------|------|-----|
| Age (years)    | 38.8     | 38.2     | -0.22| 0.83|
| Sex (M/F)      | 2/3/6    | 17/8     | 0.48 | 0.48|
| PANSS Positive | 12.2     | --       | --   | --  |
| PANSS Negative | 16.1     | --       | --   | --  |
| PANSS Activation | 9.4   | --      | --   | --  |
| PANSS Dysphoric | 11.8    | --      | --   | --  |
| PANSS Total    | 76.3     | --      | --   | --  |
| Total CPZ equiv | 1196.7  | 800.8    | --   | --  |

Note: PANSS = Positive and Negative Syndrome Scale, CPZ equiv = chlorpromazine equivalents.

Representative connectomes and images for modal participants are shown in Figure 1. Groupwise tracts and RSFC patterns are shown in Figure 2. Groupwise FA, NS, and RSFC(Z) are shown in Tables S1-S3.

Figure 1. A) FA for ROI-to-ROI tracts, B) Number of tracts for ROI-to-ROI pairings, C) resting state functional connectivity connectomes for the default mode network of a representative participant.
D) Brain surface map showing RSFC (yellow-blue color scheme) and superimposed tract (in green) for cingulate nodes of the DMN projected onto the left medial surface of the brain in a representative subject. Labels for regions of interest are: LLTL = left lateral temporal lobe, LPHP = left parahippocampal gyrus, PCC = posterior cingulate cortex, PFC = prefrontal cortex, RIPL = right inferior parietal lobule RLOFC = right lateral orbitofrontal cortex. RLTL= right lateral temporal lobe, RPHP = right parahippocampal gyrus.

Figure 2. Representative data from a study participant. Left) mean tract connecting PFC and LLTL for controls, Middle) mean tract connecting PFC and PCC for controls, and Right) Functional connectivity map of the DMN in the sample from PFC seed thresholded at Z = 0.4. Abbreviations are as in Figure 1.

For RSFC(Z), the Group effect was highly significant (Wilk’s lambda = 0.60, \( F_{[9,44]} = 2.93, p = .008 \), partial \( \eta^2 = .37 \)). Univariate tests showed that RSFC(Z) was significantly higher for patients than controls in the PFC/LLTL region pair LLTL (\( F_{[1,36]} = 8.13, p = .008 \), partial \( \eta^2 = .14 \)).

For NS, the multivariate F test was significant (Wilk’s lambda = 0.56, \( F_{[9,28]} = 2.50, p = .031 \), partial \( \eta^2 = .44 \)). Univariate tests showed that NS was higher for controls than patients between the PFC and LLTL (\( F_{[1,36]} = 12.74, p = .001 \), partial \( \eta^2 = .26 \)). For FA, however, the multivariate F test was not significant (Wilk’s lambda = .78, \( F_{[9,28]} = 0.88, p = .55 \)).

**DTI/RSFC(Z) values and correlations**

**FA.** Correlations between FA and RSFC(Z) for region pairs are shown in Table S4. For the RLTL/RLOFC pair, FA correlated negatively with RSFC(Z) in patients (\( r_{29} = -.38, p = .04 \)) and differed significantly from controls (\( r_{23} = .22, p = .31, t_{[48]} = -2.10, p = .018 \)). For controls, FA correlated positively with RSFC in the LLTL/LPHP pair (\( r_{17} = .54, p = .039 \)). For patients, FA correlated positively with RSFC in the LLTL/LPHP pair (\( r_{17} = .54, p = .039 \)), and the PCC/LPHP pair (\( r_{23} = .46, p = .029 \)). The correlation for the PFC/RLTL pair was greater in patients (\( r_{23} = .48, p = .012 \)) than controls (\( r_{23} = - .34, p = .12, t_{[48]} = 2.90, p = .002 \)). Similarly, the correlation for the PFC/RLTL pair was greater in patients (\( r_{23} = .48, p = .021 \)) than controls (\( r_{23} = .097, p = .68 \)) at a trend level (\( t_{[48]} = 1.31, p = .095 \)). The correlations for the PCC/RLOFC were significant in patients only (\( r_{17} = .58, p = .014 \)).

**NS.** Correlations between NS and RSFC for region pairs are presented in Table S5. Correlations for the PFC/PCC pair were significantly higher in patients (\( r_{27} = .48, p = .012 \)) than controls (\( r_{23} = -.34, p = .12, t_{[48]} = 2.90, p = .002 \)). Similarly, the correlation for the PFC/RLTL pair was greater in patients (\( r_{23} = .48, p = .021 \)) than controls (\( r_{23} = .097, p = .68 \)) at a trend level (\( t_{[48]} = 1.31, p = .095 \)). The correlations for the PCC/RLOFC were significant in patients only (\( r_{17} = .58, p = .014 \)).

Correlations between NS and RSFC(Z) were also significant for patients but not controls for the RLTL/RLOFC pair (\( r_{29} = -.42, p = .02; r_{23} = - .19, p = .39 \)), the latter being the only significant negative correlation in patients. Of note, none of these correlations were significant in controls. Selected scatter plots are shown in Figure 3.
Figure 3. Scatterplots for: A): Left) FA and RSFC for RTL/RIPL, and Right) PCC/LHP for patients with schizophrenia and controls. B): Left) Number of streamlines (NS) and RSFC for PFC/LLTL and Right) PCC/RLOFC. Abbreviations are as in Figure 1.

MCS

Principal component scores and eigenvalues are shown in Table S6. We examined relationships between MCS and clinical variables in correlational analyses among participants with SZ.

FA. PANSS total scores correlated negatively with MCS scores for the RLTL/RLOFC pair ($r_{20} = -.51$, $p = .021$). In addition, PANSS Activation scores correlated positively with MCS scores for the PCC/LPHP pair ($r_{21} = .43$, $p = .044$). Finally, PANSS Autism scores correlated negatively with MCS scores for the RLTL/RLOFC pair ($r_{20} = -.46$, $p = .042$).

NS. PANSS Positive scores correlated negatively with MCS scores for the PFC/LLTL pair ($r_{19} = -.54$, $p = .017$) and the PFC/PCC pair ($r_{20} = -.46$, $p = .041$). In addition, PANSS Activation scores correlated negatively with MCS scores for the RLTL/RIPL pair ($r_{21} = -.69$, $p < .001$) but positively with the PCC/RPHP pair ($r_{20} = .46$, $p = .042$). Note that the variables that comprise the RLTL/RIPL factor load negatively with respect to each other, so that a negative correlation means that higher levels of cross-modal connectivity are reflective of higher PANSS Activation scores.

4. Discussion

In this study, we examined the relationship between resting state functional connectivity and structural connectivity in the DMN in patients with SZ and healthy controls using the same ROI pairs in the same anatomical space. In general, data from the two modalities were not correlated, but those that were correlated involved connections of the PFC, PCC, and lateral temporal lobes with frontal and parietal regions. This is consistent with well-known frontotemporoparietal network dysfunction in SZ [77]. Moreover, MCS relationships correlated with psychiatric symptoms in patients, suggesting that this approach has clinical significance in SZ. In addition to the methodological advantages of this truly multimodal approach, the results have important implications for neuropathology and clinical outcomes.

In particular, the results suggest that there is no imperative link between structural and functional connectivity for a given region pair within the DMN. This is consistent with several previous studies showing that the correspondence between structural and
Functional connectivity profiles vary across neural networks. Specifically, in healthy adult samples, strong coupling is observed in primary sensory areas, while there is significant divergence between structure and function in the DMN [78,79]. Thus, low frequency oscillations between disparate region pairs that comprise networks can either be synchronized by a third region, or that synchrony may dynamically vary across the scan, such that their relationship to structural connections may only arise in specific windows of time. Conversely, regions may be structurally connected but show little RSFC. In these latter cases, it may be that they are synchronized at higher frequency ranges that cannot be interrogated by BOLD fMRI. Future research with EEG/MEG would be helpful in terms of examining these issues.

Further, in several cases, correlations between RSFC(Z) and NS were found for several region pairs in patients but not controls. In some ways, this is surprising, especially because across region pairs, NS was numerically (or significantly) higher in controls than patients. It may be that in patients, lower levels of RSFC require structural supports for these region pairs, whereas in controls, RSFC can be maintained by more flexible interactions among brain systems. This aligns with prior work showing low structural-functional convergence in the DMN among healthy adults [78,79], as well as a recent study demonstrating increased structural-functional coupling of long-distance connections among offspring of parents with SZ relative to healthy controls [54]. It is also consistent with notions of reduced complexity in the brains of patients with SZ relative to healthy controls [80,81] as well as reduced flexibility among patients relative to controls. A recent study showing reduced temporal dynamics of DMN RSFC in SZ [82] is consistent with this idea, in that it would provide a clearer picture of whether summary measures across an entire scan are representative of how connectivity changes occur throughout that scan.

Conjoint structural and functional connectivity was quantified by calculating MCS scores in each of the 9 pairs examined, and associations with clinical symptoms (PANSS) were assessed in correlational analyses. Here, we found that the Positive subscale correlated negatively with RSFC-FA MCS for the PFC/LLTL and PFC/PCC pairs. Higher scores on the Activation subscale were associated with higher connectivity of the RSFC-NS MCS for the PCC/RPHP pairs, as well as RSFC-FA MCS for the PCC/LPHP pair. The negative correlation with the RSFC-NS RLTL/RIPL pair is paradoxically a positive relation because the component scores within it are negatively correlated with each other. Finally, the Autistic Preoccupation subscale was negatively correlated with RSFC-FA MCS for the RLTL/RLOFC pair.

These relationships might be explained through a consideration of the phenomenology of each of the PANSS subscales. The Positive subscale is comprised of the Delusions, Unusual thought, Grandiosity, and Hallucinations items. The Activation subscale is comprised of the Hostility, Impulsivity, Excitement, and Uncooperativeness PANSS items. Finally, the Autistic Preoccupation is comprised of the Poor Attention, Preoccupation, Difficulty in Abstraction, Stereotyped Thinking, and Disturbed Volution items. The positive correlations with the Activation subscale may indicate that higher multimodal connectivity is associated with outward-directed (externalizing) behavior, whereas the negative correlations for the other two factors may relate to their inward-directed behavior. Further work will be necessary to determine whether this is in fact the case.

It is striking that diffusion parameters were, in general, poorly correlated. Thus, a larger number of fibers does not necessarily correlate with higher FA. This supports the idea that those metrics provide unique information about diffusion properties. It also was interesting that FA did not differ across groups. It must be borne in mind, however, that the tracts examined here are part of the DMN, and that differences are seen throughout the brain in other regions in SZ and that we are aware of no articles examining the specific tracts of the DMN in SZ.

We examined correlations among structural connectivity, quantified using FA and number of streamlines (NS) and RSFC(Z) for region pairs within the DMN. These pairs were of two kinds: homologous (for directly corresponding pairs of regions, e.g., tracts and RSFC(Z) between the PFC and PCC nodes) and nonhomologous (for regions that did
not directly correspond, e.g., tracts between PFC and PCC nodes that might significantly correlate with RSFC between PFC and RLOFC nodes). In this paper, we focused on homologous connections, but we present the nonhomologous connections in Supplementary tables. We suggest that the latter provide indirect structural pathways that might be used to support functional networks.

Several other nonstructural mechanisms likely support functional networks. Cerebrovascular/neuronal coupling is known to play an important role in the BOLD signal [83,84]. It is likely that a considerable amount of variance in fMRI based RSFC may be explained by this mechanism, and the fact that the signal itself is obtained in a BOLD contrast makes it somewhat confounded. Basic neuroscientific studies are likely to be needed to examine this relationship.

Several important caveats should be borne in mind. First, DTI is an indirect measure of white matter organization, as it measures hindered diffusion in the brain which tends to follow white matter tracts. Second, tractography is somewhat imprecise and is essentially an estimate of the primary pathway of hindered diffusion across voxels. The axons that are the source of such hindrance is on the order of microns, whereas the resolution of even the highest resolution data is at the millimeter level. DTI findings could be verified in postmortem studies of white matter. Moreover, the number of streamlines does not necessarily bear a close relationship to the actual number of tracts in a white matter bundle. Third, resting state functional connectivity is a measure of low frequency synchrony (e.g., 0.01 – 0.1 Hz) of the BOLD signal across disparate regions. It will be important to examine other frequency bands in future work. Because of the BOLD signal is sluggish, it is likely that EEG studies will be helpful going forward. In addition, the BOLD signal itself is an indirect measure of neural activity, as noted above.

There were some limitations to this study. First, the sample size was relatively small, which limited statistical power. However, this article primarily is designed to show the utility of the FATCAT method in SZ. The data presented here serve as a proof-of-concept and warrant replication in a larger sample. Second, the imaging sequences were relatively short single-band acquisitions. Third, higher numbers of diffusion directions and multishell diffusion acquisitions are likely to provide better estimates of diffusion, providing richer and more stable tractographic data. The relative brevity of our RSFC sequence restricted our ability to examine dynamic changes in RSFC that might have revealed brain states better related to tractographic measures than our static measures, and longer scans have higher reliability than a 6-minute scan. This will be an important topic for future research. Finally, patients were chronically ill and on long-term regimens of antipsychotic medication. It would be important to study medication-naïve first episode participants.

5. Conclusions

In conclusion, we developed a method to directly integrate DTI and RSFC data using network-specific ROIs and scans from the same session. In many cases, data from the two modalities were not correlated, and when they were, they were not necessarily correlated in the expected pattern. We also showed that these relationships had clinical significance in patients. We suggest that it will be useful to have such an analytic framework to parse how connectivity is mediated and how it varies across clinical populations.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Table S1: Mean number of streamlines (NS) for each region pair, Table S2: Mean fractional anisotropy (FA) for each region pair, Table S3: Mean resting state functional connectivity (RSFC) for each region pair, Table S4:. Pearson correlations (r) between resting state functional connectivity and fractional anisotropy for homologous region pairs, Table S5: Pearson correlations (r) between resting state functional connectivity and number of streamlines for homologous region pairs, Table S6: Factor loadings for patients for multimodal connectivity scores for both Fractional Anisotropy (FA) and Number of Streamlines (NS).
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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the Nathan S. Kline Institute for Psychiatric Research (protocol code 20593 and date of approval).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The de-identified data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest: Dr. Javitt reports having received consulting payments within the last 2 years from Autifony, Biogen, SK Life Sciences, Boehringer Ingelheim, and Biogen, and research support from Cerevance. He holds intellectual property rights for the use of NMDA modulators in treatment of neuropsychiatric disorders; for parcel-based diagnosis of neuropsychiatric disorders. He holds equity in Glytech, AASI, and NRx Pharma. All other authors report no disclosures (MJH, UT, KOL, and LEO).

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