Structural and Functional Default Mode Network Connectivity and Antipsychotic Treatment Response in Medication-Naïve First Episode Psychosis Patients

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ABSTRACT

Introduction: Only a few studies have comprehensively characterized DMN pathology on a structural and functional level, and definite conclusions cannot be drawn due to antipsychotic medication exposure and illness chronicity. The objective of this study was to characterize DMN pathology in medication-naïve first episode psychosis patients (FEP), and determine if DMN structural and functional connectivity (FC) have potential utility as a predictor for subsequent antipsychotic treatment response.

Methods: Diffusion imaging and resting state FC data from 42 controls and 52 FEP were analyzed. Patients then received 16 weeks of antipsychotic treatment. Using region of interest analyses, we quantified FC of the DMN and structural integrity of the white matter tracts supporting DMN function. We then did linear regressions between DMN structural and FC indices and antipsychotic treatment response.

Results: We detected reduced DMN fractional anisotropy and axial diffusivity in FEP compared to controls. No DMN FC abnormalities nor correlations between DMN structural and FC were found. Finally, DMN fractional anisotropy and radial diffusivity were associated with response to treatment.

Conclusion: Our study highlights the critical role of the DMN in the pathophysiology suggesting that axonal damage may already be present in FEP patients. We also demonstrated that DMN pathology is clinically relevant, as greater structural DMN alterations were associated with a less favorable clinical response to antipsychotic medications.

Keywords: First episode psychosis, Functional connectivity, diffusion weighted imaging, fractional anisotropy, medication-naïve, treatment response.
INTRODUCTION

The default mode network (DMN) was first described in the literature in 2001 as the default functional brain state that is suspended during specific goal-directed behaviors. It is comprised of extensive portions of frontal and posterior midline regions and the inferior parietal lobe; and spontaneous brain activity across these areas is strongly and selectively correlated. The DMN is conceptualized as a fundamental neurobiological system with physiological and cognitive properties that distinguish it from other systems, and is considered a backbone of cortical integration. While the functional anatomy of this network does not observe the boundaries of traditionally defined cortical cytoarchitectonic maps, tract tracing studies in non-human primates show that projection zones of key network nodes spatially echo the regions of the DMN, suggesting that this network is supported by direct anatomical connectivity. Consistent with this, several human studies found that the strength of functional connectivity within the DMN reflects integrity of white matter tracts that structurally connect these regions.

Dysfunction of the DMN is seen across a range of psychiatric disorders, and dysconnectivity is thought to represent a mechanism whereby clinical symptoms and cognitive deficits are induced or exacerbated. In schizophrenia spectrum disorders, disrupted functional connectivity within the DMN is frequently reported. However, only few studies have integrated both functional and anatomical measures to provide a more comprehensive assessment of DMN pathology, all of which were conducted in chronic schizophrenia patients who were treated with antipsychotic medications at the time of assessment. These reports are consistent with the idea that a structural connectivity deficit may cause a change in functional connectivity, but because non-specific factors associated with the illness such as disease chronicity and antipsychotic medication exposure impact functional and structural connectivity, it is not possible to definitively determine that this mechanism plays a pivotal role in disease expression.

The DMN has also been identified as relevant for a number of clinical variables including symptom severity, long term clinical outcomes, and response to antipsychotic treatment.
Importantly, baseline functional connectivity of the DMN was found to be the single most positive predictor for subsequent response to antipsychotic treatment in an assessment of five key functional brain networks in early illness schizophrenia patients. Studies geared at elucidating neural signatures of antipsychotic treatment response not only have the potential to inform clinical decision making, they also set the stage to distinguish variations of the illness that may represent differences in the underlying pathophysiology. But because this type of studies is not a trivial undertaking, the empirical literature on the topic remains sparse.

Here, we conducted a multimodal assessment of the DMN using resting state functional connectivity (FC) and diffusion weighted imaging (DWI) to quantitatively evaluate pathology of this network in antipsychotic medication-naïve first episode psychosis patients. We specifically chose to quantify the four commonly reported white matter diffusion metrics in an attempt to generate a broad characterization of white matter integrity and, especially since there are only few studies that have examined structural integrity of the default mode network. We then assessed change in positive symptom severity following a sixteen-week antipsychotic treatment trial as a proxy for responsiveness to antipsychotic medication treatment. This time window was chosen because longer treatment trials are deemed more robust in first episode patients and early symptom reduction does not appear to be a clinically useful predictor of antipsychotic treatment response in this population. We had two main objectives for this study: 1) to characterize the DMN on a functional and structural level and examine putative relationships between functional and structural connectivity within the network in healthy subjects and those suffering from a first psychotic episode, and 2) to determine if a more comprehensive neurobiological assessment of DMN pathology can inform clinically relevant aspects of the illness such as predicting subsequent response to antipsychotic treatment in patients. We hypothesized that structural deficits and functional abnormalities in the DMN are present in first episode psychosis patients, and that a linear relationship between functional and structural variables is evident. We further hypothesized that
greater DMN alterations at baseline would be associated with a less favorable subsequent response to antipsychotic treatment.

METHODS

Participants

FEP were recruited from outpatient, inpatient and emergency room settings at the University of Alabama at Birmingham (UAB). Healthy controls (HC) matched on age, sex and parental occupation were recruited by advertisements. Written informed consent was obtained (once FEP were deemed to have capacity to give consent\textsuperscript{28}) prior to enrollment in this UAB Institutional Review Board approved study.

Participants were excluded if they had major neurological or medical conditions, history of head trauma with loss of consciousness, substance use disorders (excluding nicotine and cannabis) within one month of imaging, were pregnant or breastfeeding, or had MRI contraindications. Patients were either medication-naive or had no more than five days of lifetime antipsychotic exposure prior to study entry (83\% of patients did not receive any antipsychotic prior to the initial scan). Controls with a personal history of a mental illness or family history in a first-degree relative of a psychotic disorder were excluded.

Clinical assessment

A consensus diagnosis was made by two board certified psychiatrists who specialize in psychosis spectrum disorders. The diagnosis was based on all clinical information available including clinical interviews with the patient and family members as well as medical records (psychiatric assessment, review of systems, family history, laboratory workup) and clinical observations and assessments over several months of follow up as available. The Brief Psychiatric Rating Scale (BPRS) and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) were used to
assess symptom severity and cognition, respectively. FEP enrolled in this longitudinal study entered into a sixteen-week trial of oral risperidone using a flexible dosing regimen. We chose risperidone because it is commonly prescribed, now available as generic medication and thus one of the more affordable second-generation antipsychotic medications in the US, and is considered one first line medications for treatment in schizophrenia, specifically in first episode patients.

Risperidone was started at 0.5-1mg and titrated in 1-2mg increments; dosing was based on therapeutic and side effects. In case of excessive side effect burden, as determined by a study physician, patients were switched to aripiprazole started at 2-5mg and titrated in 2.5-10mg increments (two patients were switched to aripiprazole; one developed hyperprolactinemia within the first week of using risperidone, the second was switched after seven weeks of treatment due to irritability). Use of concomitant medication was permitted as clinically indicated. Treatment response was defined as the percentage of change on the BPRS positive subscale from baseline to 16 weeks of treatment, where a greater percentage indicates a greater reduction in positive symptoms:

\[
\left(\frac{BPRS_{\text{Baseline}} - BPRS_{\text{Week16}}}{BPRS_{\text{Baseline}}}\right) \times (-100)
\]

Treatment response data were available for 43 patients.

**Data acquisition**

Imaging was performed on a 3T Siemens Magnetom Prisma scanner equipped with a 20-channel head coil. T1 reference (MPRAGE: TR = 2400ms; TE = 2.22ms; inversion time = 1000ms; flip angle = 8°; GRAPPA factor = 2; voxel size = 0.8mm³) and T2 weighted scans reference (TR/TE: 3200/563ms; GRAPPA factor 2; slice thickness 0.8mm; 208 slices, voxel size 0.8mm³) were acquired for anatomical. DWI data were acquired with opposing phase encoding directions (anterior > posterior, and posterior > anterior; [TR/TE: 3230ms/89.20ms; multiband acceleration factor 4, Flip angle: 84°; slice thickness 1.5mm, 92 slices, voxel size 1.5mm³, 92 diffusion weighted images distributed equally over 2 shells with b-values of -1500s/mm² and -3000s/mm², as well as 7 interspersed b= -0s/mm² images]).
Resting state functional MRI (fMRI) data were also acquired in opposing phase encoding directions (anterior > posterior and posterior > anterior; TR = 1550ms; TE = 37.80ms; flip angle = 71°, FOV = 104mm; multi-band acceleration factor = 4; voxel size= 2mm; 225 volumes). Subjects were instructed to keep their eyes open and let their mind wander during this scan.

Data preprocessing and data quality control

DWI data. Preprocessing of DWI images was performed in TORTOISE (version 3.1.2). This included correction for thermal noise, Gibbs ringing, high b-value based bulk motion and eddy-current distortions using a MAP-MRI model, resampling of images to 1mm, and rotation of gradient tables independently for each DWI phase encoding direction. Then, DR_BUDDI was used to correct EPI distortions with input from the T2 weighted anatomical image and to combine the two datasets. Tensors were computed with DIFF_CALC. To spatially normalize images to the Illinois Institute of Technology atlas (ITT) space, we used a modified version of 3dQwarp in AFNI. Finally, we calculated whole brain white matter fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) for each participant.

We visually inspected raw images for signal loss and presence of artifacts. We then assessed diffusion maps were inspected for anomalies in parameters. DWI data from 3 HC and 10 FEP did not pass quality control and were excluded from analyses. Additionally, 4 FEP terminated the scan before DWI images were acquired. In summary, diffusion datasets from 52 FEP and 42 HC were included in the final analyses.
Resting state functional connectivity data. Data were analyzed using the CONN toolbox version 37. After discarding the first 10 volumes of each scan allowing for signal equilibration, susceptibility artifacts were corrected in FSL’s topup, and merged resulting in a single 4D image of 430 total volumes 38. Functional images were then slice-timing and motion-corrected using rigid-body realignment, co-registered to the structural image, normalized to Montreal Neurological Institute (MNI) space, bandpass filtered (0.008 < f < 0.08 Hz), and spatially smoothed with a 4-mm full width at half maximum Gaussian (FWHM) kernel.

Framewise displacement (FD) and percentage of censored data were then calculated 39. Motion outliers as detected by the artifact detection (ART) toolbox were censored (composite volume-to-volume motion > 0.9mm and intensity >5 SDs), and the six motion parameters derived from rigid-body realignment and their derivatives, as well as the first 5 component time series derived from CSF and white matter using aCompCor and corresponding derivatives, were regressed out from the signal. In summary, FC datasets from 51 FEP and 42 HC were included in the final analyses.

DMN regions of interest

White matter tracts comprising the DMN were defined as outlined by Alves and colleagues 40. These tracts were obtained from the ITT4 atlas and were the following: L/R cingulum, L/R uncinate, L/R superior and L/R inferior longitudinal fasciculus, and L/R arcuate fasciculus (Figure 1A). All tracts were binarized and combined to create a single DMN white matter mask for data extraction. We also used each unilateral binarized WM mask for post-hoc analyses. For FC analysis, we used the DMN ROI defined from CONN’s independent component analysis of Human Connectome Project dataset (497 subjects). This ROI included areas from the medial prefrontal cortex, bilateral angular gyri, and posterior cingulate cortex/precuneus (Figure 1B).

Insert Figure 1 about here
Statistical analyses

For structural connectivity analyses, the mean voxelwise FA, MD, RD and AD for each subject from the whole DMN white matter mask was extracted. We also extracted WM measures from each unilateral individual tract and performed group analysis as post-hoc analyses. For FC analyses, DMN FC was calculated using the conn_withinbetweenROItest function implemented in CONN by averaging the BOLD signal across all voxels in all of the ROIs within the DMN network. This computes Pearson’s correlation across all voxels within the ROIs and then creates an average DMN FC value. The DMN FC value was z-transformed and group analyses (HC vs. FEP) were performed using separate ANCOVAs for WM and FC controlling for sex and motion parameters ($RMS_{rel}$ for white matter analysis and FD for functional connectivity). Given that age can potentially affect white matter diffusion indices, we also included it as a covariate in all of our analyses 41.

Then, we examined the relationship between white matter and FC between groups using linear regressions on each group separately and by creating an interaction term between groups and FC and regressing the interaction term as well as age, sex, motion parameters ($RMS_{rel}$ and FD), group, and FC on each WM measure. Finally, we examined the relationship between treatment response % with white matter and FC in FEP using a linear regression. Age, sex and motion parameters ($RMS_{rel}$ and FD) were included in the model. All analyses were controlled for multiple comparisons using the false discovery rate (FDR) correction method by Benjamin and Hochberg 42. All results are accompanied by effect sizes.
RESULTS

Demographics and clinical characteristics

Of the 183 patients assessed for eligibility to participate in this study between June 2016 and April 2019, 74 FEP were consented and 66 entered into the sixteen-week trial of risperidone, a total of 52 FEP completed the study. We also enrolled 45 HC, 42 were included in the final sample.

Groups did not differ in sex, age or parental socioeconomic status (Table 1). In patients, the BPRS positive subscale ($t_{42} = 11.06$, Cohen’s $d = 1.69$, $p < 0.001$) and BPRS total scores ($t_{42} = 10.71$, Cohen’s $d = 1.63$, $p < 0.001$) significantly decreased after 16 weeks of treatment, but not for -BPRS scores ($t_{42} = 0.57$, Cohen’s $d = 0.09$, $p = 0.57$). The average daily dose of risperidone at that time was $4.22 \pm 2.70$ mg.

Structural and functional connectivity of the DMN

FEP showed lower DMN FA ($F_{1, 89} = 6.64$, partial $\eta^2 = 0.07$, $p = 0.01$) and AD ($F_{1, 89} = 11.42$, partial $\eta^2 = 0.11$, $p = 0.001$) compared to HC. We found no significant-group differences for MD ($F_{1, 89} = 0.85$, partial $\eta^2 = 0.01$, $p = 0.36$) or RD ($F_{1, 88} = 0.22$, partial $\eta^2 = 0.002$, $p = 0.64$). Post-hoc analyses revealed significant group differences (HC > FEP) in FA in right inferior longitudinal fasciculus and AD in bilateral cingulum bundle (Supplementary Table 1). Functional connectivity of the DMN did not differ between groups ($F_{1, 88} = 0.95$, partial $\eta^2 = 0.01$, $p = 0.33$). All significant results survived FDR correction.
Relationships between structural and functional connectivity of the DMN

No significant associations between DMN white matter indices and FC were found in HC or FEP nor significant group interactions as well.

Relationships of DMN structure and function with treatment response

Two DMN structural connectivity indices, FA (b = 0.38, Cohen’s $f^2 = 0.51$, $p = 0.009$) and RD ($b = -0.37$, Cohen’s $f^2 = 0.44$, $p = 0.01$) were associated with response to antipsychotic treatment, however AD (b = 0.13, Cohen’s $f^2 = 0.04$, $p = 0.44$), MD, (b = -0.29, Cohen’s $f^2 = 0.23$, $p = 0.06$), and DMN FC (b = 0.28, Cohen’s $f^2 = 0.13$, $p = 0.09$) were not. All significant results survived FDR correction.

Sex and age as biological variables

No significant effects of age nor sex were found in any of our ANCOVA analyses (both WM and FC). Additionally, there were no significant effects in treatment response between the sexes in the regression analyses.

Insert Figure 3 about here
DISCUSSION

To our knowledge, this is the first study to comprehensively investigate DMN pathology on both a structural and functional level in medication-naïve first episode psychosis patients. Our results underscore the critical importance of this network for the pathophysiology of the disorder by showing that structural connectivity of the DMN is already impaired in the early illness stages. Findings also highlight the clinical relevance of DMN pathology, as we found that lower structural integrity in this network in medication-naïve patients was associated with poorer subsequent response to antipsychotic treatment.

Here, we report alterations in first episode patients across two diffusion indices, FA and AD, suggesting abnormalities in structure and organization in major white matter bundles providing the structural framework of the DMN. Our findings are consistent with diffusion imaging studies in schizophrenia reporting reduced white matter integrity in general and reduced integrity of the cingulum bundle, a white matter tract that structurally connects regions of the DMN, specifically 47. While FA is generally conceptualized as a non-specific marker of white matter integrity, other diffusion indices may yield additional information about the underlying pathophysiology. For example, preclinical studies have identified reduced AD in the corpus callosum as a potential marker of axonal damage. In contrast, demyelination is thought to be expressed as increased in RD without corresponding changes in AD. For example, an animal study conducted by Xie and colleagues found that initial stages of demyelination led to reduced axial diffusivity, but no change in radial diffusivity. In this context, reduced FA and AD in early stages of the illness in our study could be interpreted as evidence of axonal damage in structures supporting the DMN.

Surprisingly, we did not detect FC abnormalities of the DMN. This is in contrast with previous studies reporting increased or decreased functional connectivity of this network in chronic schizophrenia patients and medication-naïve first episode patients. However, a number of others also failed to detect functional DMN abnormalities in medication-naïve first-episode psychosis and chronic schizophrenia patients. These inconsistencies may be explained by...
methodological differences. For example, Gong and colleagues used a voxelwise approach where all analyses were performed in each voxel within a DMN mask and no white matter regressors nor correction for micromovement (scrubbing or censoring) were implemented. It is important to note that the multimodal approach we employed here allows us to make a more nuanced interpretation of the apparent lack of functional connectivity alterations.

While we did not find group effects between DMN WM and FC metrics, there have been no studies that have specifically looked at DMN structural and functional connectivity in FEP. Our absence of results does not entirely represent a lack of DMN FC-WM abnormalities in FEP as more advanced techniques such as data fusion can help elucidate such potential abnormalities.

Here, we report that greater FA and RD of the DMN in medication-naïve patients was associated with a more favorable subsequent response to antipsychotic treatment, which adds to the literature supporting the concept that white matter integrity has potential utility in predicting antipsychotic treatment response. Importantly, the DMN has been previously implicated as a pivotal functional network for clinical outcomes. Doucet and colleagues found that functional connectivity of the DMN was the single most important positive predictor of clinical outcome in schizophrenia spectrum patient who had an illness duration of no more than five years. While the findings of decreased DMN FA and AD in FEP compared to HC and DMN FA-treatment response association in FEP of this study are consistent with our previous work where whole brain WM integrity was examined, our additional finding of treatment response predicting DMN RD highlights the specificity of DMN in white matter pathology and its susceptibility to response to antipsychotics.

One of the major strengths of our study was the enrollment of perhaps one of the largest groups of medication-naïve FEP in an imaging study followed longitudinally in the US. This allowed us to mitigate effects from non-specific illness factors such as previous antipsychotic exposure and illness chronicity on neuroimaging variables. However, it is important to note that our group was heterogeneous in terms of diagnosis, which is to be expected in this patient population. Future
larger scale studies that are adequately powered to discern if there are pathophysiological differences in functional and structural metrics will help shed light on how this affects treatment response in different groups of patients who present with a first psychotic episode. We treated patients with risperidone for a trial duration of 16 weeks, which diminishes the possibility that late responders are incorrectly characterized as poor responders. On the same note, the way treatment response was defined in our study was in the form of a spectrum, rather than a dichotomization of responders vs. non-responders. The former accurately reflects the clinical picture progression in various degrees. In addition, since FEP cohort responses are quite high, this creates an uneven subgroup of responders compared to non-responders. Our retention rates were excellent for a clinical trial with antipsychotic medications, with only ~23% attrition. Another strength was that we used a multimodal approach, which by nature is more informative than unimodal studies and provides a more detailed description of the more complex picture of the neural correlates in FEP.

It is possible that our approach for assessing structural connectivity using the tensor method may have underestimated the extent of demyelination and overestimated the axonal damage. Nonetheless, using biophysical diffusion models such as NODDI imaging could help characterize white matter pathology more specifically. On the same note, our approach to capture functional connectivity of the DMN using region of interest analysis may not have captured functional connectivity abnormalities of the DMN that may have been evident with alternative approaches such as seed-based connectivity analyses. Even though cannabis, a major risk factor developing psychosis, may affect brain structure and function, we did not exclude patients with a history of cannabis use as this would have inadvertently biased our sample and limit the generalizability of our data. Another limitation of our study is that we did not examine possible confounding effects of tobacco smoking or body mass index.
Overall, our study highlights the critical role of the DMN in the underlying pathophysiology suggesting that axonal damage may already be present in first episode psychosis patients. We also demonstrated that DMN pathology is clinically relevant, as greater structural DMN alterations were associated with a less favorable clinical response to antipsychotic medications. Finally, our data underscore that a multimodal approach allows a more nuanced interpretation of the pathophysiology.
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**Author Contributions:** Dr. Lahti had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** NVK, ACL.

**Acquisition of data:** NVK.

**Analysis and interpretation of data:** All authors.

**Drafting of the manuscript:** JOM, NVK, ACL.

**Statistical analysis:** NVK, JOM.

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Table 1. Demographics, clinical measures, and data quality

| Demographic variables | Groups (N = 94) | P-value |
|-----------------------|-----------------|---------|
|                       | HC (n = 42)     | FEP (n = 52) |         |
| Age (in years)        | 24.33 ±5.93 (15-41) | 24.46 ±6.34 (15-40) | 0.92 |
| Sex (M/F)             | 28/14           | 33/19    | 0.75   |
| *Parental occupation  | 4.17 ±4.11 (1-20) | 5.86 ±5.12 (1-21) | 0.09   |

| Clinical Variables    | | |
|-----------------------|-----------------|---------|
|                       | HC (n = 42)     | FEP (n = 52) |         |
| Diagnosis             | | |
| Schizophrenia         | - | 26 | - |
| Schizoaffective Disorder | - | 12 | - |
| Bipolar disorder with Psychosis | - | 3 | - |
| Schizophreniform Disorder | - | 2 | - |
| Psychosis NOS         | - | 7 | - |
| Brief psychotic disorder | - | 1 | - |
| Major Depressive Disorder w/psychosis | - | 1 | - |
| BPRS Baseline         | | |
| Positive              | - | 11.85 ±3.51 (3-20) | - |
| Negative              | - | 6.17 ±3.41 (3-16) | - |
| Total                 | - | 52.02 ±11.97 (32-84) | - |
| *BPRS Week 16         | | |
| Positive              | - | 4.63 ±1.90 (3-9) | - |
| Negative              | - | 5.53 ±2.70 (3-12) | - |
| Total                 | - | 30.37 ±6.00 (20-45) | - |
| *RBANS                | | |
| Immediate Memory      | 100.08 ±17.52 (72-130) | 82.64 ±19.97 (44-125) | < 0.001 |
| Visuospatial/Constructional | 85.72±12.39 (62-117) | 79.02±17.96 (44-125) | 0.06 |
| Language              | 99.00 ±14.97 (40-120) | 82.30 ±15.82 (40-112) | < 0.001 |
| Attention             | 100.61 ±17.89 (72-141) | 80.47 ±17.63 (43-109) | < 0.001 |
| Delayed Memory        | 91.56 ±8.84 (77-122) | 79.85 ±13.96 (44-108) | < 0.001 |
| Total index           | 94.14 ±11.13 (78-120) | 76.70 ±16.69 (50-117) | < 0.001 |

Scan Quality Data

| DWI                   | | |
|-----------------------|-----------------|---------|
| RMS absolute motion (mm) | 0.34 ±0.22 (0.14 - 1.37) | 0.40 ±0.25 (0.13 - 1.10) | 0.25 |
| RMS relative motion (mm) | 0.01 ±0.01 (.001 - .03) | 0.01 ±0.01 (.001 - .04) | 0.30 |
| FC                    | | |
| Power framewise displacement (mm) | 0.21 ±0.10 (0.11 - 0.49) | 0.29 ±0.20 (0.11 - 0.89) | 0.003 |

Notes: mean ± standard deviation (range); data available for 91 subjects, 43 patients, 83 subjects; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; BPRS = Brief Psychiatric Rating Scale; DWI, diffusion weighted imaging; FC, functional connectivity; p-values are from χ² and independent samples t-tests for differences between the groups. *Ranks determined from Diagnostic Interview for Genetic Studies; higher rank (lower numerical value) corresponds to higher socioeconomic status.
Figure legends

**Figure 1.** ROIs used for A) DMN WM tract (showing unilateral tract only) and B) DMN ROIs for FC analysis rendered on a T1 IIT Human Brain Template. ROI, region of interest; DMN, default mode network; FC, functional connectivity; WM, white matter; and IIT, Illinois Institute of Technology.

**Figure 2.** Boxplots depicting DMN DWI data for each group for A) fractional anisotropy, B) axial diffusivity, C) mean diffusivity, and D) radial diffusivity; and E) boxplot depicting FC values for each group. Each individual dot is a data point from a single subject and red lines indicate average value for each group. HC, healthy control; FEP, first episode psychosis; DMN, default mode network; DWI, diffusion weighted imaging; and FC, functional connectivity. *p < 0.05, FDR corrected.

**Figure 3.** Scatterplots depicting associations between A) DMN fractional anisotropy, B) DMN axial diffusivity, C) medial diffusivity, D) radial diffusivity, and E) DMN FC with treatment response. FEP, first episode psychosis; DMN, default mode network; and FC, functional connectivity. *p < 0.05, FDR corrected.
Figure 3