2018

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HHS Public Access

Author manuscript

Mol Psychiatry. Author manuscript; available in PMC 2017 September 28.

Published in final edited form as:

Mol Psychiatry. 2018 March ; 23(3): 701–707. doi:10.1038/mp.2017.43.

Greater Extracellular Free Water in First-Episode Psychosis Predicts Better Neurocognitive Functioning

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Abstract

Free Water Imaging is a novel diffusion magnetic reasonance imaging (MRI) method that is able to separate changes affecting the extracellular space from those that reflect changes in neuronal cells and processes. A previous Free Water Imaging study in schizophrenia identified significantly

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Conflict of Interest Disclosures: All of the authors except Dr. Maurizio Fava and Dr. Malhotra have declared that there are no conflicts of interest in relation to the study presented here. For a complete list of Dr. Maurizio Fava's disclosures, please see http://mghcme.org/faculty/faculty-detail/maurizio_fava#disclosure. Dr. Malhotra has been a consultant for Genomind, Forum Pharmaceuticals, and Takeda Pharmaceuticals.

Supplementary information is available at *Molecular Psychiatry*'s website.

greater extracellular water volume in the early stages of the disorder; however, it's clinical and functional sequelae have not yet been investigated. Here, we applied Free Water Imaging to a larger cohort of 63 first-episode patients with psychosis and 70 healthy matched controls to better understand the functional significance of greater extracellular water. We used diffusion MRI data and the Tract-Based Spatial Statistics analytic pipeline to first analyze fractional anisotropy (FA), the most commonly employed metric for assessing white matter. This comparison was then followed by Free Water Imaging analysis, where two parameters, the fractional volume of extracellular free-water (FW) and cellular tissue FA (FA-t), were estimated and compared across the entire white matter skeleton between groups, and correlated with cognitive measures at baseline and following 12 weeks of antipsychotic treatment. Our results indicated lower FA across the whole brain in patients compared to healthy controls that overlap with significant increases in FW, with only limited decreases in FA-t. In addition, higher FW correlated with better neurocognitive functioning following 12 weeks of antipsychotic treatment. This is the first study to suggest that an extracellular water increase during the first-episode of psychosis, which may be indicative of an acute neuroinflammatory process, and/or cerebral edema may predict better functional outcome.

A. Introduction

Schizophrenia (SZ) is a chronic psychiatric disorder that affects almost 1% of the population (1). While the etiology of SZ is still unclear, it has been posited to be a disorder of "dysconnectivity," such that many of the behavioral symptoms and cognitive deficits in SZ can be explained by aberrations in the communication of information among cortical areas (2,3). In recent years, increased focus has been placed on cerebral white matter connections because they are purported to play a central role in SZ pathophysiology (4). The involvement of white matter pathology is supported by postmortem and histological studies that identify abnormalities in myelin and myelin-related genes in patients with SZ (5,6).

The application of diffusion tensor imaging (DTI) has permitted the interrogation of microstructural properties of white matter *in vivo* (7). The most common finding in SZ is lower fractional anisotropy (FA) in the corpus callosum, and the majority of fronto-temporal fasciculi (8,9). Lower FA in patients has frequently been interpreted to reflect changes in the "integrity" of myelinated connections. There is a high degree of variability, however, in reported findings, likely due to the fact that DTI indices (e.g., FA) are sensitive to a range of biological pathologies, such as axonal degeneration, demyelination, or increases in extracellular water volume (10). The lack of specificity of FA necessitates the development of metrics to distinguish among white matter pathologies that may underlie the neurobiology of SZ.

A promising new development is Free Water Imaging, which uses a two-compartment model of water diffusion from diffusion-weighted images (DWIs)(11). This method increases the specificity of the traditional single-compartment model, DTI, by separating the contribution of freely diffusing extracellular water from water in the proximity of brain cells and their processes. Free Water Imaging calculates two parameters. The first, FW, which reflects the fractional volume of unrestricted free-water, has been proposed to serve as an indicator of

extracellular changes that are being driven by pathologies such as atrophy, cerebral edema, or neuroinflammation (11). The second is the residual diffusion signal from restricted/hindered water, that is modeled as a diffusion tensor and termed fractional anisotropy of the "tissue" (FA-t), reflecting the microstructure of cells and their processes. By separating the extracellular free-water component from the "tissue" component, Free Water Imaging provides greater sensitivity to detect structural changes between groups through both measurements of extracellular pathology, as well as lowering the variability in the tissue-related parameter, FA-t, comparing to the traditional FA metric (12).

Using the Free Water Imaging approach in a cohort of recent-onset schizophrenia patients we showed that frequently reported widespread reductions in FA (see reviews(8,9)) can be explained by significant increases in FW (13). Interestingly, there were only circumscribed reductions in FA-t in frontal lobe white matter (13), leading to the conclusion that individuals in the early stages of schizophrenia were exhibiting a global increase of FW, indicating extracellular changes, and not widespread myelin deterioration, as previously suggested (8,9). Evidence from recent PET studies describing increased levels of activated microglia and reactive astrocytes coupled with reports of greater levels of pro-inflammatory cytokines in blood or cerebrospinal fluid in patients have led to the hypothesis that these extracellular changes are consistent with a neuroinflammatory response (14–16). Moreover, these studies further suggest that such a response is present at earlier, more acute stages of schizophrenia, than widespread axonal degeneration, which has been demonstrated to be more pronounced at later stages of the disorder (17).

The primary goal of the current study was to investigate whether increases in extracellular FW would be observed among patients experiencing a first episode of psychosis studied early in the course of illness and prior to extensive pharmacologic intervention. Moreover, because the functional significance of the extracellular FW response remains largely unknown, an additional goal was to examine the neurocognitive and clinical correlates of FW in patients.

B. Methods

Subjects—Sixty-three patients experiencing a first-episode of psychosis (FEP) were recruited from the inpatient service at The Zucker Hillside Hospital in Glen Oaks, NY, and enrolled in an NIMH-funded double blind randomized controlled trial comparing aripiprazole (n=29) versus risperidone (n=34)(18). All patients had 2 weeks or less of cumulative lifetime exposure to antipsychotics prior to entry into the clinical trial. All patient (lifetime) diagnoses were based on the SCID for Axis I DSM-IV Disorders and included schizophrenia (undifferentiated = 25 and paranoid = 15), schizophreniform disorder (n=15), schizoaffective disorder (n=1), or psychosis NOS (n=7). On average, patients had a total lifetime exposure of 6.3 (SD = 7.3) days of antipsychotic treatment prior to the baseline scan and had received their MRI exam within an average of three days (range = −23 to 30 days) of entry into the clinical trial. Twenty-one patients were antipsychotic drug-naïve at the time of the baseline scan. Mean age at first psychotic symptoms was 19.1 years (SD = 4.6); data were unavailable for three patients.

We recruited 70 healthy volunteers from advertisements to match the demographic distributions of patients. Exclusion criteria for healthy subjects included the presence of any lifetime history of a major mood or psychotic disorder as determined by clinical interview using the SCID-NP. Exclusion criteria for all study participants included MR imaging contraindications, and any serious medical disorder that could affect brain functioning or mental retardation.

This study was approved by the local Institutional Review Board and written informed consent was obtained from all study participants or their parents in the case of minors. All minors provided written informed assent to participate in the study.

Treatment Trial Antipsychotic Titration Schedule—Research psychiatrists followed a flexible dosing titration schedule. The initial daily dose for patients in the treatment trial was 5 mg for aripiprazole and 1 mg for risperidone, which was increased after three days of treatment with further adjustments made every 1–3 weeks until the patient improved, developed side effects that precluded a dose increase, or reached a maximum daily dose of 30 mg of aripiprazole or 6 mg of risperidone. Patients were not allowed to receive antidepressants, mood stabilizers, or any other psychotropic medication.

Clinical Assessments—Patients completed the 18-item Brief Psychiatric Rating Scale – Anchored version (BPRS-A(19)) and we derived a total score by summing all items. The average Brief Psychiatric Rating Scale Score was 43.6 (SD = 8.6) at the time of baseline scanning and 27.7 (SD = 8.1) at follow-up.

Cognitive Assessments—We administered the MATRICS Consensus Cognitive Battery (MCCB) to patients at baseline and following 12-weeks of antipsychotic treatment. An overall score was computed as the average of the individual domains. At baseline, of the total 63 FEP patients included in this study, 57 FEP patients (43M/14F) completed the entire MCCB, while six FEP patients (3M/3F) did not. At the 12-week follow-up, of the 57 that completed the entire baseline MCCB, 39 FEP patients (28M/11F) returned and completed the entire MCCB, while 18 FEP patients (15M/3F) did not. We did not detect any significant differences in baseline values of age, sex, handedness, years of education, total BPRS score, and global ratings of negative symptoms between individuals with and without NP data at the 12-week time point.

Diffusion MR Procedures—Diffusion MR scans were acquired at the North Shore University Medical Center on a GE 3T HDx scanner. A total of 36 diffusion weighted images (DWIs) were obtained from each subject at baseline, including 31 volumes with diffusion gradients applied along 31 non-parallel directions with b = 1000 s/mm^2 and, and 5 volumes without diffusion weighting (b = 0). Each volume consisted of 51 contiguous 2.5 mm axial slices acquired parallel to the anterior-posterior commissural line using a ramp sampled, spin-echo, single shot echo-planar imaging method (TR = 14000ms, TE = <84.8ms, matrix = 128x128, FOV = 240mm).

Image Analysis

Free Water Imaging—The Free Water Imaging analysis pipeline has been previously described (13,17). Briefly, diffusion-weighted images (DWIs) were corrected for motion and eddy-current artifacts by means of affine registration with a b=0 reference volume (FLIRT, FSL, Oxford) as in our prior work (13,17) and subsequently masked to exclude non-brain areas. We excluded 7 subjects with high motion from analysis (>2 SD from the mean)(11).

FW maps were created by fitting aligned DWIs with a two-compartment model comprised of a free-water compartment and a "tissue" compartment as described previously (11). Briefly, the free-water compartment extracts the contribution of water molecules that diffuse freely in the extracellular space, quantified by a single parameter called FW, which stands for the fractional volume of free-water. The second compartment describes the behavior of water molecules that are affected by proximity to cells, and are modeled utilizing a diffusion tensor. This produces two voxel-wise maps, one representing FW and one representing the FA values that are corrected for FW (FA-t).

White Matter Processing—We employed the tract-based spatial statistics (TBSS) pipeline (20) and the FA target image and skeleton that was created by the Enhanced Neuroimaging Genetics by Meta Analysis (ENIGMA) DTI Working Group at the University of Southern California, all of which are publicly available (http://enigma.ini.usc.edu/ongoing/dti-working-group)(21). We utilized the ENIGMA processing stream to allow for greater generalizability of results across studies, including an ongoing, multi-site meta-analysis of diffusion data from schizophrenia patients across 22 sites (22). Using this pipeline, we projected the FA, FA-t, and FW maps onto the skeleton to perform statistical analyses.

Statistical Analysis

Group comparisons were performed using a nonparametric permutation-based test (Randomise, FSL) with a threshold free cluster enhancement (TFCE) and family-wise error correction (23,24). The data were then tested against an empirical null distribution, which was generated by 5000 permutations for each contrast, resulting in statistical maps that are corrected for multiple comparisons across the whole brain and significance at a threshold of $p < 0.05$. Age and sex were included as covariates. As there was no significant difference between groups for the calculated motion parameter ($t = 0.884$, $p = 0.3781$; Means: FEP = 0.53; HC = 0.52) it was not included as a covariate. For the purpose of investigating correlates of diffusion signal, significant clusters were averaged to create a single cluster mean for FA-t and FW for each subject.

One additional set of voxel-wise statistical comparisons was computed utilizing the previously mentioned nonparametric permutation-based test (Randomise, FSL) to determine the possible effects of medication on our findings. We compared FA-t and FW values between medicated FEP patients and medication-naïve FEP patients with age and sex as covariates.

We correlated baseline averaged FA, FA-t and FW values for patients with the Overall score on the MCCB at baseline and 12 weeks following treatment. If the Overall MCCB score was significantly correlated with FA, FW or FA-t at baseline or 12 weeks, we then examined the individual domains and corrected for multiple comparisons (Bonferroni adjusted significance threshold: $p < 0.007$). Baseline averaged FA, FA-t and FW values in FEP patients were also correlated with scores on the BPRS at baseline and 12 weeks.

To explore sex effects in both healthy controls (HC) and FEP patients, we conducted a post-hoc analysis where we divided the entire sample into four groups: HC Females (n=24), HC Males (n=46), FEP Females (n=17), and FEP Males (n=46). We calculated a one-way ANCOVA to test the main effect of group while controlling for age. We utilized Tukey's Honest Significant Difference test to calculate post-hoc pairwise comparisons between means of each group with p-values that were corrected for the total number of comparisons to the confidence level of 0.95 ($p < 0.05$) using family-wise error rates.

C. Results

There were no significant differences between FEP and the HC in distributions of age, sex, and handedness, but groups did differ in education (Table 1). There were no significant differences in demographic variables between patients treated with aripiprazole versus risperidone (18).

C1. Extent and Nature of Diffusion Changes in First-Episode Schizophrenia Patients

The FEP group showed significantly ($p < 0.05$) lower FA extending over most of the white matter skeleton compared to controls (Figure 1). A significant globalized increase in FW ($p < 0.05$) in FEP compared to HC was also observed (Figure 1). As illustrated in Figure 1, there is almost complete overlap between the regions with lower FA and those with higher FW in FEP compared to HC, suggesting that FA changes can be mostly explained by alterations in the extracellular free-water compartment. In contrast, the FA-t voxel-wise analysis produced only circumscribed differences between FEP and HC. Significant reductions ($p < 0.05$) in FA-t in FEP were found in the body and genu of the corpus callosum and the left superior and posterior corona radiata as well as the left superior longitudinal fasciculus (Figure 1).

We compared the FW and FA-t values between medicated FEP (n=42) and medication-naïve FEP (n=21) patients and found no significant differences in either FW or FA-t ($p > 0.05$), suggesting that medication status at baseline does not significantly contribute to the observed group differences.

C2. Cognitive Correlates of Extracellular FW Increase in FEP Patients

At baseline, FA, FA-t and FW in the FEP were not related to overall MCCB performance. However, baseline FW values in patients showed a significant positive correlation with overall MCCB performance 12 weeks following treatment (Pearson's r = 0.4712, $p = 0.0025$) (Figure 2). Of the seven domains, all but the social cognition domain demonstrated a positive correlation with baseline FW values; however, only two domains survived Bonferonni correction (see Supplementary Figure 1): Working Memory (Pearson's r =

0.4287, $p = 0.0065$), and Verbal Memory (Pearson's r = 0.5159, $p = 0.0008$). This finding was unique to FW, as FA and FA-t at baseline did not predict performance on the overall MCCB. Baseline average FA, FW and FA-t values did not correlate significantly with BPRS scores at either baseline or 12 weeks.

C4. Sex Effects

The results of the exploratory one-way ANCOVA reveal a significant group difference in FW ($F = 9.32$, $p < 0.0001$; Figure 3). Post-hoc pairwise comparisons using Tukey's HSD for FW values (Table 2) showed significant differences for the following comparisons: FEP Females-HC Females ($p = 0.0004$), FEP Males-HC Males ($p = 0.02$), FEP Females-FEP Males ($p = 0.04$) and FEP Females-HC Males ($p < 0.0001$). There were no significant correlations between FW and MCCB overall scores at baseline for either the male or female FEP patients. FW values in both male and female FEP patients correlated significantly with overall MCCB score at the 12-week follow-up (Male FEP r = 0.5247, Female FEP r = 0.4569) with no significant difference between the correlations (z = −0.22, $p = 0.82$).

D. Discussion

We report higher FW values in FEP patients compared to HC that are widespread, encompassing multiple regions that have been previously implicated in the neurobiology of schizophrenia. In contrast to widespread FW changes, we observed reductions in FA-t in FEP patients only in circumscribed segments of the corpus callosum, left corona radiata, and left superior longitudinal fasciculus. Among patients, higher FW was associated with better cognitive functioning following 12 weeks of antipsychotic treatment.

Our study demonstrates that lower FA in FEP, a finding previously reported in multiple studies, is likely related to significant increases in FW (8,9). This result is consistent with our prior findings in recent-onset schizophrenia patients (13) and indicates that extracellular brain changes could serve as an indicator of early stage psychosis. One possible explanation for higher FW at the first-episode of psychosis is a neuroinflammatory response, as extracellular water volume is expected to be increased in neuroinflammatory states due to the accumulation of water in the extracellular space (e.g., edema). Although we acknowledge that other possible mechanisms could lead to greater extracellular water volume, the neuroinflammation hypothesis is supported by considerable evidence that abnormalities in the immune response may play a role in the pathophysiology of schizophrenia. Data from diverse fields, including genetic (25–28), blood serology (29–31), and postmortem studies (32,33) support the "inflammation hypothesis." Moreover, a recent genome-wide analysis implicated immune-related pathways as a principal risk factor in schizophrenia (28) and studies of FEP patients report greater pro-inflammatory cytokines and cytokine receptors (16,34,35).

While an increasing number of studies have identified the presence of a possible neuroinflammatory response in schizophrenia, little is known regarding its functional significance, especially early in psychosis. A prior study indicated that interleukin-6 levels were negatively correlated with FA highlighting a potential mechanism for immune system abnormalities in the neurobiology of white matter dysfunction in early-course clinically

stabilized patients with schizophrenia (Prasad et al 2015)(36). Bulzacka and colleagues (2016) also identified abnormally high C-reactive protein (CRP) levels in a subgroup of 104 chronic patients that were associated with impaired general intellectual ability (37). Similarly, Dickerson and authors (2007) reported that higher CRP levels were associated with worse functioning on the Repeatable Battery for the Assessment of Neuropsychological Status compared to patients with lower CRP levels (38).

We demonstrate that greater FW during the first-episode of psychosis has a positive relationship with cognitive functioning following 12 weeks of antipsychotic treatment. This correlation was uniquely related to FW, as reductions in FA-t observed at baseline in FEP patients were unrelated to cognitive functioning. The finding of an increased, rather than a decreased, FW response predicting better neurocognitive outcome may seem paradoxical given that a majority of studies portray brain neuroinflammation in SZ as detrimental (39–42). It is important to note, however, that while chronic inflammation is indeed a central part of the majority of neurodegenerative brain disorders, acute neuroinflammatory responses are usually intended to promote healing in cases of brain injury (43). Few studies have investigated correlates of the neuroinflammatory response early in the course of illness in relation to neurocognitive functioning. Taken together, our findings are consistent with the hypothesis that the ability to mount an inflammatory response at the onset of psychosis may portend a better neurocognitive outcome following antipsychotic treatment. Over the long term, however, it is conceivable that an inability to resolve this response, and/or the cumulative effect of chronic treatment with antipsychotic medications, may lead to white matter abnormalities and neuropsychological dysfunction. Additionally, we found that correlations between FW and MCCB domains were most robust for working and verbal memory. These domains of functioning have consistently been demonstrated to be the most impaired in schizophrenia (44,45) and have been identified as the most promising endophenotypes for SZ because they are also observed among unaffected relatives (45,46).

The relatively large number of female FEP offered the opportunity to explore sex effects. Female FEP exhibited significantly increased FW values compared to female HC, male HC, and male FEP. FEP males exhibited significant differences in FW when compared to male healthy controls; however not to the same degree as the female FEP. Our FW findings converge with a recent study reporting high levels of C-reactive protein (hsCRP), an acute phase response immune marker in schizophrenia patients (47). These investigators demonstrated greater levels of hsCRP in female patients compared to both female and male controls, as well as male schizophrenia patients (47), suggesting there might be an increased inflammatory response in the female patients' brains relative to male patients' brains. This is particularly intriguing because much of the previous literature indicates that although males and females have a similar incidence and prevalence of schizophrenia, females patients tend to have lower relapse rates and higher pre- and post-morbid functioning (48). Based on the results of our study, and the preceding study by Joseph and colleagues (47), an important focus of future studies would be the further examination of sex differences in these parameters.

There are several limitations of our study. The proportion of male and female participants was not equal and larger sample sizes will be required to confirm findings of sex differences.

Similarly, although we found no significant difference between patients minimally treated with antipsychotics compared to antipsychotic drug-naïve patients in either FW or FA-t, suggesting that short-term antipsychotic medication is not influencing the FW measure in first-episode patients, these findings should be confirmed longitudinally in patients receiving therapeutic dosages. Although no significant differences in baseline demographic or cognitive variables were found between patients that remained in the study and those that dropped out, we acknowledge the possibility that differential attrition could still conceivably affect the results presented herein. Moreover, in the absence of longitudinal imaging data, it is difficult to draw definitive conclusions about underlying biological correlates of the observed cognitive outcomes in patients. Atypical antipsychotics have been shown to have anti-inflammatory effects, which could be mediating the observed outcomes (16,49). As we report no significant association between FW and neurocognitive performance at baseline we conclude that greater baseline FW and subsequent antipsychotic treatment is associated with better cognitive performance.

We must also acknowledge that FW should be considered only a proxy for neuroinflammation because it is an indirect measures of the neuroinflammatory response, i.e., increased extracellular fractional volume (50). There are other possible underlying biological pathologies previously reported in schizophrenia patients that could explain the findings presented herein. These include pathologies such as decreased neuronal size (51), which may be related to the reductions in FA-t, or atrophy due to excessive synaptic pruning (52), which may contribute to the increased FW. Such pathology may, however, be more likely identified in the gray matter and in patients at more chronic stages of illness (51,52). Also, we note that the correlation between average whole brain FA and average whole brain FW was $r = -0.78$. In the context of the Free Water Imaging model, we expect lower FA in regions with higher FW in the absence of any reduction in FA-t. If there is a reduction in FA-t, without concomitant changes in FW, this would also be reflected as lower FA in which case FW would not be correlated with FA. Therefore, it is important to acknowledge that FA and FW should not be simply construed as “mirror opposites.” Thus, the correlation between these two measures suggests that the observed abnormality is related to an increase in extracellular water, but not restricted/hindered water.

In summary, we find that lower FA in FEP can be explained primarily by greater FW, a potential proxy for an acute neuroinflammatiory response. We present evidence that higher FW at the first-episode of psychosis predicts better cognitive outcome following 12 weeks of antipsychotic treatment. Additionally, we find that short-term antipsychotic treatment is not related to extracellular FW increases or reductions in FA-t at baseline. Finally, we show that sex can have a significant influence on FW in first-episode schizophrenia patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding:

This work was supported in part by grants from the National Institutes of Mental Health to Dr. Lyall (5T32MH016259-35), Dr. Kubicki (R01AG042512, R01MH102377), Dr. Pasternak (R01MH108574, R01MH074794, P41EB015902, R01AG042512, R01MH102377), Dr. Szeszko (R01 MH076995), Dr. Robinson (R01 MH060004), Dr. Gallego (K23 MH100264), the NSLIJ Research Institute General Clinical Research Center (M01 RR018535), an Advanced Center for Intervention and Services Research (P30 MH090590), a Center for Intervention Development and Applied Research (P50 MH080173) and NARSAD Young Investigator grants (Dr. Szeszko and Dr. Pasternak).

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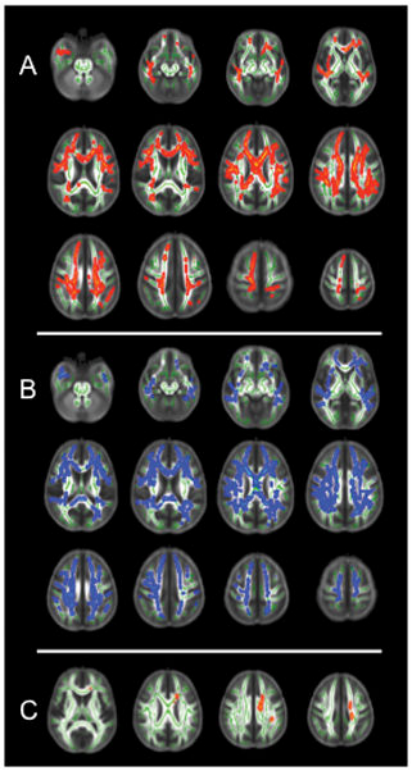

Figure 1.

Widespread significant reductions in FA (A) appear to considerably overlap with significant global increases in FW (B). Only limited reductions in FA-t are observed in first-episode patients (C). No differences between medicated and medication- naïve patients were found for FA, FW, or FA-t.

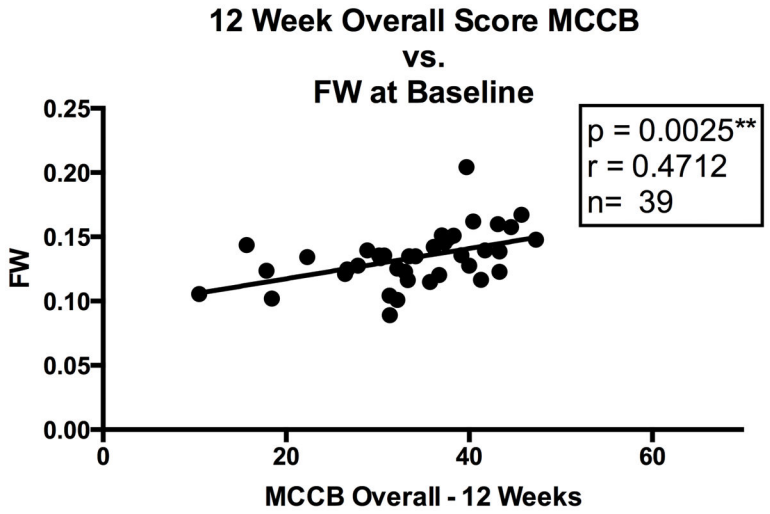

Figure 2.

Average baseline FW values in first-episode patients show a significant positive correlation with overall performance on the MCCB 12 weeks following antipsychotic treatment. This suggests that greater FW values at the time of presentation of frank psychosis predict better neurocognitive functioning 12 weeks later. This finding was unique to FW, as baseline FA-t was not correlated with MCCB scores at either baseline or 12 weeks following treatment.

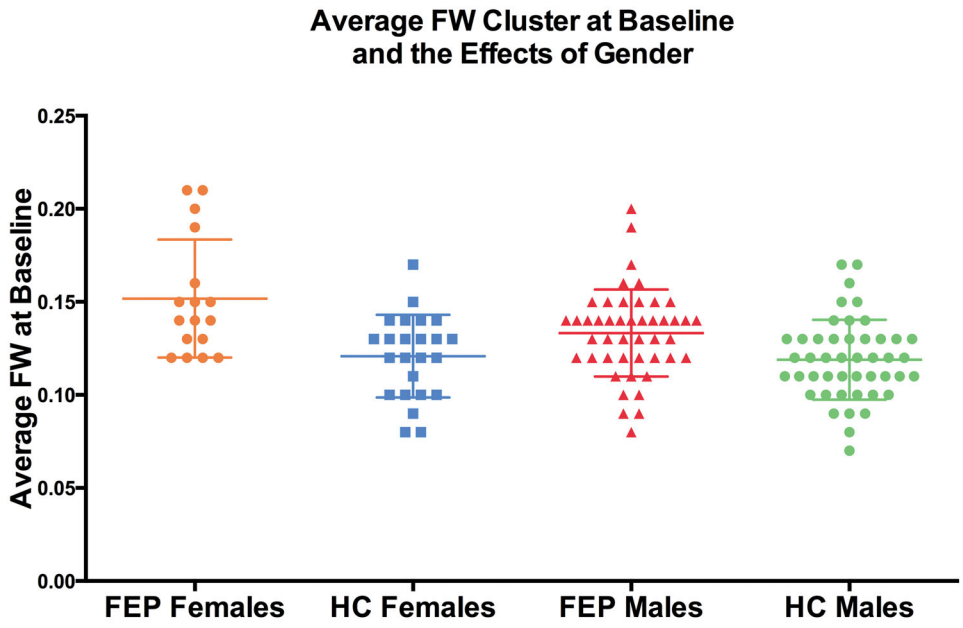

Figure 3.

Our results show a significant influence of sex on the FW response at baseline. FW values were significantly greater in female first-episode patients (n = 17) compared to male first-episode patients (n = 46) as well as both male and female healthy controls. Male first-episode patients also exhibited significantly greater FW values when compared to healthy controls. There was no significant difference in the correlations between the overall MCCB scores and FW values when comparing male and female FEP patients (See Table 2).

Table 1

	Healthy Controls Mean (SD)	First-Episode Patients Mean (SD)	P-value
Total Sample (N)	70	63	0.47
Males	46	46	
Females	24	17	
Age (years)	21.51 (5.01)	21.38 (4.89)	0.8756
Edinburgh	0.6986 (0.47)	0.6967 (0.44)	0.9815
Education (years)	13.33 (2.69)	12.32 (1.91)	0.0129
Medication Status			
Medicated		30 M/12 F	
Medication-Naïve		16 M/5 F	

Table 2

Pairwise Comparison of Mean for Sex by Diagnosis Groups: Tukey's HSD

FW	Difference in Means	Adjusted P-value
FEP-F vs. HC-F	0.031	0.0004*
FEP-M vs. HC-M	0.014	0.023*
FEP-F vs. FEP-M	0.019	0.035*
FEP-F vs. HC-M	0.033	0.00002*
HC-F vs. FEP-M	−0.012	0.168
HC-F vs. HC-M	0.002	0.988