Schizophrenia Research 209 (2019) 64–71

Contents lists available at ScienceDirect

Schizophrenia Research

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

# Role of glia in prefrontal white matter abnormalities in first episode psychosis or mania detected by diffusion tensor spectroscopy

Kathryn E. Lewandowski [a,b,*], Fei Du [a,b], Xiaoying Fan [a,b], Xi Chen [a,b], Polly Huynh [a], Dost Öngür [a,b]

[a] McLean Hospital, 115 Mill St., Belmont, MA 02478, United States of AmericaMcLean Hospital, Belmont, Massachusetts, 115 Mill St., Belmont MA 02478
[b] Harvard Medical School, 25 Shattuck St., Boston, MA 02115, United States of AmericaHarvard Medical School, Boston, Massachusetts, 25 Shattuck St., Boston, MA 02115

ARTICLE INFO

*Article history:*
Received 24 October 2018
Received in revised form 8 April 2019
Accepted 6 May 2019
Available online 14 May 2019

*Keywords:*
White matter
Glia
Diffusion
Schizophrenia
Bipolar disorder
First episode

ABSTRACT

*Background:* White matter (WM) abnormalities are amongst the most commonly described neuroimaging findings in patients with psychotic disorders including schizophrenia (SZ) and bipolar disorder (BD), and may be central to pathophysiology. Few studies have directly compared WM abnormalities in patients with SZ and BD in the first episode of illness, and no studies to date have attempted to separate abnormalities of axon and myelin using complementary MRI techniques.
*Methods:* We examined WM abnormalities in young adults with SZ ($n = 19$) or BD ($n = 16$) within the first year of illness onset, and healthy controls ($n = 22$) using a combination of diffusion tensor spectroscopy to measure NAA, creatine (Cr), and choline (Cho), and magnetization transfer ratio (MTR). MTR reflects myelin content, NAA diffusion is neuron specific, and Cr and Cho diffusion reflect both neuron and glial signal.
*Results:* We found no differences in MTR or NAA ADC in either patient group compared to controls, but significant elevations of both Cr and Cho diffusion in patients with SZ, and elevations of Cho diffusion in patients with BD. Elevations in Cr and Cho diffusion in the absence of NAA diffusion abnormalities indicate that the aberrant signal arises in glia.
*Conclusions:* Glial abnormalities were present and detectable by the first episode of psychosis, whereas major abnormalities in axon and myelin were not. Examination of these neurobiological markers early in the course of illness may clarify the neuroprogressive nature of these distinct aspects of WM, and their associations with early clinical phenotypes.



## 1. Introduction

White matter (WM) abnormalities are amongst the most commonly described neuroimaging findings in patients with psychotic disorders including schizophrenia (SZ) and bipolar disorder (BD), and may be central to pathophysiology (Hasler et al., 2006; Kubicki et al., 2007; Kyriakopoulos et al., 2008; Linke et al., 2013; Sussmann et al., 2009). WM integrity is essential for healthy signal transduction, and abnormalities are associated with behavioral correlates of illness, including poor cognitive functioning (Canu et al., 2015; Kuswanto et al., 2012; Linke et al., 2013) and more severe mood and psychotic symptoms (Canu et al., 2015; Hatton et al., 2014; Kuswanto et al., 2012).

Given overlapping risk factors and clinical manifestations of illness in patients with SZ and BD, it is not surprising that patients with BD and SZ appear to share some common neurobiological markers, including abnormalities of WM (Sussmann et al., 2009). However, there is also evidence of distinct aspects in the presentation and evolution of illness markers between these diagnoses (Colombo et al., 2012; O'Donoghue et al., 2017), suggesting that some pathophysiological processes may be distinct between them. Comparison of patients with SZ or BD in the first episode of illness may help elucidate what is shared and distinct in the neuroprogression of WM abnormalities early in the course of illness.

Abnormalities of WM appear to be present early in the course of SZ, and even prior to onset. DTI studies have found that structural connectivity abnormalities are already present by the first episode of SZ (Samartzis et al., 2014). Decreased fractional anisotropy (FA) and increased diffusivity are also reported in patients in the early course of illness (Canu et al., 2015; Hatton et al., 2014; Kuswanto et al., 2012; Lee et al., 2013; Ohtani et al., 2015), including in drug-naïve patients (Zeng et al., 2016), and are associated with clinical and cognitive symptoms. Studies of patients at ultra high risk for the development of psychosis or reporting subclinical psychotic symptoms have found WM abnormalities similar to patients in a first episode (Canu et al., 2015; Drakesmith et al., 2016; Kuswanto et al., 2012; Rigucci et al., 2016). A study using tract-based spatial statistics (TBSS) in patients at ultra high risk and in the first episode found that high risk participants who went on to develop psychosis had WM abnormalities similar to those

* Corresponding author at: 115 Mill St., AB South 349, Belmont, MA 02478, United States of America.
*E-mail address:* klewandowski@mclean.harvard.edu (K.E. Lewandowski).

https://doi.org/10.1016/j.schres.2019.05.018
0920-9964/

in the first episode group, whereas high risk participants who did not develop psychosis were more similar to controls (Rigucci et al., 2016), suggesting that WM abnormalities may be an illness marker. Additionally, a recent review found strong evidence of WM abnormalities in unaffected relatives of patients with SZ (Arat et al., 2015).

Patients experiencing a first episode of mania also appear to show WM abnormalities including total volume reduction, decreased FA, increased diffusivity, and evidence of axonal disorganization (Adler et al., 2006; Chan et al., 2010; De Peri et al., 2012; Keramatian et al., 2016); however, the literature in this population is sparse compared to that in SZ, and not all studies found abnormalities (Colombo et al., 2012).

The development and course of WM abnormalities in SZ compared to BD is unclear. A comparison of patients with BD with psychosis and SZ found WM abnormities in both groups, which did not differ from each other (Cui et al., 2011). Similarly, a study using TBSS in patients with SZ or BD found evidence of WM disconnectivity in both patient groups compared to controls; again, patient groups did not differ from each other (Kumar et al., 2015). However, a recent study found more pronounced NAA reductions in patients with BD compared to patients with SZ in younger subject only (Bustillo et al., 2019), and a recent selective review of white matter abnormalities in SZ and BD found abnormalities of frontal connectivity in both disorders, with more pronounced fronto-temporal alterations in SZ and more pronounced interhemispheric and limbic alterations in BD. These studies suggest that there are some common and some distinct pathways between these disorders (O'Donoghue et al., 2017). One of the only studies to directly compare patients with BD or SZ after a first episode found decreased WM volume in patients with SZ/SZA, but no volume reductions in patients with mania (Colombo et al., 2012).

The specific nature and pathophysiology of white matter abnormalities remain unclear, as DTI measures are relatively nonspecific insofar as they do not clearly differentiate between axon- and myelin-specific abnormalities (Mori and Zhang, 2006). Mechanistically, differentiation of neuronal and glial, and axon and myelin abnormalities may elucidate specific pathophysiological processes in psychosis. This may be particularly important in the examination of common and distinct pathways in the early course of SZ or BD, as some evidence suggests that patients may experience distinct premorbid or prodromal pathophysiological processes even if they arrive at similar neurobiological or phenotypic states via illness progression. Thus, examination of multiple elements of cell structure and function in the early course of these two disorders within the same study may help clarify these issues.

Novel MR techniques have opened the door to examination of brain microstructure in vivo via characterization of diffusion properties of various metabolites (Palombo et al., 2018). Because *N*-acetylaspartate (NAA) is found exclusively in neurons whereas Choline (Cho) and Creatine (Cr) are in both neurons and glia and actually appear to be more concentrated in glia (Choi et al., 2007; Le Belle et al., 2002; Urenjak et al., 1993), examination of these metabolites allows detection of differential signals from neuronal and glial abnormalities. In patients with SZ, consistent evidence supports reductions in NAA concentrations suggestive of neuronal abnormalities (e.g. (Kraguljac et al., 2012; Steen et al., 2005)), with less evidence of changes in Cho or Cr concentrations. Patients with BD also show NAA reductions, although perhaps in more limited brain regions (Kraguljac et al., 2012). Evidence of abnormalities in Cho or Cr in patients with BD is mixed, with some studies finding no differences from controls (Bustillo, 2013), and others reporting elevations (Cao et al., 2016; Dager et al., 2004; Hamakawa et al., 1998; Kubo et al., 2017; Moore et al., 2000). Two recent studies found abnormalities in Cr concentration in patients in a first episode in both SZ and BD (Du et al., 2018; Plitman et al., 2016). Increased Cho signal in neurodegenerative disorders is believed to be associated with gliosis and/or increased membrane turnover (Albrecht et al., 2016; Zahr et al., 2014), suggesting that these elevations may reflect neurodegenerative processes in both chronic and first episode psychosis.

A novel technique allows for the differentiation of myelin and axon measures using a combination of diffusion tensor spectroscopy (DTS) and magnetization transfer ratio (MTR; (Du and Ongür, 2013)). MTR quantifies proton exchange between "free" water molecules and water molecules "bound" to macromolecules such as myelin lipids (Henkelman et al., 2001). MTR measures have been found to be strongly associated with myelin content in human brain (Schmierer et al., 2004; Schmierer et al., 2007). DTS measures the diffusion of intracellular metabolites such as NAA, Cr, and Cho. Water exists in both intracellular and extracellular space and is exchanged between the two; NAA, Cr, and Cho, on the other hand, are located in intracellular space. Thus, the combined use of MTR and DTS offers the opportunity to study myelin and axon separately. Additionally, because choline-containing compounds are enriched in glia compared to neurons (Choi et al., 2007; Le Belle et al., 2002; Urenjak et al., 1993), examination of these intracellular metabolites separately permits exploration of both neuronal and glial integrity.

This approach revealed reduced MTR (suggesting reduced myelin content) and elevated apparent diffusion coefficient (ADC) of NAA (suggesting abnormal intra-neuronal content) in patients with SZ compared to age- and sex-matched healthy control participants (Du et al., 2013). In patients with BD, the same technique revealed reduced MTR, but no difference in NAA diffusion compared to controls, suggesting abnormalities of myelin content but not axon diameter (Lewandowski et al., 2015). These findings suggest some commonality and some distinction in WM abnormalities between these diagnoses, which may reflect neurodevelopmental processes or neurodegenerative effects of illness.

As noted above, few studies have directly compared WM abnormalities in patients with SZ and BD in the early course of illness, and no studies to date have applied combined MTR and DTS techniques in these populations to differentiate abnormalities of axon and myelin. Examination of these neurobiological markers early in the course of illness may clarify the neuroprogressive nature of these distinct aspects of WM, and their associations with early clinical phenotypes. Thus, we aimed to examine WM abnormalities in the first episode of illness in patients with BD or SZ using DTS and MTR in order to determine which abnormalities are present at the time of the first episode, and if and how these abnormalities differ by diagnosis. Given findings of more pronounced premorbid deficits in SZ and our own previous work in patients with chronic illness, we hypothesized that patients experiencing a first episode of SZ would show both axon and myelin abnormalities, whereas patients experiencing a first episode of mania would show myelin but not axon abnormalities. Additionally, we hypothesized that both patient groups would show abnormal Cr and Cho diffusion compared to controls, indicative of glial reactivity in response to neuronal damage; because of evidence of early premorbid neuroprogression in SZ with less evidence of this in BD (Kozicky et al., 2016; Martino et al., 2016; Passos et al., 2016), we hypothesized Cr and Cho diffusion abnormalities would be greater in SZ than in BD.

## 2. Materials and methods

### 2.1. Participants

Participants ($n = 57$) with primary psychosis including SZ or schizoaffective disorder ($n = 19$), BDI with psychosis ($n = 16$), and healthy controls ($n = 22$) were recruited through the McLean Hospital OnTrack first episode psychosis clinic as part of an ongoing research study (SZ and BD groups) and fliers posted at the hospital (Control group). McLean OnTrack is an outpatient program that admits adults ages 18–30 (average age at entry: 21.4 years) who have experienced new onset of psychosis, with or without mood symptoms, within the past 12 months. Diagnosis was determined by trained staff using the SCID-IV diagnostic interview in conjunction with all available collateral information from medical records, treatment providers, and family members. Exclusion criteria for patients included history of head injury

with loss of consciousness, seizure disorder, and MRI contraindications. Exclusion criteria for controls also included head injury with loss of consciousness, seizure disorder, and MRI contraindications, as well personal history of psychiatric diagnosis or treatment, and first degree relative with a history of SZ or BD. All procedures contributing to this work comply with and were approved by the McLean Hospital IRB and comply with the Helsinki Declaration of 1975, as revised in 2008.

### 2.2. Materials

#### 2.2.1. Clinical assessment

Clinical and community functioning were assessed using the Positive and Negative Syndrome Scale (PANSS), the Young Mania Rating Scale (YMRS), the Montgomery-Asberg Depression Rating Scale (MADRS) and the Multnomah Community Ability Scale (MCAS). The MCAS measures functioning in multiple domains including social interest/effectiveness, independence in daily living, and instrumental role functioning. The North American Adult Reading Test (NAART) was used as a measure of premorbid intelligence quotient (IQ). Information regarding current psychiatric medication use was collected by patient report, and chlorpromazine (CPZ) equivalents were calculated according to the recommendations of Baldessarini (2012).

#### 2.2.2. Magnetization transfer ratio

MTR data were collected from a $1 \times 3 \times 3$ cm voxel within the right prefrontal cortex white matter at 4 Tesla (Fig. 1). For details of anatomical imaging and voxel placement please see Du et al. (2013). A BISTRO saturation pulse train constructed with multiple hyperbolic Sec pulses (width: 50 msec) with varied radiofrequency pulse amplitudes was used, applied at the beginning of a standard point-resolved spectroscopy (PRESS) sequence (before the 90-degree pulse) to saturate "bound-water" signal with a specific frequency offset (Du et al., 2013). Data were obtained in 50-Hz steps at multiple frequencies offset 400–1000 Hz in either direction from the water signal, and an average MTR frequency was calculated. Saturation time ($t_{sat}$) was 2.6 s with repetition time/echo time (TR/TE) of 3000/30 msec and 2 signal averages.

#### 2.2.3. Diffusion tensor spectroscopy

DTS data were collected from the same $1 \times 3 \times 3$ cm voxel within the right prefrontal cortex white matter as noted above (Fig. 1). DTS procedures are described in detail by Du et al. (2013). Briefly, we modified the standard PRESS sequence by incorporating diffusion gradients for DTS measurements. Bipolar diffusion gradients with six directions and one control (seven total spectra) were applied to calculate diffusion tensors from water and metabolites. The applied b value of 1412 s/mm$^2$ was calibrated using a phantom with water ADC assumed to be 2.1 $\times 10^{-3}$ mm$^2$/s at room temperature (44). TR/TE was 3000/135 msec, and diffusion time ($D_t$) was 60 msec, with 48 signal averages for metabolites and 8 for water, respectively. Metabolite spectra were acquired with water saturation with VAPOR (Tkác et al., 1999). Concentrations of NAA, tCr, and tCho were quantified using the $b_0$ spectrum (TE = 135 ms) of DTS and normalized to the water signal from the same region (Supplementary Table 1). Values were consistent with findings from previous reports (Posse et al., 2007) and did not differ significantly by group.

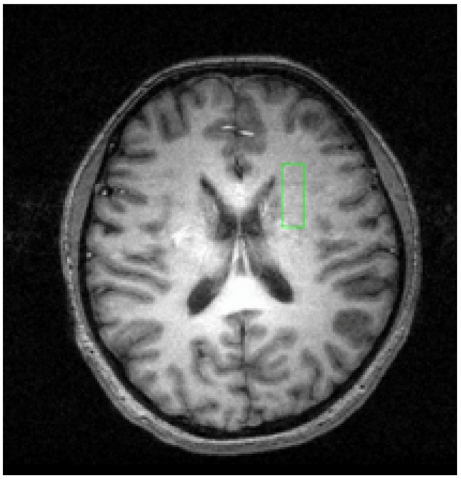

**Fig. 1.** Voxel placement. Depiction of placement of the voxel from which all imaging data were derived.

### 2.3. Procedures

#### 2.3.1. Data acquisition

Clinical and imaging data were collected in one or two sessions, as part of a larger study being conducted at McLean OnTrack. Clinical and functional measures took approximately 40–60 min to administer. Total MRI experiment time was approximately 70 min. A phantom DTS was run between human subject studies to correct for possible measurement errors from any potential machine instability.

#### 2.3.2. MRI and MRS data processing/analysis

Data were processed by an MR physicist (FD) who was blind to diagnosis using the techniques described by Du et al. (2013). Post-processing of the free induction decays (FIDs) was conducted using available software (Varian) and home-grown software running on MATLAB. Diffusion outcomes (ADC, RD, and AD) are reported in the following units: mm$^2$/s $\times 10^{-3}$.

### 2.4. Statistical approach

All analyses were performed using STATA (V. 12). First, we conducted ANOVAs or Chi2 tests to compare patients with SZ, BD, and healthy controls on demographic characteristics and premorbid IQ; patient groups were compared on clinical variables and community functioning. Groups were then compared on neurobiological measures including MTR, water ADC, NAA ADC, Cr ADC and Cho ADC. For all outcome measures with significant group findings pairwise *t*-tests were conducted with Bonferroni correction for multiple comparisons. Lastly, we examined the correlations amongst MTR, water ADC, NAA ADC, Cr ADC and Cho ADC.

In order to examine the association between our imaging measures and age, we used partial correlations to examine associations between imaging measures and age by diagnostic group. We then used correlation analyses to examine associations between our imaging measures and demographic variables (gender; race; education), clinical variables (duration of illness; PANSS; YMRS; MADRS; CPZ), and community functioning (MCAS). We chose not to correct for multiple comparisons in these exploratory correlational analyses in order to detect even modest relationships, which may be pursued in future work.

## 3. Results

### 3.1. DTS and MTR comparisons by group

Groups differed on several demographic and clinical variables, including gender, race, educational attainment, depression and community functioning (Table 1). In terms of diffusion and MTR, groups did not differ on water or NAA diffusion, or on MTR (Table 2). Inclusion of gender in the model did not change the findings, and gender did not contribute significantly to any of the models. Effect size calculations showed negligible effects between patient groups on all MTR and diffusion measures ($d = 0.06$ - $d = 0.15$) and small effects between patients and controls on MTR (SZ: $d = 0.15$; BD: $d = 0.30$) and water ADC (SZ: $d = 0.36$; BD: $d = 0.13$). Compared to controls, patients with BD also

**Table 1**
Demographic and clinical data by group.

| | BD ($n$ = 16) | SZ ($n$ = 19) | HC ($n$ = 22) | Test statistic | Pairwise |
|---|---|---|---|---|---|
| Age | 22.4 (3.2) | 21.7 (2.3) | 23.0 (3.3) | $F_{(2,54)} = 0.98$ | – |
| Gender (% female) | 25% | 5% | 55% | **$Chi2_{(2)} = 12.08$**** | |
| Race (% Caucasian) | 94% | 89% | 55% | **$Chi2_{(2)} = 10.53$**** | |
| Education | 4.9 (1.4) | 4.1 (1.2) | 6.0 (1.5) | $F_{(2,54)} = $ **9.72***** | SZ < HC |
| NAART VIQ | 113.2 (6.7) | 108.4 (6.5) | 107.6 (8.9) | $F_{(2,46)} = 2.64$ | – |
| YMRS | 5.8 (5.9) | 4.8 (5.5) | – | $F_{(1,33)} = 0.22$ | – |
| MADRS | 6.7 (7.2) | 12.11 (7.4) | – | **$F_{(1,33)} = 4.77$*** | SZ > BD |
| PANSS | 10.7 (5.3) | 12.1 (6.0) | – | $F_{(1,33)} = 0.51$ | – |
| CPZ | 158.1 (95.8) | 334.0 (253.2) | – | $F_{(1,18)} = 3.47$ | – |
| Age at onset | 21.0 (4.0) | 19.8 (1.9) | – | $F_{(1,22)} = 0.95$ | – |
| MCAS | 47.0 (4.8) | 39.9 (4.7) | – | **$F_{(1,32)} = 18.93$***** | SZ < BD |

Group-wise comparisons of imaging outcomes; pairwise comparisons with Bonferroni correction were conducted for all significant group findings. NAART VIQ: North American Adult Reading Test Verbal IQ; YMRS: Young Mania Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; PANSS: Positive and Negative Syndrome Scale; CPZ: chlorpromazine equivalent; MCAS: Multnomah Community Ability Scale.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

showed a small effect on NAA ADC ($d = 0.33$); patients with SZ showed a small to medium effect on NAA ADC ($d = 0.49$).

In contrast, groups differed significantly on Cr ADC and Cho ADC measures. Post-hoc analyses with Bonferroni correction revealed that patients with SZ showed elevations in both Cr ADC and Cho ADC compared to controls, and patients with BD showed elevated Cho ADC compared to controls. The two patient groups did not differ from each other. Effect sizes were calculated for Cr ADC and Cho ADC between groups. Group differences between both patient groups and controls were large for Cho ADC (BD vs. HC: $d = 1.15$; SZ vs. HC: $d = 1.02$); the effect size between patient groups was negligible ($d = 0.11$). For Cr ADC, we found a medium effect between the patient groups ($d = 0.64$) and a medium to large effect between patients with BD and controls ($d = 0.77$). The effect between patients with SZ and controls was large ($d = 1.08$).

Correlations amongst imaging measures across the total sample revealed significant correlations between Cho ADC and NAA ADC ($r = 0.49$, $p < .001$) and Cho ADC and MTR ($r = -0.31$, $p < .05$), with elevations in Cho ADC associated with increased NAA ADC and decreased MTR. Given the association between age and several imaging measures (see below), partial correlations by diagnosis accounting for age revealed a significant negative correlation between MTR and NAA ADC in patients with SZ but not BD. We found correlations between Cho ADC and MTR and NAA ADC in patients with SZ; In patients with BD, we found significant correlations between both Cr and Cho and MTR and NAA ADC (Table 3). There were no significant correlations amongst any imaging variables in the control group.

**Table 3**
Partial correlations amongst MTR and diffusion measures.

| | MTR | NAA ADC | Cr ADC | Cho ADC |
|---|---|---|---|---|
| SZ | | | | |
| MTR | – | – | – | – |
| NAA ADC | **−0.48*** | – | – | – |
| Cr ADC | −0.11 | −0.05 | – | – |
| Cho ADC | **−0.37*** | **0.57**** | 0.11 | – |
| BD | | | | |
| MTR | – | – | – | – |
| NAA ADC | −0.01 | – | – | – |
| Cr ADC | **−0.34*** | **0.72**** | – | – |
| Cho ADC | **−0.75**** | **0.39*** | **0.58**** | – |

Partial correlations amongst imaging measures by patient group accounting for age. MTR: Magnetization transfer ratio; NAA: *N*-acetylaspartate; ADC: Apparent diffusion coefficient; Cr: Creatine; Cho: Choline.
* $p < .05$.
** $p < .01$.

### 3.2. Association between neuroimaging measures and age

Correlational analyses showed a modest positive correlation between MTR and age ($r = 0.28$, $p = .02$) suggesting that as age increases myelin content increases. These findings support a hypothesis that myelin may not be at maximum levels yet in this young population. Line fits by diagnosis showed no evidence of an interaction. NAA showed a significant negative correlation with age (−0.46, $p = .02$), suggesting that as age increases mean diffusivity decreases. Line fits by diagnosis suggest similar slopes for Controls and SZ patients, but a steeper decrease in the BD group (Fig. 2). Correlations by subgroup showed a significant association in patients with BD (−0.67, $p < .05$); correlations in the SZ and control groups were not significant.

Cho ADC was significantly negatively correlated with age across the sample ($r = -0.34$, $p = .02$); this association was significant and large for BD ($r = -0.74$, $p = .01$) and moderate but non-significant for SZ ($r = -0.41$, $p = .14$). There was no association between Cho and age in Controls ($r = 0.04$) (Fig. 3).

### 3.3. Association between diffusion measures and clinical and cognitive measures

Within the patient groups there were no significant correlations between MTR, diffusion measures of NAA, Cr, or Cho and state clinical or functional variables (YMRS, MADRS, and PANSS scores, and MCAS). Diffusion measures were also not associated with age at illness onset. However, NAA ADC was positively correlated with CPZ ($r = 0.78$, $p = .003$). A post-hoc regression predicting NAA ADC by diagnosis, CPZ, and the diagnosis X CPZ interaction showed no significant interaction effect, suggesting that the relationship between CPZ and NAA did not differ by diagnosis. In terms of cognition, NAART scores were not correlated with any diffusion measure.

**Table 2**
DTS and MTR data by diagnostic group.

| | BD ($n$ = 16) | SZ ($n$ = 19) | HC ($n$ = 22) | F-statistic | Pairwise |
|---|---|---|---|---|---|
| MTR | 0.144 (0.026) | 0.148 (0.026) | 0.152 (0.028) | 0.52 | – |
| Water ADC | 0.641 (0.069) | 0.653 (0.080) | 0.616 (0.123) | 0.69 | – |
| NAA ADC | 0.208 (0.082) | 0.212 (0.056) | 0.186 (0.049) | 1.00 | – |
| Cr ADC | 0.222 (0.082) | 0.318 (0.216) | 0.162 (0.074) | **5.64**** | SZ > HC |
| Cho ADC | 0.218 (0.088) | 0.208 (0.086) | 0.136 (0.055) | **6.35**** | SZ, BD > HC |

Group-wise comparisons of imaging outcomes; pairwise comparisons with Bonferroni correction were conducted for all significant group findings. MTR: Magnetization transfer ratio; ADC: Apparent diffusion coefficient; NAA: *N*-acetylaspartate; Cr: Creatine; Cho: Choline.
** $p < .01$.

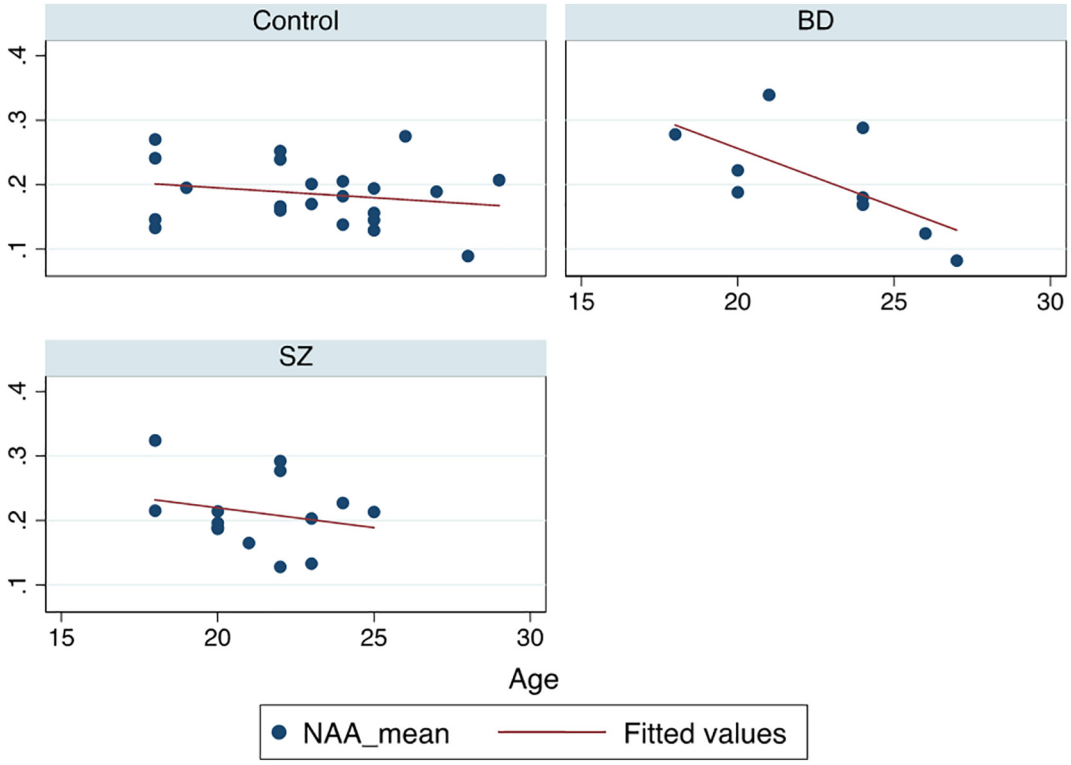


**Fig. 2.** NAA ADC X age by diagnosis. Partial correlations between *N*-acetylaspartate and age by diagnostic group. NAA: *N*-acetylaspartate; ADC: apparent diffusion coefficient; BD: bipolar disorder; SZ: schizophrenia.

## 4. Discussion

The present study used a combination of MRI-based MTR and DTS techniques to examine WM abnormalities in a cross-diagnostic group of patients after a first episode of psychosis or mania. Contrary to our hypotheses, we found no significant differences in MTR or NAA ADC in either patient group compared to controls, although effect size calculations showed that the difference between patients with SZ and

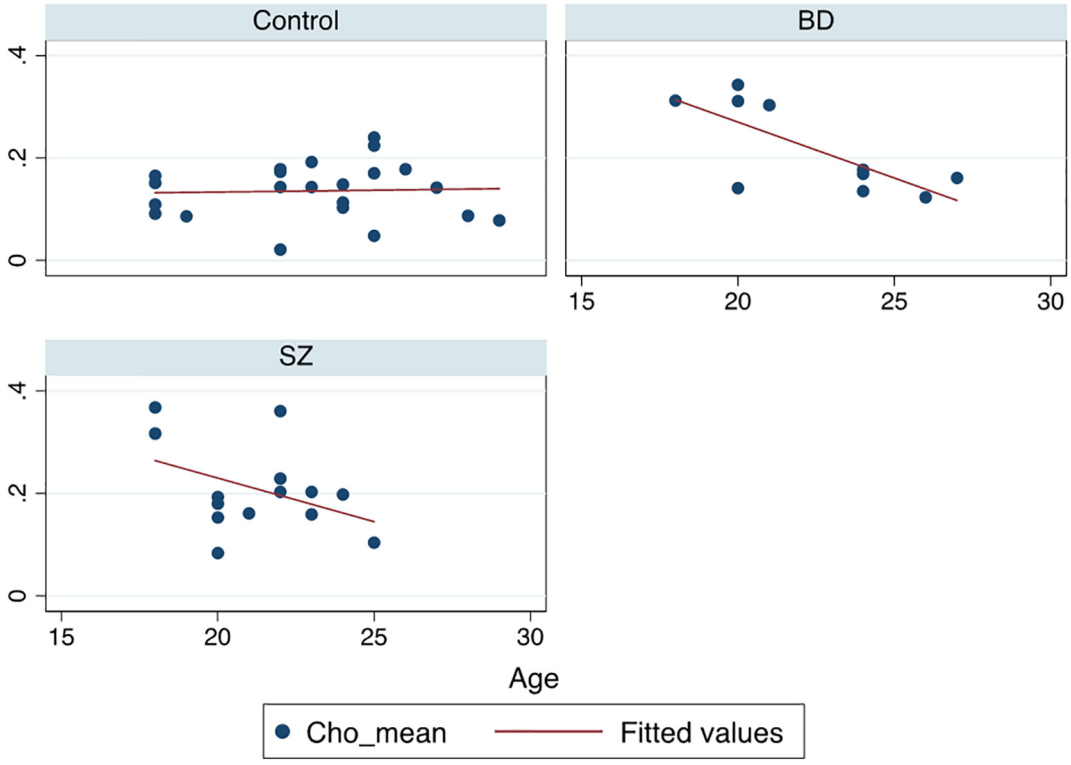


**Fig. 3.** Cho ADC X age by diagnosis. Partial correlations between Choline and age by diagnostic group. Cho: Choline; ADC: apparent diffusion coefficient; BD: bipolar disorder; SZ: schizophrenia.

controls on NAA ADC was in the small to medium range. Together, these findings suggest that significant abnormalities of myelination and axon morphology are not evident in the very early phase of SZ or BD, although effects may be emerging in patients with SZ. These findings differ from those in patients with chronic illness, in which we have reported reductions in myelin in both SZ and BD (Du et al., 2013; Lewandowski et al., 2015), and abnormalities in axon geometry in SZ (Du et al., 2013). We found elevations of both Cr and Cho diffusion in patients with first episode SZ, and elevations of Cho diffusion in patients with first episode BD, all with large effects. Elevations in Cr and Cho ADC in the absence of NAA ADC abnormalities suggest that the aberrant signal may arise in glia, suggesting that glial abnormalities are present in the first episode in both SZ and BD, perhaps more pronounced in patients with SZ. Together with our myelin and axon outcomes, these findings suggest that major abnormalities in axon and myelin may not yet be pronounced in the first episode of psychosis, but glial abnormalities are. Indeed, Cho ADC was associated with decreased myelination and increased NAA diffusivity in both patient groups; Cr ADC (which was positively correlated with Cho ADC in the BD group) was also associated with myelin and NAA diffusion in the BD group. We did not see any evidence of these associations in the healthy control group. We interpret this overall picture as suggesting an active glial process in early psychosis, with subsequent neurodegeneration into chronic illness.

One possibility for increased glial process early in illness is that it is reflective of neuroinflammation. Other reports have found acute processes in early psychosis suggestive of neuroinflammation using a variety of methodologies, including assessment of glial activation, inflammatory cytokines (Bloomfield et al., 2016; Miller et al., 2011), and free water imaging, which assesses extracellular free water as a marker of active inflammatory processes (Pasternak et al., 2012). Previous reports suggest that these inflammatory processes are more active in the early course of illness without significant evidence of axonal change, and less prominent in chronicity when axonal abnormalities are more consistently reported (Pasternak et al., 2015). Whether these changes reflect the evolution of a single process or two separate processes remains an open question.

Age was associated with increased MTR and decreased NAA ADC across groups, which may reflect continued myelination throughout late adolescence and early adulthood in both healthy young people and young patients with SZ and BD (Patel et al., 2018). We found decreased Cho ADC with age in the SZ and BD groups only. Again, together with the overall elevation of Cho in both patient groups, this finding suggests that the active glial process seen in early psychosis may begin to stabilize with increasing age.

We did not find any associations amongst MTR and DTS measures and clinical or cognitive outcomes. This is not surprising, given that we did not see major disruptions of myelin or axon geometry. The lack of association with Cr ADC and Cho ADC suggest that these measures in the first episode of illness may be reflective of active processes, but in the absence of pronounced impact on myelin and axon structure these changes do not yet exert a major influence on behavioral and clinical measures. We did, however, find a strong association between NAA diffusion and CPZ equivalent in both patient groups. Several possible interpretations of this finding may be considered, including direct effects of medication on axon integrity, or more severe lifetime illness associated with both reduced axon integrity and higher CPZ doses. While we did not find evidence of association between NAA and clinical symptoms, our clinical measures only ascertained state clinical symptomatology amongst a sample of relatively stable outpatients. Future studies assessing lifetime illness severity, patients during more acute illness states, or antipsychotic naïve patients in the first episode may clarify this issue.

The present study must be considered in light of several limitations, including a relatively small sample, and differences in the patient and controls groups on several demographic variables including education and gender. As noted above, including gender as a covariate in the group comparisons did not alter our findings. Controlling for factors such as educational attainment or estimated IQ can be controversial, as these variables differ systematically between patients and healthy adults and matching may introduce selection bias. Nevertheless, group differences on these variables should be considered, as previous studies have found associations between education and imaging outcomes. Additionally, in this work we consider glial cells together as a class. There are three major classes of glial cells: astrocytes, oligodendrocytes, and microglia. Our current results do not allow us to distinguish which glial cell type the signals may be arising from. Lastly, each of the methods we have used in this study relies on certain assumptions, a necessary feature of in vivo human neuroimaging research. For example, MTR reflects macromolecule interactions with water molecules, and not specifically myelin. But in the white matter, myelin is the predominant macromolecule class (Du and Ongür, 2013). Likewise, NAA is predominantly but not exclusively found within neurons, and Cr and Cho are over-represented in glial cells but not solely there (Choi et al., 2007; Duarte et al., 2012; Le Belle et al., 2002; Tsai and Coyle, 1995; Urenjak et al., 1993). Therefore, the interpretation of our findings needs further support from other cell biology or pathology studies.

Our findings of Cr and Cho diffusion abnormalities in the absence of MTR and NAA diffusion abnormalities in first episode SZ and BD suggest active neuroprogressive processes, possibly reflecting neuroinflammation, during this phase of illness. In light of previous findings in chronic patients (Du et al., 2013; Lewandowski et al., 2015; Pasternak et al., 2015), the present work suggests that active neuroprogression in the first episode of illness has not yet resulted in major alterations of axon geometry or myelination, but with illness progression WM abnormalities become more pronounced, particularly in patients with SZ, with subsequent reduction in active glial involvement. These findings have implications for understanding of neuroprogressive processes in the early course of illness and into chronicity, and for the development of interventions aimed at targeting these processes while they are active and amenable to change.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.05.018.

**Contributors**

KEL conducted the statistical analyses and wrote the first draft of the manuscript. DO and FD were responsible for the imaging study design and developed and oversaw the imaging procedures and data processing. XF and XC participated in the imaging data processing and analysis. All authors contributed to and have approved the final manuscript.

## Financial support

This work was supported by the National Institute of Mental Health (grant R21MH110699 (KEL); NIMH grant K24MH104449 (DO); NIMH grant R21MH114020 (FD)) and NARSAD (award 22592 (FD)).

## Declaration of Competing Interest

All authors declare that they have no conflicts of interest in association with this work.

**Acknowledgment**

None.

## References

Adler, C.M., Adams, J., DelBello, M.P., Holland, S.K., Schmithorst, V., Levine, A., Jarvis, K., Strakowski, S.M., 2006. Evidence of white matter pathology in bipolar disorder adolescents experiencing their first episode of mania: a diffusion tensor imaging study. Am. J. Psychiatry 163 (2), 322–324.Adler, C.M., Adams, J., DelBello, M.P., Holland, S.K., Schmithorst, V., Levine, A., Jarvis, K., & Strakowski, S.M., 2006. Evidence of white matter pathology in bipolar disorder adolescents experiencing their first episode of mania: a diffusion tensor imaging study. Am. J. Psychiatry. 163(2) 322-324.

Albrecht, D.S., Granziera, C., Hooker, J.M., Loggia, M.L., 2016. *In vivo* imaging of human neuroinflammation. ACS Chem. Neurosci. 7 (4), 470–483.Albrecht, D.S., Granziera, C., Hooker, J.M., & Loggia, M.L., 2016. In Vivo imaging of human neuroinflammation. ACS Chem. Neurosci. 7(4) 470–483.

Arat, H.E., Chouinard, V.A., Cohen, B.M., Lewandowski, K.E., Öngür, D., 2015. Diffusion tensor imaging in first degree relatives of schizophrenia and bipolar disorder patients. Schizophr. Res. 161 (2–3), 329–339.Arat, H.E., Chouinard, V.A., Cohen, B.M., Lewandowski, K.E., & Öngür, D., 2015. Diffusion tensor imaging in first degree relatives of schizophrenia and bipolar disorder patients. Schizophr. Res. 161(2-3) 329-339.

Baldessarini, R.J., 2012. Chemotherapy in Psychiatry. Springer Verlag, New York. Baldessarini, R.J., 2012. Chemotherapy in Psychiatry. New York: Springer Verlag.

Bloomfield, P.S., Selvaraj, S., Veronese, M., Rizzo, G., Bertoldo, A., Owen, D.R., Bloomfield, M.A., Bonoldi, I., Kalk, N., Turkheimer, F., McGuire, P., de Paola, V., Howes, O.D., 2016. Microglial activity in people at ultra high risk of psychosis and in schizophrenia: an [(11)C]PBR28 PET brain imaging study. Am. J. Psychiatry 173 (1), 44–52. Bloomfield, P.S., Selvaraj, S., Veronese, M., Rizzo, G., Bertoldo, A., Owen, D.R., Bloomfield, M.A., Bonoldi, I., Kalk, N., Turkheimer, F., McGuire, P., de Paola, V., & Howes, O.D., 2016. Microglial activity in people at ultra high risk of psychosis and in schizophrenia: An [(11)C]PBR28 PET brain imaging study. Am. J. Psychiatry. 173(1) 44-52.

Bustillo, J.R., 2013. Use of proton magnetic resonance spectroscopy in the treatment of psychiatric disorders: a critical update. Dialogues Clin. Neurosci. 15 (3), 329–337. Bustillo, J.R., 2013. Use of proton magnetic resonance spectroscopy in the treatment of psychiatric disorders: a critical update. Dialogues Clin. Neurosci. 15(3) 329-337.

Bustillo, J.R., Jones, T., Qualls, C., Chavez, L., Lin, D., Lenroot, R.K., Gasparovic, C., 2019. Proton magnetic resonance spectroscopic imaging of gray and white matter in bipolar-I and schizophrenia. J. Affect. Disord. 246, 745–753.Bustillo, J.R. Jones, T., Qualls, C., Chavez, L., Lin, D., Lenroot, R.K., & Gasparovic, C., 2019. Proton magnetic resonance spectroscopic imaging of gray and white matter in bipolar-I and schizophrenia. J. Affect. Disord. 246 745-753

Canu, E., Agosta, F., Filippi, M., 2015. A selective review of structural connectivity abnormalities of schizophrenic patients at different stages of the disease. Schizophr. Res. 161 (1), 19–28.Canu, E., Agosta, F., & Filippi, M., 2015. A selective review of structural connectivity abnormalities of schizophrenic patients at different stages of the disease. Schizophr. Res. 161(1) 19-28.

Cao, B., Stanley, J.A., Selvaraj, S., Mwangi, B., Passos, I.C., Zunta-Soares, G.B., Soares, J.C., 2016. Evidence of altered membrane phospholipid metabolism in the anterior cingulate cortex and striatum of patients with bipolar disorder I: a multi-voxel (1)H MRS study. J. Psychiatr. Res. 81, 48–55.Cao, B., Stanley, J.A., Selvaraj, S., Mwangi, B., Passos, I.C., Zunta-Soares, G.B., & Soares, J.C., 2016. Evidence of altered membrane phospholipid metabolism in the anterior cingulate cortex and striatum of patients with bipolar disorder I: A multi-voxel (1)H MRS study. J. Psychiatr. Res. 81 48-55.

Chan, W.Y., Yang, G.L., Chia, M.Y., Woon, P.S., Lee, J., Keefe, R., Sitoh, Y.Y., Nowinski, W.L., Sim, K., 2010. Cortical and subcortical white matter abnormalities in adults with remitted first-episode mania revealed by Tract-Based Spatial Statistics. Bipolar Disord. 12 (4), 383–389.Chan, W.Y., Yang, G.L., Chia, M.Y., Woon, P.S., Lee, J., Keefe, R., Sitoh, Y.Y., Nowinski, W.L., & Sim, K., 2010. Cortical and subcortical white matter abnormalities in adults with remitted first-episode mania revealed by Tract-Based Spatial Statistics. Bipolar Disord. 12(4) 383-389.

Choi, J.K., Dedeoglu, A., Jenkins, B.G., 2007. Application of MRS to mouse models of neurodegenerative illness. NMR Biomed. 20 (3), 216–237.Choi, J.K., Dedeoglu, A., & Jenkins, B.G., 2007. Application of MRS to mouse models of neurodegenerative illness. NMR Biomed. 20(3) 216-237.

Colombo, R.R., Schaufelberger, M.S., Santos, L.C., Duran, F.L., Menezes, P.R., Scazufca, M., Busatto, G.F., Zanetti, M.V., 2012. Voxelwise evaluation of white matter volumes in first-episode psychosis. Psychiatry Res. 202 (3), 198–205.Colombo, R.R., Schaufelberger, M.S., Santos, L.C., Duran, F.L., Menezes, P.R., Scazufca, M., Busatto, G.F., & Zanetti, M.V., 2012. Voxelwise evaluation of white matter volumes in first-episode psychosis. Psychiatry Res. 202(3) 198-205.

Cui, L., Chen, Z., Deng, W., Huang, X., Li, M., Ma, X., Huang, C., Jiang, L., Wang, Y., Wang, Q., Collier, D.A., Gong, Q., Li, T., 2011. Assessment of white matter abnormalities in paranoid schizophrenia and bipolar mania patients. Psychiatry Res. 194 (3), 347–353.Cui, L., Chen, Z., Deng, W., Huang, X., Li, M., Ma, X., Huang, C., Jiang, L., Wang, Y., Wang, Q., Collier, D.A., Gong, Q., & Li, T., 2011. Assessment of white matter abnormalities in paranoid schizophrenia and bipolar mania patients. Psychiatry Res. 194(3) 347-353.

Dager, S.R., Friedman, S.D., Parow, A., Demopulos, C., Stoll, A.L., Lyoo, I.K., Dunner, D.L., Renshaw, P.F., 2004. Brain metabolic alterations in medication-free patients with bipolar disorder. Arch. Gen. Psychiatry 61 (5), 450–458.Dager, S.R., Friedman, S.D., Parow, A., Demopulos, C., Stoll, A.L., Lyoo, I.K., Dunner, D.L., & Renshaw, P.F., 2004. Brain metabolic alterations in medication-free patients with bipolar disorder. Arch. Gen. Psychiatry. 61(5) 450-458.

De Peri, L., Crescini, A., Deste, G., Fusar-Poli, P., Sacchetti, E., Vita, A., 2012. Brain structural abnormalities at the onset of schizophrenia and bipolar disorder: a meta-analysis of controlled magnetic resonance imaging studies. Curr. Pharm. Des. 18 (4), 486–494. De Peri, L., Crescini, A., Deste, G., Fusar-Poli, P., Sacchetti, E., & Vita, A., 2012. Brain structural abnormalities at the onset of schizophrenia and bipolar disorder: a meta-analysis of controlled magnetic resonance imaging studies. Curr. Pharm. Des. 18 (4) 486-494.

Drakesmith, M., Dutt, A., Fonville, L., Zammit, S., Reichenberg, A., Evans, C.J., Lewis, G., Jones, D.K., David, A.S., 2016. Mediation of developmental risk factors for psychosis by white matter microstructure in young adults with psychotic experiences. JAMA Psychiat. 73 (4), 396–406.Drakesmith, M., Dutt, A., Fonville, L., Zammit, S., Reichenberg, A., Evans, C.J., Lewis, G., Jones, D.K., & David, A.S., 2016. Mediation of Developmental Risk Factors for Psychosis by White Matter Microstructure in Young Adults With Psychotic Experiences. JAMA Psychiatry. 73(4) 396-406.

Du, F., Ongür, D., 2013. Probing myelin and axon abnormalities separately in psychiatric disorders using MRI techniques. Front. Integr. Neurosci. 7 (24).Du, F., & Ongür, D., 2013. Probing myelin and axon abnormalities separately in psychiatric disorders using MRI techniques. Front. Integr. Neurosci. 7 24.

Du, F., Cooper, A.J., Thida, T., Shinn, A.K., Cohen, B.M., Ongür, D., 2013. Myelin and axon abnormalities in schizophrenia measured with magnetic resonance imaging techniques. Biol. Psychiatry 74 (6), 451–457.Du, F., Cooper, A.J., Thida, T., Shinn, A.K., Cohen, B.M., & Ongür, D., 2013. Myelin and axon abnormalities in schizophrenia measured with magnetic resonance imaging techniques. Biol. Psychiatry. 74(6) 451-457.

Du, F., Yuksel, C., Chouinard, V.A., Huynh, P., Ryan, K., Cohen, B.M., Öngür, D., 2018. Abnormalities in high-energy phosphate metabolism in first-episode bipolar disorder measured using 31P-magnetic resonance spectroscopy. Biol. Psychiatry 84 (11), 797–802. Du, F., Yuksel, C., Chouinard, V.A., Huynh, P., Ryan, K., Cohen, B.M., & Öngür, D., 2017. Abnormalities in High-Energy Phosphate Metabolism in First-Episode Bipolar Disorder Measured Using 31P-Magnetic Resonance Spectroscopy. Biol. Psychiatry.

Duarte, J.M., Lei, H., Mlynárik, V., Gruetter, R., 2012. The neurochemical profile quantified by in vivo 1H NMR spectroscopy. Neuroimage 61 (2), 342–362.Duarte, J.M., Lei, H., Mlynárik, V., & Gruetter, R., 2012. The neurochemical profile quantified by in vivo 1H NMR spectroscopy. Neuroimage. 61(2) 342-362.

Hamakawa, H., Kato, T., Murashita, J., Kato, N., 1998. Quantitative proton magnetic resonance spectroscopy of the basal ganglia in patients with affective disorders. Eur. Arch. Psychiatry Clin. Neurosci. 248 (1), 53–58.Hamakawa, H., Kato, T., Murashita, J., & Kato, N., 1998. Quantitative proton magnetic resonance spectroscopy of the basal ganglia in patients with affective disorders. Eur Arch Psychiatry Clin. Neurosci. 248(1) 53-58.

Hasler, G., Drevets, W.C., Gould, T.D., Gottesman, I.I., Manji, H.K., 2006. Toward constructing an endophenotype strategy for bipolar disorders. Biol. Psychiatry 60 (2), 93–105. Hasler, G., Drevets, W.C., Gould, T.D., Gottesman, I.I., & Manji, H.K., 2006. Toward constructing an endophenotype strategy for bipolar disorders. Biol. Psychiatry. 60(2) 93-105.

Hatton, S.N., Lagopoulos, J., Hermens, D.F., Hickie, I.B., Scott, E., Bennett, M.R., 2014. White matter tractography in early psychosis: clinical and neurocognitive associations. J. Psychiatry Neurosci. 39 (6), 417–427.Hatton, S.N., Lagopoulos, J., Hermens, D.F., Hickie, I.B., Scott, E., & Bennett, M.R., 2014. White matter tractography in early psychosis: clinical and neurocognitive associations. J. Psychiatry Neurosci. 39(6) 417-427.

Henkelman, R.M., Stanisz, G.J., Graham, S.J., 2001. Magnetization transfer in MRI: a review. NMR Biomed. 14, 57–64.Henkelman, R.M., Stanisz, G.J., & Graham, S.J., 2001. Magnetization transfer in MRI: a review. NMR Biomed. 14 57–64.

Keramatian, K., Dhanoa, T., McGirr, A., Lang, D.J., Honer, W.G., Lam, R.W., Yatham, L.N., 2016. Structural brain changes in first episode mania with and without psychosis: data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM). World J. Biol. Psychiatry 1–11.Keramatian, K., Dhanoa, T., McGirr, A., Lang, D.J., Honer, W.G., Lam, R.W., & Yatham, L.N., 2016. Structural brain changes in first episode mania with and without psychosis: Data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM). World J. Biol. Psychiatry. 1-11.

Kozicky, J.M., McGirr, A., Bond, D.J., Gonzalez, M., Silveira, L.E., Keramatian, K., Torres, I.J., Lam, R.W., Yatham, L.N., 2016. Neuroprogression and episode recurrence in bipolar I disorder: a study of gray matter volume changes in first-episode mania and association with clinical outcome. Bipolar Disord. 18 (6), 511–519.Kozicky, J.M., McGirr, A., Bond, D.J., Gonzalez, M., Silveira, L.E., Keramatian, K., Torres, I.J., Lam, R.W., & Yatham, L.N., 2016. Neuroprogression and episode recurrence in bipolar I disorder: A study of gray matter volume changes in first-episode mania and association with clinical outcome. Bipolar Disord. 18(6) 511-519.

Kraguljac, N.V., Reid, M., White, D., Jones, R., den Hollander, J., Lowman, D., Lahti, A.C., 2012. Neurometabolites in schizophrenia and bipolar disorder - a systematic review and meta-analysis. Psychiatry Res. 203 (2–3), 111–125.Kraguljac, N.V., Reid, M., White, D., Jones, R., den Hollander, J., Lowman, D., & Lahti, A.C., 2012. Neurometabolites in schizophrenia and bipolar disorder - a systematic review and meta-analysis. Psychiatry Res. 203(2-3) 111-125.

Kubicki, M., McCarley, R., Westin, C.F., Park, H.J., Maier, S., Kikinis, R., Jolesz, F.A., Shenton, M.E., 2007. A review of diffusion tensor imaging studies in schizophrenia. J. Psychiatry Res. 41 (1–2), 15–30.Kubicki, M., McCarley, R., Westin, C.F., Park, H.J., Maier, S., Kikinis, R., Jolesz, F.A., & Shenton, M.E., 2007. A review of diffusion tensor imaging studies in schizophrenia. J Psychiatry Res. 41(1-2) 15-30.

Kubo, H., Nakataki, M., Sumitani, S., Iga, J.I., Numata, S., Kameoka, N., Watanabe, S.Y., Umehara, H., Kinoshita, M., Inoshita, M., Tamaru, M., Ohta, M., Nakayama-Yamauchi, C., Funakoshi, Y., Harada, M., Ohmori, T., 2017. 1H-magnetic resonance spectroscopy study of glutamate-related abnormality in bipolar disorder. J. Affect. Disord. 208, 139–144.Kubo, H., Nakataki, M., Sumitani, S., Iga, J.I., Numata, S., Kameoka, N., Watanabe, S.Y., Umehara, H., Kinoshita, M., Inoshita, M., Tamaru, M., Ohta, M., Nakayama-Yamauchi, C., Funakoshi, Y., Harada, M., & Ohmori, T., 2017. 1H-magnetic resonance spectroscopy study of glutamate-related abnormality in bipolar disorder. J. Affect. Disord. 208 139-144.

Kumar, J., Iwabuchi, S., Oowise, S., Balain, V., Palaniyappan, L., Liddle, P.F., 2015. Shared white-matter dysconnectivity in schizophrenia and bipolar disorder with psychosis. Psychol. Med. 45 (4), 759–770.Kumar, J., Iwabuchi, S., Oowise, S., Balain, V., Palaniyappan, L., & Liddle, P.F., 2015. Shared white-matter dysconnectivity in schizophrenia and bipolar disorder with psychosis. Psychol. Med. 45(4) 759-770.

Kuswanto, C.N., Teh, I., Lee, T.S., Sim, K., 2012. Diffusion tensor imaging findings of white matter changes in first episode schizophrenia: a systematic review. Clin. Psychopharmacol. Neurosci. 10 (1), 13–24.Kuswanto, C.N., Teh, I., Lee, T.S., & Sim, K., 2012. Diffusion tensor imaging findings of white matter changes in first episode schizophrenia: a systematic review. Clin. Psychopharmacol. Neurosci. 10(1) 13-24.

Kyriakopoulos, M., Bargiotas, T., Barker, G.J., Frangou, S., 2008. Diffusion tensor imaging in schizophrenia. Eur. Psychiatry 23 (4), 255–273.Kyriakopoulos, M., Bargiotas, T., Barker, G.J., & Frangou, S., 2008. Diffusion tensor imaging in schizophrenia. Eur. Psychiatry. 23(4) 255-273.

Le Belle, J.E., Harris, N.G., Williams, S.R., Bhakoo, K.K., 2002. A comparison of cell and tissue extraction techniques using high-resolution 1H-NMR spectroscopy. NMR Biomed. 15

(1), 37–44.Le Belle, J.E., Harris, N.G., Williams, S.R., & Bhakoo, K.K., 2002. A comparison of cell and tissue extraction techniques using high-resolution 1H-NMR spectroscopy. NMR Biomed. 15(1) 37-44.

Lee, S.H., Kubicki, M., Asami, T., Seidman, L.J., Goldstein, J.M., Mesholam-Gately, R.I., McCarley, R.W., Shenton, M.E., 2013. Extensive white matter abnormalities in patients with first-episode schizophrenia: a Diffusion Tensor Iimaging (DTI) study. Schizophr. Res. 143 (2–3), 231–238.Lee, S.H., Kubicki, M., Asami, T., Seidman, L.J., Goldstein, J.M., Mesholam-Gately, R.I., McCarley, R.W., & Shenton, M.E., 2013. Extensive white matter abnormalities in patients with first-episode schizophrenia: a Diffusion Tensor Iimaging (DTI) study. Schizophr. Res. 143(2-3) 231-238.

Lewandowski, K.E., Ongür, D., Sperry, S.H., Cohen, B.M., Sehovic, S., Goldbach, J.R., Du, F., 2015. Myelin vs axon abnormalities in white matter in bipolar disorder. Neuropsychopharmacology 40 (5), 1243–1249.Lewandowski, K.E., Ongür, D., Sperry, S.H., Cohen, B.M., Sehovic, S., Goldbach, J.R., & Du, F., 2015. Myelin vs axon abnormalities in white matter in bipolar disorder. Neuropsychopharmacology. 40(5) 1243-1249.

Linke, J., King, A.V., Poupon, C., Hennerici, M.G., Gass, A., Wessa, M., 2013. Impaired anatomical connectivity and related executive functions: differentiating vulnerability and disease marker in bipolar disorder. Biol. Psychiatry 74 (12), 908–916.Linke, J., King, A.V., Poupon, C., Hennerici, M.G., Gass, A., & Wessa, M., 2013. Impaired anatomical connectivity and related executive functions: differentiating vulnerability and disease marker in bipolar disorder. Biol. Psychiatry. 74(12) 908-916.

Martino, D.J., Samamé, C., Marengo, E., Igoa, A., Strejilevich, S.A., 2016. A critical overview of the clinical evidence supporting the concept of neuroprogression in bipolar disorder. Psychiatry Res. 235, 1–6.Martino, D.J., Samamé, C., Marengo, E., Igoa, A., & Strejilevich, S.A., 2016. A critical overview of the clinical evidence supporting the concept of neuroprogression in bipolar disorder. Psychiatry Res. 235 1-6.

Miller, B.J., Buckley, P., Seabolt, W., Mellor, A., Kirkpatrick, B., 2011. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol. Psychiatry 70 (7), 663–671.Miller, B.J., Buckley, P., Seabolt, W., Mellor, A., & Kirkpatrick, B., 2011. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol. Psychiatry. 70(7) 663-671.

Moore, C.M., Breeze, J.L., Gruber, S.A., Babb, S.M., Frederick, B.B., Villafuerte, R.A., Stoll, A.L., Hennen, J., Yurgelun-Todd, D.A., Cohen, B.M., Renshaw, P.F., 2000. Choline, myo-inositol and mood in bipolar disorder: a proton magnetic resonance spectroscopic imaging study of the anterior cingulate cortex. Bipolar Disord. 2 (3 Pt 2), 207–216.Moore, C.M., Breeze, J.L., Gruber, S.A., Babb, S.M., Frederick, B.B., Villafuerte, R.A., Stoll, A.L., Hennen, J., Yurgelun-Todd, D.A., Cohen, B.M., & Renshaw, P.F., 2000. Choline, myo-inositol and mood in bipolar disorder: a proton magnetic resonance spectroscopic imaging study of the anterior cingulate cortex. Bipolar Disord. 2(3 Pt 2) 207-216.

Mori, S., Zhang, J., 2006. Principles of diffusion tensor imaging and its applications to basic neuroscience research. Neuron 51 (5), 527–539.Mori, S., & Zhang, J., 2006. Principles of diffusion tensor imaging and its applications to basic neuroscience research. Neuron. 51(5) 527-539.

O'Donoghue, S., Holleran, L., Cannon, D.M., McDonald, C., 2017. Anatomical dysconnectivity in bipolar disorder compared with schizophrenia: a selective review of structural network analyses using diffusion MRI. J. Affect. Disord. 209, 217–228.O'Donoghue, S., Holleran, L., Cannon, D.M., & McDonald, C., 2017. Anatomical dysconnectivity in bipolar disorder compared with schizophrenia: A selective review of structural network analyses using diffusion MRI. J. Affect. Disord. 209 217-228.

Ohtani, T., Bouix, S., Lyall, A.E., Hosokawa, T., Saito, Y., Melonakos, E., Westin, C.F., Seidman, L.J., Goldstein, J., Mesholam-Gately, R., Petryshen, T., Wojcik, J., Kubicki, M., 2015. Abnormal white matter connections between medial frontal regions predict symptoms in patients with first episode schizophrenia. Cortex 71, 264–276.Ohtani, T., Bouix, S., Lyall, A.E., Hosokawa, T., Saito, Y., Melonakos, E., Westin, C.F., Seidman, L.J., Goldstein, J., Mesholam-Gately, R., Petryshen, T., Wojcik, J., & Kubicki, M., 2015. Abnormal white matter connections between medial frontal regions predict symptoms in patients with first episode schizophrenia. Cortex. 71 264-276.

Palombo, M., Shemesh, N., Ronen, I., Valette, J., 2018. Insights into brain microstructure from in vivo DW-MRS. Neuroimage 182, 97–116.Palombo, M., Shemesh, N., Ronen, I., & Valette, J., 2017. Insights into brain microstructure from in vivo DW-MRS. Neuroimage.

Passos, I.C., Mwangi, B., Vieta, E., Berk, M., Kapczinski, F., 2016. Areas of controversy in neuroprogression in bipolar disorder. Acta Psychiatr. Scand. 134 (2), 91–103.Passos, I.C., Mwangi, B., Vieta, E., Berk, M., & Kapczinski, F., 2016. Areas of controversy in neuroprogression in bipolar disorder. Acta Psychiatr. Scand. 134(2) 91-103.

Pasternak, O., Westin, C.F., Bouix, S., Seidman, L.J., Goldstein, J.M., Woo, T.U., Petryshen, T.L., Mesholam-Gately, R.I., McCarley, R.W., Kikinis, R., Shenton, M.E., Kubicki, M., 2012. Excessive extracellular volume reveals a neurodegenerative pattern in schizophrenia onset. J. Neurosci. 32 (48), 17365–17372.Pasternak, O., Westin, C.F., Bouix, S., Seidman, L.J., Goldstein, J.M., Woo, T.U., Petryshen, T.L., Mesholam-Gately, R.I., McCarley, R.W., Kikinis, R., Shenton, M.E., & Kubicki, M., 2012. Excessive extracellular volume reveals a neurodegenerative pattern in schizophrenia onset. J. Neurosci. 32 (48) 17365-17372.

Pasternak, O., Westin, C.F., Dahlben, B., Bouix, S., Kubicki, M., 2015. The extent of diffusion MRI markers of neuroinflammation and white matter deterioration in chronic schizophrenia. Schizophr. Res. 161 (1), 113–118.Pasternak, O., Westin, C.F., Dahlben, B., Bouix, S., & Kubicki, M., 2015. The extent of diffusion MRI markers of neuroinflammation and white matter deterioration in chronic schizophrenia. Schizophr. Res. 161 (1) 113-118.

Patel, Y., Shin, J., Gowland, P.A., Pausova, Z., Paus, T., IMAGEN consortium, 2018. Maturation of the human cerebral cortex during adolescence: myelin or dendritic arbor? Cereb. Cortex https://doi.org/10.1093/cercor/bhy204 (Epub ahead of print).Patel, Y., Shin, J., Gowland, P.A., Pausova, Z., Paus, T., IMAGEN consortium., 2018. Maturation of the human cerebral cortex during adolescence: Myelin or dendritic arbor? Cereb. Cortex. [Epub ahead of print].

Plitman, E., de la Fuente-Sandoval, C., Reyes-Madrigal, F., Chavez, S., Gómez-Cruz, G., León-Ortiz, P., Graff-Guerrero, A., 2016. Elevated myo-inositol, choline, and glutamate levels in the associative striatum of antipsychotic-naive patients with first-episode psychosis: a proton magnetic resonance spectroscopy study with implications for glial dysfunction. Schizophr. Bull. 42 (2), 415–424.Plitman, E., de la Fuente-Sandoval, C., Reyes-Madrigal, F., Chavez, S., Gómez-Cruz, G., León-Ortiz, P., & Graff-Guerrero, A., 2016. Elevated Myo-Inositol, Choline, and Glutamate Levels in the Associative Striatum of Antipsychotic-Naive Patients With First-Episode Psychosis: A Proton Magnetic Resonance Spectroscopy Study With Implications for Glial Dysfunction. Schizophr. Bull. 42(2) 415-424.

Posse, S., Otazo, R., Caprihan, A., Bustillo, J., Chen, H., Henry, P.G., Marjanska, M., Gasparovic, C., Zuo, C., Magnotta, V., Mueller, B., Mullins, P., Renshaw, P., Ugurbil, K., Lim, K.O., Alger, J.R., 2007. Proton echo-planar spectroscopic imaging of J-coupled resonances in human brain at 3 and 4 Tesla. Magn. Reson. Med. 58 (2), 236–244.Posse, S., Otazo, R., Caprihan, A., Bustillo, J., Chen, H., Henry, P.G., Marjanska, M., Gasparovic, C., Zuo, C., Magnotta, V., Mueller, B., Mullins, P., Renshaw, P., Ugurbil, K., Lim, K.O., & Alger, J.R., 2007. Proton echo-planar spectroscopic imaging of J-coupled resonances in human brain at 3 and 4 Tesla. Magn. Reson. Med. 58(2) 236-244.

Rigucci, S., Santi, G., Corigliano, V., Imola, A., Rossi-Espagnet, C., Mancinelli, I., De Pisa, E., Manfredi, G., Bozzao, A., Carducci, F., Girardi, P., Comparelli, A., 2016. White matter microstructure in ultra-high risk and first episode schizophrenia: a prospective study. Psychiatry Res. 247, 42–48.Rigucci, S., Santi, G., Corigliano, V., Imola, A., Rossi-Espagnet, C., Mancinelli, I., De Pisa, E., Manfredi, G., Bozzao, A., Carducci, F., Girardi, P., & Comparelli, A., 2016. White matter microstructure in ultra-high risk and first episode schizophrenia: A prospective study. Psychiatry Res. 247 42-48.

Samartzis, L., Dima, D., Fusar-Poli, P., Kyriakopoulos, M., 2014. White matter alterations in early stages of schizophrenia: a systematic review of diffusion tensor imaging studies. J. Neuroimaging 24 (2), 101–110.Samartzis, L., Dima, D., Fusar-Poli, P., & Kyriakopoulos, M., 2014. White matter alterations in early stages of schizophrenia: a systematic review of diffusion tensor imaging studies. J Neuroimaging. 24(2) 101-110.

Schmierer, K., Scaravilli, F., Altmann, D.R., Barker, G.J., Miller, D.H., 2004. Magnetization transfer ratio and myelin in postmortem multiple sclerosis brain. Ann. Neurol. 56, 407–415.Schmierer, K., Scaravilli, F., Altmann, D.R., Barker, G.J., & Miller, D.H., 2004. Magnetization transfer ratio and myelin in postmortem multiple sclerosis brain. Ann. Neurol. 56 407-415.

Schmierer, K., Tozer, D.J., Scaravilli, F., Altmann, D.R., Barker, G.J., Tofts, P.S., Miller, D.H., 2007. Quantitative magnetization transfer imaging in postmortem multiple sclerosis brain. J. Magn. Reson. Imaging 26 (1), 41–51 2007 Jul.Schmierer, K., Tozer, D.J., Scaravilli, F., Altmann, D.R., Barker, G.J., Tofts, P.S., & Miller, D.H., 2007. Quantitative magnetization transfer imaging in postmortem multiple sclerosis brain. J. Magn. Reson. Imaging. 2007 Jul;26(1):41-51.

Steen, R.G., Hamer, R.M., Lieberman, J.A., 2005. Measurement of brain metabolites by 1H magnetic resonance spectroscopy in patients with schizophrenia: a systematic review and meta-analysis. Neuropsychopharmacology 30 (11), 1949–1962.Steen, R.G., Hamer, R.M., & Lieberman, J.A., 2005. Measurement of brain metabolites by 1H magnetic resonance spectroscopy in patients with schizophrenia: a systematic review and meta-analysis. Neuropsychopharmacology. 30(11) 1949-1962.

Sussmann, J.E., Lymer, G.K., McKirdy, J., Moorhead, T.W., Muñoz Maniega, S., Job, D., Hall, J., Bastin, M.E., Johnstone, E.C., Lawrie, S.M., McIntosh, A.M., 2009. White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging. Bipolar Disord. 11 (1), 11–18.Sussmann, J.E., Lymer, G.K., McKirdy, J., Moorhead, T.W., Muñoz Maniega, S., Job, D., Hall, J., Bastin, M.E., Johnstone, E.C., Lawrie, S.M., & McIntosh, A.M., 2009. White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging. Bipolar Disord. 11(1) 11-18.

Tkác, I., Starcuk, Z., Choi, I.Y., Gruetter, R., 1999. In vivo 1H NMR spectroscopy of rat brain at 1 ms echo time. Magn. Reson. Med. 41 (4), 649–656.Tkác, I., Starcuk, Z., Choi, I.Y., & Gruetter, R., 1999. In vivo 1H NMR spectroscopy of rat brain at 1 ms echo time. Magn. Reson. Med. 41(4) 649-656.

Tsai, G., Coyle, J.T., 1995. N-acetylaspartate in neuropsychiatric disorders. Prog. Neurobiol. 46 (5), 531–540.Tsai, G., & Coyle, J.T., 1995. N-acetylaspartate in neuropsychiatric disorders. Prog. Neurobiol. 46(5) 531-540.

Urenjak, J., Williams, S.R., Gadian, D.G., Noble, M., 1993. Proton nuclear magnetic resonance spectroscopy unambiguously identifies different neural cell types. J. Neurosci. 13 (3), 981–989.Urenjak, J., Williams, S.R., Gadian, D.G., & Noble, M., 1993. Proton nuclear magnetic resonance spectroscopy unambiguously identifies different neural cell types. J. Neurosci. 13(3) 981-989.

Zahr, N.M., Mayer, D., Rohlfing, T., Sullivan, E.V., Pfefferbaum, A., 2014. Imaging neuroinflammation? A perspective from MR spectroscopy. Brain Pathol. 24, 654–664.Zahr, N.M., Mayer, D., Rohlfing, T., Sullivan, E.V., & Pfefferbaum, A., 2014. Imaging neuroinflammation? A perspective from MR spectroscopy. Brain Pathology. 24 654–664.

Zeng, B., Ardekani, B.A., Tang, Y., Zhang, T., Zhao, S., Cui, H., Fan, X., Zhuo, K., Li, C., Xu, Y., Goff, D.C., Wang, J., 2016. Abnormal white matter microstructure in drug-naive first episode schizophrenia patients before and after eight weeks of antipsychotic treatment. Schizophr. Res. 172 (1–3), 1–8.Zeng, B., Ardekani, B.A., Tang, Y., Zhang, T., Zhao, S., Cui, H., Fan, X., Zhuo, K., Li, C., Xu, Y., Goff, D.C., & Wang, J., 2016. Abnormal white matter microstructure in drug-naive first episode schizophrenia patients before and after eight weeks of antipsychotic treatment. Schizophr. Res. 172(1-3) 1-8.