

White matter structure in schizophrenia and autism: Abnormal diffusion across the brain in schizophrenia

Sarah M. Haigh^{a,b,c,*}, Shaun M. Eack^{d,f}, Timothy Keller^a, Nancy J. Minshew^{d,e}, Marlene Behrmann^{a,b}

^a Department of Psychology, Carnegie Mellon University, USA

^b Center for the Neural Basis of Cognition, Carnegie Mellon University, USA

^c Department of Psychology and Center for Integrative Neuroscience, University of Nevada, Reno, USA

^d Department of Psychiatry, University of Pittsburgh School of Medicine, USA

^e Department of Neurology, University of Pittsburgh, USA

^f School of Social Work, University of Pittsburgh, USA

ARTICLE INFO

Keywords:

Autism
Schizophrenia
DTI
White matter
Mean diffusivity
TBSS

ABSTRACT

Background: Schizophrenia and autism share many behavioral and neurological similarities, including altered white matter tract structure. However, because schizophrenia and autism are rarely compared directly, it is difficult to establish whether white matter abnormalities are disorder-specific or are common across these disorders that share some symptomatology.

Methods: In the current study, we compared white matter water diffusion using tensor imaging in 25 adults with autism, 15 adults with schizophrenia, all with IQ scores above 88, and 19 neurotypical adults.

Results: Although the three groups evinced no statistically significant differences in measures of fractional anisotropy (FA), the schizophrenia group showed significantly greater mean diffusivity (MD; Cohen's $d > 0.77$), due to greater radial diffusivity (RD; Cohen's $d > 0.92$), compared to both the autism and control groups. This effect was evident across the brain rather than specific to a particular tract.

Conclusions: The greater MD and RD in schizophrenia appears to be diagnosis-specific. The altered diffusion may reflect subtle abnormalities in myelination, which could be a potential mechanism underlying the widespread behavioral deficits associated with schizophrenia.

1. Introduction

Schizophrenia and autism are both characterized by problems with social and communication abilities and by sensory abnormalities (Eack et al., 2017; Ciaramidaro et al., 2018; Mançe Çalışır et al., 2018; Noel et al., 2018). Half of the individuals with autism satisfy the criteria for schizophrenia reflecting the similarities across the two profiles (Konstantareas and Hewitt, 2001; Ghaziuddin et al., 1992). The overlap in these disorders extends to the neuropsychological profiles, which are nearly identical when the groups are matched on IQ scores (Eack et al., 2013). Recent research has shown that 3.6–12.8% of individuals with autism develop schizophrenia as adults (see review (Chisholm et al., 2015)). Despite these similarities and overlaps, the disorders have a very different age of onset and are further distinguished by the absence of psychosis in autism. As a result, these two conditions have been

demarcated as separate conditions since the DSM-II.

In addition to the behavioral similarities, brain imaging studies in schizophrenia and autism highlight several abnormalities that are common across the two conditions (Chisholm et al., 2015). One meta-analysis showed reduced grey matter volume in right limbic-striato-thalamic circuitry in both conditions (Cheung et al., 2010), while a separate review paper reported reduced fractional anisotropy (FA), one possible measure of white matter structure derived from diffusion tensor imaging, indicating impairments in the white matter structure in both conditions (Mueller et al., 2012), although in both studies, there were more dissociations among the conditions than similarities. A third study of functional imaging reported under-activity in emotion-related neural circuits in both schizophrenia and autism (see review by Sugranyes et al., 2011; Abdi and Sharma, 2004).

Most of the studies alluded to above investigated each disorder

* Corresponding author. Department of Psychology, Carnegie Mellon University, 1664 N Virginia Street, Reno, NV, 89557-0296, USA.

E-mail address: shaigh@unr.edu (S.M. Haigh).

separately rather than directly comparing the two disorders. A few functional imaging studies have directly compared individuals with schizophrenia and autism and have typically found abnormal functioning, for example, under-activation of fMRI responses in the social cognitive network (Pinkham et al., 2008), but often the direction of the abnormal functioning differs. One such study examining fMRI responses during social situations reported increased connectivity between right posterior superior temporal sulcus and ventral medial prefrontal cortex in schizophrenia but decreased connectivity in autism (Ciaramidaro et al., 2015). Another study found reduced signal to noise ratios in all sensory modalities (visual, auditory, and somatosensory) in the schizophrenia and autism groups compared to age- and gender-matched controls (Haigh et al., 2016). However, the cause of the reduced SNR differed between schizophrenia and autism: adults with schizophrenia tended to under-respond to the sensory stimulation, whereas the adults with autism exhibited more variable responses from one trial to the next (intra-trial inconsistency).

Both schizophrenia and autism have long been associated with abnormalities in white matter tracts (as mentioned above). However, it should be noted that, in autism, the majority of the studies showing abnormal diffusion properties indicating weaker white matter structure in autism were conducted in children (Cheon et al., 2011; Weinstein et al., 2011; Billeci et al., 2012; Ameis et al., 2013; Abdel Razek et al., 2014; Cheung et al., 2009; Pryweller et al., 2014; Lazar et al., 2014; Kirkovski et al., 2015; Noriuchi et al., 2010; Shukla et al., 2011a), with a minority focusing on adults (Shukla et al., 2011b; Jou et al., 2015; Gibbard et al., 2013; Roine et al., 2015; Libero et al., 2015). Of those that did focus on adults with autism, there was no clear indication as to the specific mechanism underlying the deficit. Some showed widespread abnormalities (Roine et al., 2015; Libero et al., 2015), or specific deficits in tracts such as in the forceps minor (Gibbard et al., 2013), or in anterior thalamic radiation and cingulum (Haigh et al., 2019). Other studies have found no significant differences in diffusion properties between adults with autism and neurotypical individuals (Roine et al., 2015; Libero et al., 2015), highlighting the debate as to where and how severe white matter alterations are in autism.

On the other hand, diffusion studies in schizophrenia have been conducted in adults, as the first episode of psychosis that diagnostically defines the onset of schizophrenia typically occurs in late adolescence and early adulthood. Early-onset schizophrenia that occurs during childhood and adolescence may have a different etiology to schizophrenia that occurs in adulthood (for a review, see Tamnes and Agartz, 2016). Measures of diffusion appear to be impacted even before the first-episode (for a review see Samartzis et al., 2013), suggesting that changes in diffusion could be a risk marker for schizophrenia. However, there is also a disagreement as to whether atypical diffusion in those with chronic schizophrenia is present across the brain (Asami et al., 2014; Fujino et al., 2014; Nakamura et al., 2012; Nakamura et al., 2012; Roalf et al., 2013; Roalf et al., 2015; Sasamoto et al., 2014; Scheel et al., 2013) or is restricted to certain tracts (Kochunov et al., 2014; Levitt et al., 2012; Kelly et al., 2018 (FA but not MD) Nazeri et al., 2013; Ohtani et al., 2014; Prasad et al., 2015; Wagner et al., 2015).

A couple of studies have directly examined the structural correlates of autism compared to schizophrenia. One study showed autism-specific differences in grey matter volume (compared to schizophrenia) in the insula and amygdala that correlated with symptoms (Radeloff et al., 2014). A second study also found differences between autism and schizophrenia in grey matter volume specific to prefrontal cortex and anterior cingulate, and found similar reductions in fractional anisotropy measures of white matter, particularly in the left inferior fasciculus compared to neurotypical controls (Katz et al., 2016). A third study found increased metabolic rate in white matter in schizophrenia but more so in autism in a variety of regions of interest across the brain (Mitelman et al., 2018), emphasizing abnormal white matter structures as potential biomarkers.

One point to consider is that all of the studies of altered diffusion

discussed above focused on fractional anisotropy (FA) which has been suggested to reflect a variety of factors that contribute to tract structure (Beaulieu, 2002): the higher the FA, the more intact the tract. However, water diffusion can also be measured by mean diffusivity, which reflects the microstructure of white matter tracts: the lower the MD, the greater hindrance of water diffusion, indicative of more robust microstructure (Winkowski et al., 2018). Several studies report increased MD in chronic schizophrenia compared to neurotypical controls (Narr et al., 2009; Lee et al., 2009; only MD Ardekani et al., 2011; Leroux et al., 2014; Knöchel et al., 2012; Spalletta et al., 2015; Spoletini et al., 2011), whereas this result is less common in adults with autism (Gibbard et al., 2013; Itahashi et al., 2015). In autism, there is some evidence that MD normalizes by adulthood (for example, Kleinhans et al., 2012), suggesting differences in the developmental trajectory and, thus, MD may be a dissociable marker between adults with autism or schizophrenia.

We focused on differences in measures of diffusion, to indicate differences in white matter tract structure, between individuals with schizophrenia, individuals with autism, and neurotypical controls. Specifically, we used Diffusion Tensor Imaging (DTI) to measure fractional anisotropy (FA) and mean diffusivity (MD) across the brain using Tract-Based Spatial Statistics (TBSS). We focused on adults with schizophrenia or autism with IQ scores in the normal range, as both conditions persist throughout their lifetime, but have different developmental trajectories – the onset of schizophrenia typically occurs in late adolescence to early adulthood, whereas autism is generally diagnosed in early childhood. Therefore, we were able to match all participants on age and ensure that they were stable on their medication. We predict that schizophrenia and autism will exhibit different abnormalities in diffusion that will be specific to their diagnosis. Deficits specific to one condition might highlight structural biomarkers that are unique and diagnostically relevant. However, if white matter tract abnormalities are common across schizophrenia and autism, then this could highlight a possible transdiagnostic mechanism that might be related to their shared behavioral characteristics.

2. Methods and materials

2.1. Participants

Fifteen individuals with schizophrenia (10 males; mean age 25, range 19–33 years), 25 individuals with Autism Spectrum Disorder (ASD) (21 males; mean age 29, range 19–42 years), and 19 neurotypical controls were compared (14 males; mean age 26, range 21–40 years).

The individuals in the schizophrenia group were either diagnosed with schizophrenia or schizoaffective disorder (diagnosed using the Structured Clinical Interview for DSM-IV (First et al., 2002) and symptoms were measured using the Brief Psychiatric Rating Scale (BPRS; Lukoff et al., 1986, by an expert diagnostician). Thirteen of the individuals with schizophrenia were taking antipsychotics (see Table 1 for demographic and diagnostic information), and all had IQ above 88. There is a potential link between larger doses of antipsychotic medication and greater reductions in white matter volume (Emsley et al., 2017) and so, here, we conducted an exploratory correlation on the relationship between medication dosage and diffusion measures.

The individuals in the autism group all met DSM-IV criteria for autism and had IQ scores above 88. Clinical diagnosis was confirmed with the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1989) and Autism Diagnostic Interview (ADI) (Le Couteur et al., 1989; Lord et al., 1994) assessments carried out by expert clinicians at the Center For Excellence in Autism Research at the University of Pittsburgh (see Table 2 for demographic and diagnostic information). A study comparing the DSM-IV and the DSM-V criteria showed that the participants who met the criteria for autism under the DSM-IV also met the criteria for autism under the DSM-V (Mazefsky et al., 2013). One individual with autism was taking an antipsychotic medication, and 5 were taking medication for depression.

Table 1
Demographic and medication information for the individuals with autism.

Participant	Gender	Age (years)	ADOS social	ADOS comm	ADOS stereotypical	ADI social	ADI comm	ADI stereotypical	Full scale IQ
1	M	35							
2	M	20	4	3	3	11	10	6	129
3	M	21	8	4	2	21	17	6	123
4	M	23	6	4	1	21	18	8	123
5	F	19	7	5	3	27	20	6	107
6	M	41	6	4	2	24	18	10	96
7	M	19	7	3	3	22	15	5	96
8	M	20	8	5	1	27	22	5	124
9	M	33	5	3	3	26	18	12	131
10	M	27	6	2	3	20	16	7	104
11	F	31	10	6	3	15	9	6	121
12	F	31	7	2	4	10	8	6	123
13	M	44	9	4	3	24	19	5	108
14	M	32	9	4	0	18	18	9	92
15	M	36	8	2	1	20	11	3	125
16	M	39	7	4	1	21	16	8	116
17	M	24	13	6	3	10	16	3	118
18	M	22	11	5	3	20	15	3	107
19	M	30	13	5	3	20	13	3	134
20	M	30				19	13	5	121
21	M	27	9	4	3	20	17	7	100
22	M	29	6	3	1	15	12	2	116
23	M	31	7	4	2	25	9	8	117
24	M	30	10	6	2	23	17	6	128
Mean/Count	F = 3; M = 21	28.92 7.03	8.00 2.35	4.00 1.23	2.27 1.03	19.96 4.97	15.09 3.81	6.04 2.44	115.61 12.07

Table 2
Demographic and medication information for the individuals with schizophrenia. BPRS=Brief Psychiatric Rating Scale; CPZ = chlorpromazine equivalents.

Participant	Gender	Age (years)	BPRS Score	Medication CPZ (mg/day)	Full-Scale IQ
1	F	24	28	93.3	96
2	M	33	47	75.0	94
3	M	34	30	200.0	95
4	F	31	28	33.3	96
5	M	23	32	266.7	100
6	M	24	36	0.0	102
7	M	19	23	100.0	117
8	M	25	29	50.0	102
9	F	30	33	507.1	112
10	M	25	33	968.1	97
11	M	22	28	33.3	129
12	F	19	33	783.3	101
13	M	28	29	0.0	113
14	F	24	44	100.0	89
15	M	26	18	100.0	109
Mean/Count	F = 5; M = 10	25.80 4.59	31.40 7.22	220.67 297.33	103.47 10.61

Groups did not differ from each other on age or gender. However, the ASD group had higher IQ than the schizophrenia group ($t(32.8) = 3.26, p = .003$). IQ was not collected for the control group, although all of the control participants were students at Carnegie Mellon University. All participants gave informed consent to take part in the 90-min study and were paid \$75 for their time. The Institutional Review Boards at Carnegie Mellon University (CMU) and the University of Pittsburgh approved the experimental procedures, which were in compliance with the safety guidelines for MRI research.

2.2. DTI data acquisition

A 3T Siemens MRI scanner at the Carnegie Mellon University Scientific Imaging and Brain Research Center was used to acquire diffusion data. A diffusion-weighted, single-shot, spin-echo, echo-planar imaging sequence was used with TR = 5300 ms, TE = 95 ms,

bandwidth = 1860 Hz/voxel, FOV = 200 mm, and matrix size = 96 x 96. There were 50 2.4-mm thick slices (no slice gap) with no diffusion-weighting ($b = 0 \text{ s/mm}^2$, 8 repetitions equally spaced during acquisition), and with diffusion-weighting gradients applied in 128 orthogonal directions ($b = 2000 \text{ s/mm}^2$). The diffusion data took 24 min to acquire. A gradient echo field map was also collected for correction of distortions in the diffusion-weighted images. The acquisition of this field map used an EPI sequence with TR = 550 ms, TE1 = 5 ms, TE2 = 7.46 ms, bandwidth = 300 Hz/Voxel, FOV = 230 mm, matrix size = 128 x 128, and slices were acquired in the same planes as the diffusion data.

2.3. Data processing and analysis

Diffusion-weighted data were preprocessed with a scripted pipeline calling tools from the FMRIB Software Library (Jenkinson et al., 2012; <http://www.fmrib.ox.ac.uk/fsl>). The images with no diffusion weighting ($b = 0$) were motion-corrected and averaged to serve as an initial reference for further processing. The gradient echo field map images were used to correct for geometric distortions in these images and in the diffusion weighted images using the prelude and fugue tools. All images were then corrected for motion and eddy currents using the eddy_correct tool. The vectors specifying the diffusion-weighted gradient directions were then rotated to compensate from head motion prior to fitting the diffusion tensor model with the dtfit tool.

Participant movement in the scanner was calculated as a z-score of Euclidean distance for each individual and then compared across groups. There were no significant overall nor pairwise differences in absolute head motion ($F(2,55) = 1.33, p = .273$), or normalized brain volume ($F(2,55) = 1.77, p = .181$) across the ASD group, the schizophrenia group, or the neurotypical controls. Voxelwise statistical analysis of the fractional anisotropy (FA) and mean diffusivity (MD) data were carried out using TBSS (Tract-Based Spatial Statistics, Smith et al., 2006), part of FSL (Smith et al., 2004), using the following approach.

First, FA images were created by fitting a tensor model to raw diffusion data using FMRIB's Diffusion Toolbox (FDT), and second, by extracting the brain using the Brain Extracted Toolbox (BET; Smith, 2002). All FA data were then aligned into a common space using the

nonlinear registration tool FNIRT (Andersson et al., 2007a, 2007b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centers of all tracts common to all participants regardless of group identity (threshold at 0.2). Each aligned FA data was then projected onto this skeleton and the resulting data entered voxelwise cross-subject statistics. Finally, the randomise method was used to compare schizophrenia, ASD, and neurotypical groups (Winkler et al., 2014) using 500 permutations to compute the null distribution. Familywise corrected Threshold-Free Cluster Enhancement p-values (TFCE; corrected by using the null distribution of the max voxelwise test statistic across the image; Smith and Nichols, 2009) were used to identify clusters where there was a significant difference in FA between the experimental groups. MD data were similarly registered into a common nonlinear space and projected onto the mean FA skeleton. A random permutation testing method was used, using the randomise tool included in FSL. The permutation test was used to compare schizophrenia, ASD, and control groups, and the multiple comparison corrected p-values (corrected using Threshold-Free Cluster Enhancement) were used to examine the significance of any between-group differences.

The mean FA, MD, axial (L1 direction), and radial (averaged L2 and L3 directions) diffusion were calculated for each participant across the whole white matter skeleton (see Fig. 1). Results were the same when median was used as the summary statistic. Group effects were analyzed using one-way ANOVAs and independent-samples t-tests were used for post-hoc comparisons.

3. Results

3.1. Comparing measures of fractional anisotropy (FA) and mean diffusivity (MD)

We compared the schizophrenia, autism and control groups on measures of diffusion to indicate white matter structure across the brain. First, we focused on FA as a measure of efficient diffusion along tracts and found that there was no statistically significant difference between the three groups ($F(2,55) = 1.47, p = .074$). However, when we focused on MD, which provides a measure of the white matter microstructure, individuals with schizophrenia exhibited greater MD ($F(2,55) = 3.29, p = .045$), compared to ASD individuals ($t(26) = 3.37, p = .002$), and neurotypical controls ($t(20) = 2.48, p = .022$), and there was no difference between ASD and controls ($t(39) = 0.45, p = .658$; Fig. 2). The mean diffusivity measures were calculated using the mean of the axial (AD) and radial (RD) diffusion directions. Therefore, to uncover the source of the group differences, we compared groups on AD and RD, and found that whereas individuals with schizophrenia show greater diffusivity in the radial direction ($F(2,55) = 4.01, p = .024$; Fig. 3), there was no group difference in the axial direction ($F(2,55) = 2.73, p = .074$). Despite there being no significant difference between groups on age or

gender, we included age and gender as covariates to ensure that there were no unexpected effects on MD. There was no significant main effect of age ($F(1,52) = 0.10, p = .752$) or gender ($F(2,52) = 0.03, p = .971$), and the effect of group still held ($F(2,52) = 3.12, p = .053$).

Due to the smaller sample size in the schizophrenia group, two additional analyses were conducted. First, Cohen's d effect sizes were calculated for all group comparisons and for FA, MD, AD, and RD measures of diffusion (Table 3). The effect sizes for the increased MD, AD, and RD in schizophrenia compared to autism and control groups were by far the largest (despite the group comparisons only trending to be statistically significant in the axial). However, the effect sizes comparing autism to schizophrenia and control groups on FA were in the medium range (>0.2), suggesting that there may be decreased FA in autism, but the smaller sample sizes for the schizophrenia and control groups may have prevented this effect from reaching significance.

Second, a subset of 15 individuals with autism and 15 control participants who still matched the schizophrenia group on age and gender were selected and the analyses recalculated. The results were the same. There was no significant difference between the groups on FA ($F(2,42) = 1.50, p = .235$), but there was for MD ($F(2,42) = 3.43, p = .042$), and in the radial direction ($F(2,42) = 4.02, p = .025$), with a trend toward significance in the axial direction ($F(2,42) = 2.89, p = .067$).

3.2. Including measures of head motion and brain volume

Despite the fact that there were no group differences in measures of head motion and brain volume, it is possible that these physiological measures were indirectly related to the group differences in MD. Therefore, we used an ANCOVA to show that when normalized brain volume was accounted for, there was still a significant group difference in MD ($F(2,52) = 3.15, p = .051$), no significant effect of brain volume ($F(1,52) = 0.01, p = .916$), and no significant interaction between group and brain volume ($F(2,52) = 0.34, p = .713$). However, when head motion was accounted for in an ANCOVA, there was still a significant effect of group ($F(2,52) = 6.09, p = .004$), but there was also a significant effect of absolute head motion on MD ($F(1,52) = 47.09, p < .001$). Despite this, there was no significant interaction between group identity and head motion ($F(2,55) = 1.36, p = .265$). Together, this suggests that head motion does not account for the differences in mean diffusivity between groups (as the interaction is not significant) but does highlight the importance of accounting for head motion in DTI analyses.

For FA, even when accounting for head motion and brain volume, there was no significant difference between groups (head motion: $F(2,52) = 2.29, p = .112$; brain volume: $F(2,52) = 1.54, p = .225$). Therefore, there is no evidence in this sample that there are significant differences in FA measures of white matter structure between schizophrenia, autism and controls.

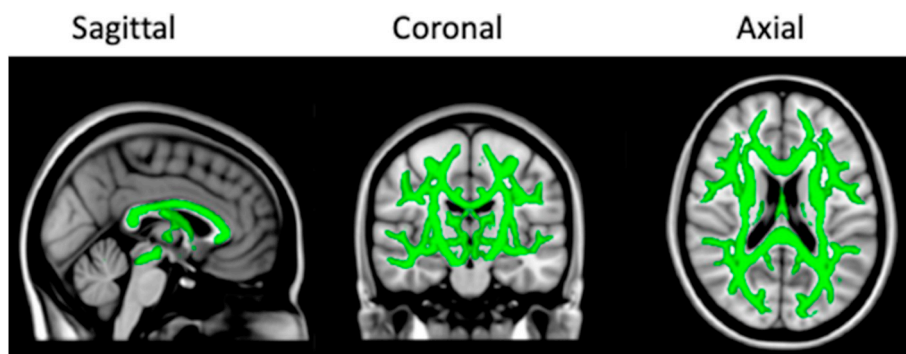


Fig. 1. The white matter skeleton common across all individuals with schizophrenia, autism, and neurotypical controls. The skeleton was inflated for illustration.

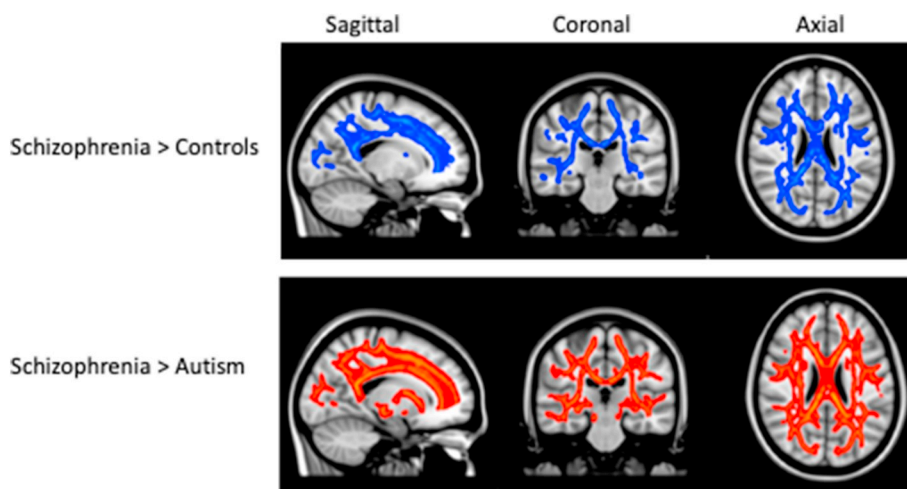


Fig. 2. White matter tracts with greater mean diffusivity in schizophrenia compared to controls (top row in blue) and compared to individuals with autism (bottom row in red), shown in sagittal, coronal, and axial slices across the brain. Differences in TFCE-selected clusters significant at $p < .05$ by permutation testing and, corrected for multiple comparisons. Significant clusters were inflated for illustration. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

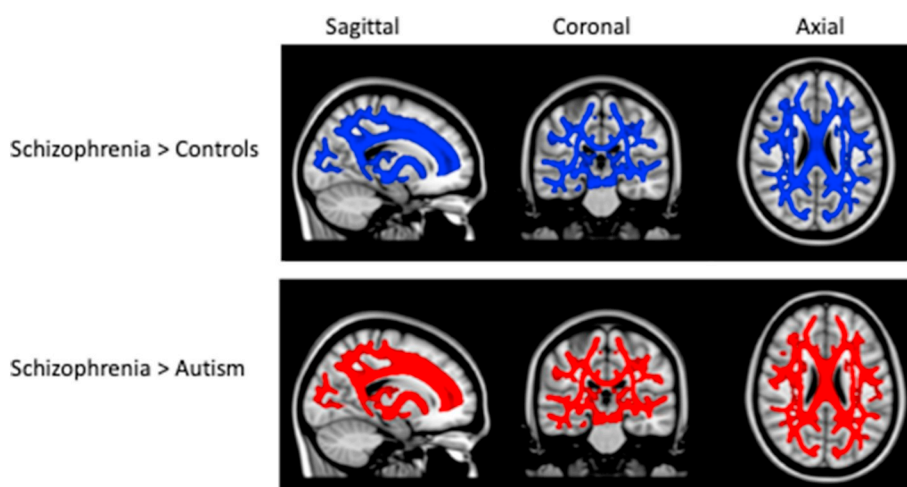


Fig. 3. White matter tracts with greater radial diffusivity in schizophrenia compared to controls (top row in blue) and compared to individuals with autism (bottom row in red), shown in sagittal, coronal, and axial slices across the brain. Differences in TFCE-selected clusters significant at $p < .05$ by permutation testing and, corrected for multiple comparisons. Significant clusters were inflated for illustration. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 3

Effect sizes (Cohen's d) comparing group differences on fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). Group comparisons are the effect size of (1) the autism group (ASD) having increased diffusion compared to controls (HC), (2) the schizophrenia group (Sz) having increased diffusion compared to the autism group, and (3) the schizophrenia group having increased diffusion compared to controls. Negative effect sizes denote the effect in the opposite direction. Significant comparisons are in bold.

Group Comparison	Fractional Anisotropy (FA)	Mean Diffusivity (MD)	Axial Diffusivity (AD)	Radial Diffusivity (RD)
ASD > HC	-0.47	-0.14	-0.21	-0.03
Sz > ASD	0.34	0.89	0.82	0.93
Sz > HC	-0.19	0.77	0.61	0.92

3.3. Correlations with symptom measures

Finally, measures of MD were correlated with symptom scores in the schizophrenia and ASD groups separately. In the schizophrenia group, there was no significant correlation between MD and Brief Psychotic Rating Score (BPRS; $r(13) = 0.10$, $p = .721$) but there was a significant correlation with amount of antipsychotic medication ($r(13) = -0.60$, $p = .018$), suggesting that those on higher dosage had reduced MD. This appears to be primarily driven by two individuals who were on high

levels of medication. The higher dosage may have helped improve MD over time, but there is no evidence here that this is the case. In the ASD group, the only correlation that was significant was between MD and ADOS measures of communication ($r(22) = -0.48$, $p = .024$), suggesting that poorer communicative behaviors were associated with less MD, which is in the opposite direction to our hypothesis. Correlations were not significant for ADOS social or stereotypical behavior scores, or with any ADI scores. There were no significant correlations with IQ in either the ASD or the schizophrenia group.

4. Discussion

In this study, we investigated measures of diffusion to investigate white matter tract structure in adults with schizophrenia and in adults with autism compared to age- and gender-matched controls. IQ was not measured in the controls. There were no significant group differences in fractional anisotropy (FA) across the brain, but the adults with schizophrenia did show greater mean diffusivity (MD). Specific deficits in MD but not FA (despite normal brain volume) have been suggested to reflect abnormal myelination (Song et al., 2005; Winkowski et al., 2018), which could impact the efficiency of the tracts when transferring information across the brain. The abnormal diffusion was specific to schizophrenia and was not evident in the autism group. One other study is known to have previously focused on diffusion measures in autism and schizophrenia and found FA reductions in autism and schizophrenia

groups compared to controls, but this reduction was specific to left fronto-occipital inferior fasciculus (Katz et al., 2016). The current study found reductions in MD that appear to be specific to schizophrenia.

A review of the literature reveals several studies reporting increased MD in schizophrenia compared to controls (Narr et al., 2009; Lee et al., 2009; only MD Ardekani et al., 2011; Leroux et al., 2014; Knöchel et al., 2012; Spalletta et al., 2015; both Spalletta et al., 2015). There were relatively few studies reporting a MD difference in adults with autism versus controls (Gibbard et al., 2013; Itahashi et al., 2015), perhaps consistent with the claim that greater MD may be a specific abnormality in schizophrenia.

Interestingly, the greater MD in schizophrenia was due to significantly greater radial diffusivity, and slightly greater axial diffusivity. However, when these measures were normalized to calculate FA, the overall diffusion from the white matter tracts were unimpaired. Increased radial diffusivity (perpendicular to the length of the tract) has been associated with demyelination (Song et al., 2005; Winkowski et al., 2018), although this conclusion will need to be verified with in vivo studies as measures of radial diffusivity alone can be misleading when inferring myelination (Wheeler-Kingshott and Cercignani, 2009; Jones and Cercignani, 2010; see Jones et al., 2013, for a review of the difficulties in interpreting structural properties from DTI measures). This finding of greater radial diffusivity in schizophrenia has been reported previously (Scheel et al., 2013), and evidence of demyelination has been found in structural MRI scans focusing on myelin water fractions (Flynn et al., 2003).

Impaired myelination impacts the transfer of information across the brain (Fields, 2008), and reduced processing speed has been shown to be related to impaired diffusion properties in schizophrenia (Wright et al., 2015). However, both schizophrenia and autism are associated with slower processing speeds (Eack et al., 2013), and yet the individuals with autism in this study did not evince with the same white matter abnormalities as schizophrenia. Furthermore, we have shown in another study that FA is not associated with processing speed in adults with autism (Haigh et al., 2019). Therefore, the functional impairments in schizophrenia and autism may be differentially impacted by structural abnormalities.

There were no significant correlations between MD and symptom measures in autism or in schizophrenia, except in the autism group where worse MD correlated with better scores on ADOS social communication. However, this correlation is in the opposite direction to what would be predicted and will need to be replicated before any conclusions can be drawn. Future studies should correlate MD with the same measure of social communication across both groups to gain better insight into the functional impact of increased MD.

The lack of significant differences between groups in FA is somewhat surprising, considering the wealth of studies showing reduced FA in both schizophrenia and in autism compared to neurotypical individuals. This is in direct contrast to Katz et al., 2016 who reported that both autism and schizophrenia exhibited reduced FA that was specific to the left fronto-occipital inferior fasciculus compared to neurotypical individuals. The current study did not show any significant FA reductions along any part of the white matter skeleton. There is a possibility that this lack of significant effect may have been due to smaller sample sizes in the schizophrenia group, although the additional analyses equating the groups on sample size resulted in the same effects of greater MD in schizophrenia (but of course reduced statistical power). Effect sizes showed that there was a medium effect in the direction of weaker FA in autism compared to the neurotypical control group, but also compared to the adults with schizophrenia. However, the effect sizes comparing MD in schizophrenia to autism and control groups were much larger, suggesting that weaker FA in autism may not be as fundamental to distinguishing between schizophrenia and autism as the MD differences.

The main limitation of this study is the somewhat smaller sample size for the schizophrenia group, relative to the other two groups. Increasing the sample size in the schizophrenia group is, however, unlikely to alter

the results: a main result was greater MD in schizophrenia compared to autism and control groups and these comparisons had large effect sizes, demonstrating that even with a small sample, greater MD was a significant result. A larger sample size may have generated a significant effect of weaker FA in autism, as this comparison had a medium effect size although we note that a group of 25 ASD participants is larger than many of the groups in existing studies. Critically, even if this latter result did differ with a larger group, this would not alter the concluding finding that the main effect of MD when comparing the three groups is a defining feature distinguishing schizophrenia from autism. One caveat is that the ASD group had higher IQ than the schizophrenia group. This may have impacted the groups differences in their diffusion measures of white matter tract structure. However, there were no significant correlations between IQ and MD in either group, suggesting that IQ differences would not have had a large impact on the results.

5. Conclusions

The functional impact of the differences in diffusivity in schizophrenia and autism are unclear but illustrate potential endophenotypic distinctions that may be diagnostically specific. Building a more complete picture of how schizophrenia and autism are related but differ in their neurological manifestations can help to create individualized treatments. What is clear is that the impacted water diffusion in schizophrenia is evident across the brain and is not located in specific areas of the brain. Future studies investigating the behavioral impact will help to ascertain the value of the increase in MD and RD as a biomarker of schizophrenia.

Declarations of competing interest

None.

CRedit authorship contribution statement

Sarah M. Haigh: Data curation, Formal analysis, Investigation, Project administration, Visualization, Writing - original draft, Writing - review & editing. **Shaun M. Eack:** Data curation, Formal analysis, Writing - review & editing. **Timothy Keller:** Formal analysis, Software, Visualization, Writing - review & editing. **Nancy J. Minshew:** Funding acquisition, Writing - review & editing. **Marlene Behrmann:** Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing - review & editing.

Acknowledgements

Brain and Behavior Research Foundation issue NARSAD awards. They are not separate. Similarly, the NSF issues EPSCoR awards. The National Institute of Child Health and Human Development is a part of the National Institutes of Health and so do not need to be listed separately. All funders are correctly identified as being based in the US.

References

- Abdel Razek, A., Mazroa, J., Baz, H., 2014. Assessment of white matter integrity of autistic preschool children with diffusion weighted MR imaging. *Brain Dev.* 36, 28–34. <https://doi.org/10.1016/j.braindev.2013.01.003>.
- Abdi, Z., Sharma, T., 2004. Social cognition and its neural correlates in schizophrenia and autism. *CNS Spectr.* 9, 335–343.
- Ameis, S.H., Fan, J., Rockel, C., Soorya, L., Wang, A.T., Anagnostou, E., 2013. Altered cingulum bundle microstructure in autism spectrum disorder. *Acta Neuropsychiatr.* 25, 275–282. <https://doi.org/10.1017/neu.2013.2>.
- Andersson, J.L.R., Jenkinson, M., Smith, S., 2007. Non-linear Optimisation. *FMRIB technical report TR07JA1*.
- Andersson, J.L.R., Jenkinson, M., Smith, S., 2007. Non-linear Registration. *aka Spatial normalisation FMRIB technical report TR07JA2*.
- Ardekani, B.A., Tabesh, A., Sevy, S., Robinson, D.G., Bilder, R.M., Szeszko, P.R., 2011. Diffusion tensor imaging reliably differentiates patients with schizophrenia from

- healthy volunteers. *Hum. Brain Mapp.* 32, 1–9. <https://doi.org/10.1002/hbm.20995>.
- Asami, T., Lee, S.H., Bouix, S., Rath, Y., Whitford, T.J., Niznikiewicz, M., Nestor, P., McCarley, R.W., Shenton, M.E., Kubicki, M., 2014. Cerebral white matter abnormalities and their associations with negative but not positive symptoms of schizophrenia. *Psychiatry Res.* 222, 52–59. <https://doi.org/10.1016/j.psychres.2014.02.007>.
- Beaulieu, C., 2002. The basis of anisotropic water diffusion in the nervous system – a technical review. *NMR Biomed.* 15, 435–455. <https://doi.org/10.1002/nbm.782>.
- Billeci, L., Calderoni, S., Tosetti, M., Catani, M., Muratori, F., 2012. White matter connectivity in children with autism spectrum disorders: a tract-based spatial statistics study. *BMC Neurol.* 12, 148. <https://doi.org/10.1186/1471-2377-12-148>.
- Cheon, K.-A., Kim, Y.-S., Oh, S.-H., Park, S.-Y., Yoon, H.-W., Herrington, J., Nair, A., Koh, Y.-J., Jang, D.-P., Kim, Y.-B., Leventhal, B.L., Cho, Z.-H., Castellanos, F.X., Schultz, R.T., 2011. Involvement of the anterior thalamic radiation in boys with high functioning autism spectrum disorders: a Diffusion Tensor Imaging study. *Brain Res.* 1417, 77–86. <https://doi.org/10.1016/j.brainres.2011.08.020>.
- Cheung, C., Chua, S.E., Cheung, V., Khong, P.L., Tai, K.S., Wong, T.K.W., Ho, T.P., McAlonan, G.M., 2009. White matter fractional anisotropy differences and correlates of diagnostic symptoms in autism. *JCPP (J. Child Psychol. Psychiatry)* 50, 1102–1112. <https://doi.org/10.1111/j.1469-7610.2009.02086.x>.
- Cheung, C., Yu, K., Fung, G., Leung, M., Wong, C., Li, Q., Sham, P., Chua, S., McAlonan, G., 2010. Autistic disorders and schizophrenia: related or remote? An anatomical likelihood estimation. *PLoS One* 5, e12233.
- Chisholm, K., Lin, A., Abu-Akel, A., Wood, S.J., 2015. The association between autism and schizophrenia spectrum disorders: a review of eight alternate models of co-occurrence. *Neurosci. Biobehav. Rev.* 55, 173–183. <https://doi.org/10.1016/j.neubiorev.2015.04.012>.
- Ciaramidaro, A., Bölte, S., Schlitt, S., Hainz, D., Poustka, F., Weber, B., Bara, B.G., Freitag, C., Walter, H., 2015. Schizophrenia and autism as contrasting minds: neural evidence for the hypo-hyper-intentionality hypothesis. *Schizophr. Bull.* 41, 171–179. <https://doi.org/10.1093/schbul/sbu124>.
- Ciaramidaro, A., Bölte, S., Schlitt, S., Hainz, D., Poustka, F., Weber, B., Freitag, C., Walter, H., 2018. Transdiagnostic deviant facial recognition for implicit negative emotion in autism and schizophrenia. *Eur. Neuropsychopharmacol.* 28, 264–275. <https://doi.org/10.1016/j.euroneuro.2017.12.005>.
- Eack, S.M., Bahorik, A.L., McKnight, S.A.F., Hogarty, S.S., Greenwald, D.P., Newhill, C.E., Phillips, M.L., Keshavan, M.S., Minshew, N.J., 2013. Commonalities in social and non-social cognitive impairments in adults with autism spectrum disorder and schizophrenia. *Schizophr. Res.* 148, 24–28. <https://doi.org/10.1016/j.schres.2013.05.013>.
- Eack, S.M., Hogarty, S.S., Greenwald, D.P., Litschge, M.Y., Shannondora Porton, A., Mazefsky, C.A., Minshew, N.J., 2017. Cognitive enhancement therapy for adult autism spectrum disorder: results of an 18-month randomized clinical trial. *Autism Res.* 11, 519–530. <https://doi.org/10.1002/aur.1913>.
- Emsley, R., Asmal, L., du Plessis, S., Chiliza, B., Phahladira, L., Kilian, S., 2017. Brain volume changes over the first year of treatment in schizophrenia: relationships to antipsychotic treatment. *Psychol. Med.* 47, 2187–2196. <https://doi.org/10.1017/S0033291717000642>.
- Fields, R.D., 2008. White matter in learning, cognition and psychiatric disorders. *Trends Neurosci.* 31, 361–370. <https://doi.org/10.1016/j.tins.2008.04.001>.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 2002. Structured Clinical Interview for DSM-IV-TR axis I Disorders. research version, patient edition. SCID-I/P. Flynn, S.W., Lang, D.J., Mackay, A.L., Goghari, V., Vavasour, I.M., Whittall, K.P., Smith, G.N., Arango, V., Mann, J.J., Dwork, A.J., Falkai, P., Honer, W.G., 2003. Abnormalities of myelination in schizophrenia detected in vivo with MRI, and post-mortem with analysis of oligodendrocyte proteins. *Mol. Psychiatry* 8, 811.
- Fujino, J., Takahashi, H., Miyata, J., Sugihara, G., Kubota, M., Sasamoto, A., Fujiwara, H., Aso, T., Fukuyama, H., Murai, T., 2014. Impaired empathic abilities and reduced white matter integrity in schizophrenia. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 48, 117–123. <https://doi.org/10.1016/j.pnpb.2013.09.018>.
- Ghaziuddin, M., Tsai, L., Ghaziuddin, N., 1992. Comorbidity of autistic disorder in children and adolescents. *Eur. Child Adolesc. Psychiatry* 1, 209–213. <https://doi.org/10.1007/BF02094180>.
- Gibbard, C.R., Ren, J., Seunarine, K.K., Clayden, J.D., Skuse, D.H., Clark, C.A., 2013. White matter microstructure correlates with autism trait severity in a combined clinical–control sample of high-functioning adults. *Neuroimage* 3, 106–114. <https://doi.org/10.1016/j.neuroimage.2013.07.007>.
- Haigh, S.M., Gupta, A., Barb, S.M., Glass, S.A.F., Minshew, N.J., Dinstein, I., Heeger, D.J., Eack, S.M., Behrmann, M., 2016. Differential sensory fMRI signatures in autism and schizophrenia: analysis of amplitude and trial-to-trial variability. *Schizophr. Res.* 175, 12–19. <https://doi.org/10.1016/j.schres.2016.03.036>.
- Haigh, S.M., Keller, T.A., Minshew, N.J., Eack, S.M., 2019. n.d. Reduced white matter integrity and deficits in neuropsychological functioning in adults with autism spectrum disorder. *J. Autism Dev. Disord.*
- Itahashi, T., Yamada, T., Nakamura, M., Watanabe, H., Yamagata, B., Jimbo, D., Shioda, S., Kuroda, M., Torizuka, K., Kato, N., Hashimoto, R., 2015. Linked alterations in gray and white matter morphology in adults with high-functioning autism spectrum disorder: a multimodal brain imaging study. *Neuroimage* 7, 155–169. <https://doi.org/10.1016/j.neuroimage.2014.11.019>.
- Jenkinson, M., Beckmann, C.F., Behrens, T.E.J., Woolrich, M.W., Smith, S.M., 2012. FSL. *Neuroimage* 62, 782–790. <https://doi.org/10.1016/j.neuroimage.2011.09.015>.
- Jones, D.K., Cercignani, M., 2010. Twenty-five pitfalls in the analysis of diffusion MRI data. *NMR Biomed.* 23, 803–820. <https://doi.org/10.1002/nbm.1543>.
- Jones, D.K., Knösche, T.R., Turner, R., 2013. White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. *Neuroimage* 73, 239–254. <https://doi.org/10.1016/j.neuroimage.2012.06.081>.
- Jou, R.J., Reed, H.E., Kaiser, M.D., Voos, A.C., Volkmar, F.R., Pelphrey, K.A., 2015. White matter abnormalities in autism and unaffected siblings. *J. Neuropsychiatry Clin. Neurosci.* 28, 49–55. <https://doi.org/10.1176/appi.neuropsych.15050109>.
- Katz, J., d'Albis, M.-A., Boisgontier, J., Poupon, C., Mangin, J.-F., Guevara, P., Duclap, D., Hamdani, N., Petit, J., Monnet, D., Le Corvoisier, P., Leboyer, M., Delorme, R., Houenou, J., 2016. Similar white matter but opposite grey matter changes in schizophrenia and high-functioning autism. *Acta Psychiatr. Scand.* 134, 31–39. <https://doi.org/10.1111/acps.12579>.
- Kelly, S., Jahanshad, N., Zalesky, A., Kochunov, P., Agartz, I., Alloza, C., Andreassen, O.A., Arango, C., Banaj, N., Bouix, S., Bousman, C.A., Brouwer, R.M., Bruggemann, J., Bustillo, J., Cahn, W., Calhoun, V., Cannon, D., Carr, V., Catts, S., Chen, J., Chen, J.-X., Chen, X., Chiapponi, C., Cho, K.K., Ciullo, V., Corvin, A.S., Crespo-Facorro, B., Croyley, V., De Rossi, P., Diaz-Caneja, C.M., Dickie, E.W., Ehrlich, S., Fan, F.-M., Faskowitz, J., Fatouros-Bergman, H., Flyckt, L., Ford, J.M., Fouché, J.-P., Fukunaga, M., Gill, M., Glahn, D.C., Gollub, R., Goudzwaard, E.D., Guo, H., Gur, R.E., Gur, R.C., Gurholt, T.P., Hashimoto, R., Hattori, S.N., Henskens, F.A., Hibar, D.P., Hickie, I.B., Hong, L.E., Horacek, J., Howells, F.M., Hulshoff Pol, H.E., Hyde, C.L., Isaev, D., Jablensky, A., Jansen, P.R., Janssen, J., Jönsson, E.G., Jung, L.A., Kahn, R.S., Kikinis, Z., Liu, K., Klausner, P., Knöchel, C., Kubicki, M., Lagopoulos, J., Langen, C., Lawrie, S., Lenroot, R.K., Lim, K.O., Lopez-Jaramillo, C., Lyall, A., Magnotta, V., Mandl, R.C.W., Mathalon, D.H., McCarley, R.W., McCarthy-Jones, S., McDonald, C., McEwen, S., McIntosh, A., Melicher, T., Mesholam-Gately, R.I., Michie, P.T., Mowry, B., Mueller, B.A., Newell, D.T., O'Donnell, P., Oertel-Knöchel, V., Oestreich, L., Paciga, S.A., Pantelis, C., Pasternak, O., Pearlson, G., Pellicano, G.R., Pereira, A., Pineda Zapata, J., Piras, F., Potkin, S.G., Preda, A., Rasser, P.E., Roalf, D.R., Roiz, R., Roos, A., Rotenberg, D., Satterthwaite, T.D., Savadjiev, P., Schall, U., Scott, R.J., Seal, M.L., Seidman, L.J., Shannon Weickert, C., Whelan, C.D., Shenton, M.E., Kwon, J.S., Spalletta, G., Spaniel, F., Sprooten, E., Stäblein, M., Stein, D.J., Sundram, S., Tan, Y., Tan, S., Tang, S., Temmingh, H.S., Westlye, L.T., Tønnesen, S., Tordesillas-Gutierrez, D., Doan, N.T., Vaidya, J., van Haren, N.E.M., Vargas, C.D., Vecchio, D., Velakoulis, D., Voineskos, A., Voyvodic, J. Q., Wang, Z., Wan, P., Wei, D., Weickert, T.W., Whalley, H., White, T., Whitford, T. J., Wojcik, J.D., Xiang, H., Xie, Z., Yamamori, H., Yang, F., Yao, N., Zhang, G., Zhao, J., van Erp, T.G.M., Turner, J., Thompson, P.M., Donohoe, G., 2018. Widespread white matter microstructural differences in schizophrenia across 4322 individuals: results from the ENIGMA Schizophrenia DTI Working Group. *Mol. Psychiatry* 23, 1261–1269. <https://doi.org/10.1038/mp.2017.170>.
- Kirkovski, M., Enticott, P.G., Maller, J.J., Rossell, S.L., Fitzgerald, P.B., 2015. Diffusion tensor imaging reveals no white matter impairments among adults with autism spectrum disorder. *Psychiatry Res. Neuroimage* 233, 64–72. <https://doi.org/10.1016/j.psychres.2015.05.003>.
- Kleinhaus, N.M., Pauley, G., Richards, T., Neuhaus, E., Martin, N., Corrigan, N.M., Shaw, D.W., Estes, A., Dager, S.R., 2012. Age-related abnormalities in white matter microstructure in autism spectrum disorders. *Brain Res.* 1479, 1–16. <https://doi.org/10.1016/j.brainres.2012.07.056>.
- Knöchel, C., Oertel-Knöchel, V., Schönmeyer, R., Rotarska-Jagiela, A., van de Ven, V., Prvulovic, D., Haenschel, C., Uhlhaas, P., Pantel, J., Hampel, H., Linden, D.E.J., 2012. Interhemispheric hypoconnectivity in schizophrenia: fiber integrity and volume differences of the corpus callosum in patients and unaffected relatives. *Neuroimage* 59, 926–934. <https://doi.org/10.1016/j.neuroimage.2011.07.088>.
- Kochunov, P., Chiappelli, J., Wright, S.N., Rowland, L.M., Patel, B., Wijtenburg, S.A., Nugent, K., McMahon, R.P., Carpenter, W.T., Muellerklein, F., Sampath, H., Hong, L.E., 2014. Multimodal white matter imaging to investigate reduced fractional anisotropy and its age-related decline in schizophrenia. *Psychiatry Res.* 223, 148–156. <https://doi.org/10.1016/j.psychres.2014.05.004>.
- Konstantareas, M.M., Hewitt, T., 2001. Autistic disorder and schizophrenia: diagnostic overlaps. *J. Autism Dev. Disord.* 31, 19–28. <https://doi.org/10.1023/A:1005605528309>.
- Lazar, M., Miles, L.M., Babb, J.S., Donaldson, J.B., 2014. Axonal deficits in young adults with High Functioning Autism and their impact on processing speed. *Neuroimage* 4, 417–425. <https://doi.org/10.1016/j.neuroimage.2014.01.014>.
- Le Couteur, A., Rutter, M., Lord, C., Rios, P., Robertson, S., Holdgrafer, M., McLennan, J., 1989. Autism diagnostic interview: a standardized investigator-based instrument. *J. Autism Dev. Disord.* 19, 363–387.
- Lee, K., Yoshida, T., Kubicki, M., Bouix, S., Westin, C.-F., Kindlmann, G., Niznikiewicz, M., Cohen, A., McCarley, R.W., Shenton, M.E., 2009. Increased diffusivity in superior temporal gyrus in patients with schizophrenia: a diffusion tensor imaging study. *Schizophr. Res.* 108, 33–40. <https://doi.org/10.1016/j.schres.2008.11.024>.
- Leroux, E., Delcroix, N., Dollfus, S., 2014. Left fronto-temporal dysconnectivity within the language network in schizophrenia: an fMRI and DTI study. *Psychiatry Res. Neuroimage* 223, 261–267. <https://doi.org/10.1016/j.psychres.2014.06.002>.
- Levitt, J.J., Alvarado, J.L., Nestor, P.G., Rosow, L., Pelavin, P.E., McCarley, R.W., Kubicki, M., Shenton, M.E., 2012. Fractional anisotropy and radial diffusivity: diffusion measures of white matter abnormalities in the anterior limb of the internal capsule in schizophrenia. *Schizophr. Res.* 136, 55–62. <https://doi.org/10.1016/j.schres.2011.09.009>.
- Liberio, L.E., DeRamus, T.P., Lahti, A.C., Deshpande, G., Kana, R.K., 2015. Multimodal neuroimaging based classification of autism spectrum disorder using anatomical, neurochemical, and white matter correlates. *Cortex* 66, 46–59. <https://doi.org/10.1016/j.cortex.2015.02.008>.

- Lord, C., Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L., Schopler, E., 1989. Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. *J. Autism Dev. Disord.* 19, 185–212.
- Lord, C., Rutter, M., Le Couteur, A., 1994. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J. Autism Dev. Disord.* 24, 659–685.
- Lukoff, D., Nuechterlein, K.H., Ventura, J., 1986. Manual for the expanded brief psychiatric rating scale. *Schizophr. Bull.* 12, 594–602.
- Mançe Çalıřır, Ö., Atbařođlu, E.C., Devrimci Özgüven, H., Ölmez, a., 2018. Cognitive features of high-functioning adults with autism and schizophrenia spectrum disorders. *Türk Psikiyatri Derg.* 29, 1–10.
- Mazefsky, C.A., Herrington, J., Siegel, M., Scarpa, A., Maddox, B.B., Scahill, L., White, S. W., 2013. The role of emotion regulation in autism spectrum disorder RH: emotion regulation in ASD. *J. Am. Acad. Child Adolesc. Psychiatry* 52, 679–688. <https://doi.org/10.1016/j.jaac.2013.05.006>.
- Mitelman, S.A., Buchsbaum, M.S., Young, D.S., Haznedar, M.M., Hollander, E., Shihabuddin, L., Hazlett, E.A., Bralet, M.-C., 2018. Increased white matter metabolic rates in autism spectrum disorder and schizophrenia. *Brain Imag. Behav.* 12, 1290–1305. <https://doi.org/10.1007/s11682-017-9785-9>.
- Mueller, S., Keeser, D., Reiser, M.F., Teipel, S., Meindl, T., 2012. Functional and structural MR imaging in neuropsychiatric disorders, Part 2: application in schizophrenia and autism. *Am. J. Neuroradiol.* 33, 2033. LP – 2037.
- Nakamura, K., Kawasaki, Y., Takahashi, T., Furuichi, A., Noguchi, K., Seto, H., Suzuki, M., 2012. Reduced white matter fractional anisotropy and clinical symptoms in schizophrenia: a voxel-based diffusion tensor imaging study. *Psychiatry Res. Neuroimaging* 202, 233–238. <https://doi.org/10.1016/j.psychres.2011.09.006>.
- Narr, K.L., Hageman, N., Woods, R.P., Hamilton, L.S., Clark, K., Phillips, O., Shattuck, D. W., Asarnow, R.F., Toga, A.W., Nuechterlein, K.H., 2009. Mean diffusivity: a biomarker for CSF-related disease and genetic liability effects in schizophrenia. *Psychiatry Res.* 171, 20–32. <https://doi.org/10.1016/j.psychres.2008.03.008>.
- Nazeri, A., Chakravarty, M.M., Felsky, D., Lobaugh, N.J., Rajji, T.K., Mulsant, B.H., Voineskos, A.N., 2013. Alterations of superficial white matter in schizophrenia and relationship to cognitive performance. *Neuropsychopharmacology* 38, 1954–1962. <https://doi.org/10.1038/npp.2013.93>.
- Noel, J.-P., Stevenson, R.A., Wallace, M.T., 2018. Atypical audiovisual temporal function in autism and schizophrenia: similar phenotype, different cause. *Eur. J. Neurosci.* 47, 1230–1241. <https://doi.org/10.1111/ejn.13911>.
- Noriuchi, M., Kikuchi, Y., Yoshiura, T., Kira, R., Shigeto, H., Hara, T., Tobimatsu, S., Kamio, Y., 2010. Altered white matter fractional anisotropy and social impairment in children with autism spectrum disorder. *Brain Res.* 1362, 141–149. <https://doi.org/10.1016/j.brainres.2010.09.051>.
- Ohtani, T., Bouix, S., Hosokawa, T., Saito, Y., Eckbo, R., Ballinger, T., Rausch, A., Melonakos, E., Kubicki, M., 2014. Abnormalities in white matter connections between orbitofrontal cortex and anterior cingulate cortex and their associations with negative symptoms in Schizophrenia: a DTI Study. *Schizophr. Res.* 157, 190–197. <https://doi.org/10.1016/j.schres.2014.05.016>.
- Pinkham, A.E., Hopfinger, J.B., Pelphrey, K.A., Piven, J., Penn, D.L., 2008. Neural bases for impaired social cognition in schizophrenia and autism spectrum disorders. *Schizophr. Res.*
- Prasad, K.M., Upton, C.H., Nimgaonkar, V.L., Keshavan, M.S., 2015. Differential susceptibility of white matter tracts to inflammatory mediators in schizophrenia: an integrated DTI study. *Schizophr. Res.* 161, 119–125. <https://doi.org/10.1016/j.schres.2014.09.043>.
- Prywesler, J.R., Schauder, K.B., Anderson, A.W., Heacock, J.L., Foss-Feig, J.H., Newsom, C.R., Loring, W.A., Cascio, C.J., 2014. White matter correlates of sensory processing in autism spectrum disorders. *Neuroimage* 6, 379–387. <https://doi.org/10.1016/j.neuroimage.2014.09.018>.
- Radeloff, D., Ciaramidaro, A., Siniatchkin, M., Hainz, D., Schlitt, S., Weber, B., Weber, B., Freitag, C.M., 2014. Structural Alterations of the Social Brain: A Comparison between Schizophrenia and Autism. *PLOS ONE* 9 (9), e106539.
- Roalf, D.R., Gur, R.E., Verma, R., Parker, W.A., Quarmley, M., Ruparel, K., Gur, R.C., 2015. White matter microstructure in schizophrenia: associations to neurocognition and clinical symptomatology. *Schizophr. Res.* 161, 42–49. <https://doi.org/10.1016/j.schres.2014.09.026>.
- Roalf, D.R., Ruparel, K., Verma, R., Elliott, M.A., Gur, R.E., Gur, R.C., 2013. White matter organization and neurocognitive performance variability in schizophrenia. *Schizophr. Res.* 143, 172–178. <https://doi.org/10.1016/j.schres.2012.10.014>.
- Roine, U., Salmi, J., Roine, T., Wendt, T.N., Leppämäki, S., Rintahaka, P., Tani, P., Leemans, A., Sams, M., 2015. Constrained spherical deconvolution-based tractography and tract-based spatial statistics show abnormal microstructural organization in Asperger syndrome. *Mol. Autism.* 6, 4. <https://doi.org/10.1186/2040-2392-6-4>.
- Rueckert, D., Sonoda, L.I., Hayes, C., Hill, D.L.G., Leach, M.O., Hawkes, D.J., 1999. Nonrigid registration using free-form deformations: application to breast MR images. *Med. Imag. IEEE Trans.* 18, 712–721. <https://doi.org/10.1109/42.796284>.
- Samartzis, L., Dima, D., Fusar-Poli, P., Kyriakopoulos, M., 2013. White matter alterations in early stages of schizophrenia: a systematic review of diffusion tensor imaging studies. *J. Neuroimaging* 24, 101–110. <https://doi.org/10.1111/j.1552-6569.2012.00779.x>.
- Sasamoto, A., Miyata, J., Kubota, M., Hirao, K., Kawada, R., Fujimoto, S., Tanaka, Y., Hazama, M., Sugihara, G., Sawamoto, N., Fukuyama, H., Takahashi, H., Murai, T., 2014. Global association between cortical thinning and white matter integrity reduction in schizophrenia. *Schizophr. Bull.* 40, 420–427. <https://doi.org/10.1093/schbul/sbt030>.
- Scheel, M., Prokscha, T., Bayerl, M., Gallinat, J., Montag, C., 2013. Myelination deficits in schizophrenia: evidence from diffusion tensor imaging. *Brain Struct. Funct.* 218, 151–156. <https://doi.org/10.1007/s00429-012-0389-2>.
- Shukla, D.K., Keehn, B., Müller, R.-A., 2011. Tract-specific analyses of diffusion tensor imaging show widespread white matter compromise in autism spectrum disorder. *JCPP (J. Child Psychol. Psychiatry)* 52, 286–295. <https://doi.org/10.1111/j.1469-7610.2010.02342.x>.
- Shukla, D.K., Keehn, B., Smylie, D.M., Müller, R.-A., 2011. Microstructural abnormalities of short-distance white matter fiber tracts in autism spectrum disorder. *Neuropsychologia* 49, 1378–1382. <https://doi.org/10.1016/j.neuropsychologia.2011.02.022>.
- Smith, S.M., 2002. Fast robust automated brain extraction. *Hum. Brain Mapp.* 17, 143–155. <https://doi.org/10.1002/hbm.10062>.
- Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., Behrens, T.E.J., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 31, 1487–1505. <https://doi.org/10.1016/j.neuroimage.2006.02.024>.
- Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 23, Supple, S208–S219. <https://doi.org/10.1016/j.neuroimage.2004.07.051>.
- Smith, S.M., Nichols, T.E., 2009. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage* 44, 83–98. <https://doi.org/10.1016/j.neuroimage.2008.03.061>.
- Song, S.-K., Yoshino, J., Le, T.Q., Lin, S.-J., Sun, S.-W., Cross, A.H., Armstrong, R.C., 2005. Demyelination increases radial diffusivity in corpus callosum of mouse brain. *Neuroimage* 26, 132–140. <https://doi.org/10.1016/j.neuroimage.2005.01.028>.
- Spalletta, G., De Rossi, P., Piras, F., Iorio, M., Dacquino, C., Scanu, F., Girardi, P., Caltagirone, C., Kirkpatrick, B., Chiapponi, C., 2015. Brain white matter microstructure in deficit and non-deficit subtypes of schizophrenia. *Psychiatry Res. Neuroimaging* 231, 252–261. <https://doi.org/10.1016/j.psychres.2014.12.006>.
- Spoleitini, L., Cherubini, A., Banfi, G., Rubino, I.A., Peran, P., Caltagirone, C., Spalletta, G., 2011. Hippocampi, thalami, and accumbens microstructural damage in schizophrenia: a volumetry, diffusivity, and neuropsychological study. *Schizophr. Bull.* 37, 118–130. <https://doi.org/10.1093/schbul/sbp058>.
- Sugranyes, G., Kyriakopoulos, M., Corrigall, R., Taylor, E., Frangou, S., 2011. Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition. *PLoS One* 6, e25322.
- Tamnes, C.K., Agartz, I., 2016. White matter microstructure in early-onset schizophrenia: a systematic review of diffusion tensor imaging studies. *J. Am. Acad. Child Adolesc. Psychiatry* 55, 269–279.
- Wagner, G., De la Cruz, F., Schachtzabel, C., Güllmar, D., Schultz, C.C., Schlösser, R.G., Bär, K.-J., Koch, K., 2015. Structural and functional dysconnectivity of the fronto-thalamic system in schizophrenia: a DCM-DTI study. *Cortex* 66, 35–45. <https://doi.org/10.1016/j.cortex.2015.02.004>.
- Weinstein, M., Ben-Sira, L., Levy, Y., Zachor, D.A., Itzhak, E. Ben, Artzi, M., Tarrasch, R., Eksteine, P.M., Hendler, T., Bashat, D. Ben, 2011. Abnormal white matter integrity in young children with autism. *Hum. Brain Mapp.* 32, 534–543. <https://doi.org/10.1002/hbm.21042>.
- Wheeler-Kingshott, C.A.M., Cercignani, M., 2009. About “axial” and “radial” diffusivities. *Magn. Reson. Med.* 61, 1255–1260. <https://doi.org/10.1002/mrm.21965>.
- Winkler, A.M., Ridgway, G.R., Webster, M.A., Smith, S.M., Nichols, T.E., 2014. Permutation inference for the general linear model. *Neuroimage* 92, 381–397. <https://doi.org/10.1016/j.neuroimage.2014.01.060>.
- Winkowski, P.J., Sabisz, A., Naumczyk, P., Jodzio, K., Szurowska, E., Szarmach, A., 2018. Understanding the physiopathology behind axial and radial diffusivity changes—what do we know? *Front. Neurol.*
- Wright, S.N., Hong, L.E., Winkler, A.M., Chiappelli, J., Nugent, K., Muellerklein, F., Du, X., Rowland, L.M., Wang, D.J.J., Kochunov, P., 2015. Perfusion shift from white to gray matter may account for processing speed deficits in schizophrenia. *Hum. Brain Mapp.* 36, 3793–3804. <https://doi.org/10.1002/hbm.22878>.