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Abnormalities in Brain White Matter in Adolescents with 22q11.2 Deletion Syndrome and Psychotic Symptoms

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Abstract

Background—22q11.2 Deletion Syndrome (22q11DS) is considered to be a promising cohort to explore biomarkers of schizophrenia risk based on a 30% probability of developing schizophrenia in adulthood. In this study, we investigated abnormalities in the microstructure of white matter in adolescents with 22q11DS and their specificity to prodromal symptoms of schizophrenia.

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None of the authors have a financial conflict of interest regarding this report.

Informed consent:
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

Endnote: A preliminary analysis of this study has been included in an abstract for the 2014 meeting of the International Society for Developmental Neuroscience (Kikinis et al. 2015).

Methods—Diffusion Magnetic Resonance Imaging (dMRI) data were acquired from 50 subjects with 22q11DS (9 with and 41 without prodromal psychotic symptoms), and 47 matched healthy controls (mean age 18 +/-2 years). DMRI measures, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were calculated and compared between groups using the Tract Based Spatial Statistics (TBSS) method. Additionally, correlations between dMRI measures and scores on positive symptoms were performed.

Results—Reductions in MD, AD and RD (but not FA) were found in the corpus callosum (CC), left and right superior longitudinal fasciculus (SLF), and left and right corona radiata in the entire 22q11DS group. In addition, the 22q11DS subgroup with prodromal symptoms showed reductions in AD and MD, but no changes in RD when compared to the non-prodromal subgroup, in CC, right SLF, right corona radiata and right internal capsule. Finally, AD values in these tracts correlated with the scores on the psychosis subscale.

Conclusion—Microstructural abnormalities in brain white matter are present in adolescent subjects with prodromal psychotic symptoms.

Keywords

22q11.2 deletion syndrome (22q11DS); Velo-Cardio-facial syndrome (VCFS); brain white matter; diffusion tensor magnetic resonance imaging (dMRI); Tract-based Spatial Statistics (TBSS)

1. Introduction

While there are several theories to explain the origin of schizophrenia, a large number of findings support a neurodevelopmental model. In this model, genetic and/or environmental insults are thought to occur prenatally, during early childhood or adolescence, and lead to the later emergence of psychotic symptoms (Lewis and Levitt 2002; Rapoport et al. 2012; Owen et al. 2011; Weinberger and Lipska 1995; Bayer et al. 1999). This model is supported by findings of reduced cortical volumes and increased ventricle size at the onset of schizophrenia (Cannon et al. 2002; Ettinger et al. 2012; Jones et al. 1994). Alternatively, the late neurodevelopmental model advocates for schizophrenia risk factors derived from a faulty synaptic pruning during adolescence (Feinberg 1982) and is supported by progressive reductions of gray matter volume during the earliest stages of psychosis in subjects that convert to schizophrenia (Pantelis et al. 2005; Sun et al. 2009; Borgwardt et al. 2008). While the neurodevelopmental hypothesis has mainly been based on results in studies of cortical gray matter, recent findings point to white matter as also contributing to the disease pathophysiology. More specifically, it is postulated that changes in white matter at the second decade of life contribute to the schizophrenia onset (Kochunov et al. 2011; Kochunov and Hong 2014).

Imaging methods developed during the past 15 years make possible the exploration of brain white matter *in vivo*. While structural Magnetic Resonance Imaging (MRI) can provide information about the volume of white matter, diffusion MRI (dMRI) is sensitive to changes in white matter microstructure, and can detect subtle pathology. DMRI is a method that measures the diffusion of water molecules in tissue and diffusion indices, including fractional anisotropy (FA), mean (MD), axial (AD) and radial diffusivity (RD), are derived

from dMRI. Such measures reveal subtle changes in white matter that are interpreted as microstructural changes to the axon (AD), myelin (RD), or fiber organization (FA) (Budde et al. 2009; Klawiter et al. 2011; Song et al. 2002; Beaulieu 2002). DMRI has, in fact, become the tool of choice to explore white matter *in vivo*.

Individuals with 22q11 deletion syndrome (22q11DS) represent a population of high interest to explore changes in white matter prior to schizophrenia onset based on a 30% prevalence of the disorder in adult life (e.g., Schneider et al., 2014). The syndrome is characterized by a copy number variation (CNV), namely a deletion of over 40 genes on one copy of chromosome 22 (Karayiorgou et al. 1995; Murphy et al. 1999). White matter abnormalities are present in 22q11DS and include reduced FA in interhemispheric connections, as well as across the frontal, parietal**,** temporal **and limbic** regions (Villalon-Reina et al. 2013; Sundram et al. 2010; Simon et al. 2005; Barnea-Goraly et al. 2003; Kates et al. 2015; Perlstein et al. 2014; Deng et al. 2015; da Silva Alves et al. 2011; Jalbrzikowski et al. 2014; Radoeva et al. 2012; Barnea-Goraly et al. 2005)**.** Abnormalities in maturational trajectories of white matter development (based on cross-sectional data) have also been reported in children and young adults with 22q11DS (Jalbrzikowski et al. 2014). Associations between psychotic symptoms and abnormalities in white matter have been reported in a cohort of children with 22q11DS (Sundram et al. 2010), in a cohort of 22q11DS subjects in the age range of 10 to 26 years (Jalbrzikowski et al. 2014), and in a cohort of adult individuals with 22q11DS who were also diagnosed with schizophrenia (da Silva Alves et al. 2011). While results of these studies suggest abnormalities in white matter in relation to prodromal/ psychotic symptoms, to the best of our knowledge, very little is known about the localization of white matter pathology in 22q11DS subjects with prodromal symptoms.

Our study had three objectives: i) to localize changes in brain white matter in adolescent subjects with 22q11DS relative to controls, ii) to explore whether or not white matter abnormalities within the sample of individuals with 22q11DS differ between those with and without positive symptoms of psychosis, and iii) to explore whether or not changes in white matter relate to the severity of positive psychotic symptoms. In order to reveal microstructural changes of white matter *in-vivo* we compared dMRI measures, including FA, MD, AD and RD, among the subject groups. Our study subjects were adolescents (mean age 18 +/-2 years) with 22q11DS, a disorder that has an increased risk for converting to psychosis.

2. Methods

2.1. Subjects

Scans were acquired from 50 individuals with 22q11.2DS and 47 healthy individuals matched for age, handedness, and gender (Table 1). The subjects were between the ages of 16 and 20 years and were recruited at SUNY Upstate Medical University, Syracuse, NY. The same subjects' images were used in two tractography studies of white matter microstructure (Perlstein et al. 2014; Kates et al. 2015) and in an atlas-based study of white matter microstructure on a subset of study participants, i.e., 48 out of 97 study subjects (Radoeva et al. 2012). For participants with 22q11DS, deletion of the chromosomal region 22q11.2 was confirmed by Fluorescent-In-Situ-Hybridization (FISH). Subject's handedness was based on

clinicians' observation. Full scale IQ was based on scores from the WAIS-III (subjects of 17 years or older) (Wechsler 1994) and from the WISC-III (for participants under 17 years of age)(Wechsler 1991). Evaluation for psychiatric disorders was performed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al. 1997) (**Table 1**). Symptoms were rated using the Brief Psychiatric Rating Scale (BPRS) (Overall JE 1962) and the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al. 2003). The BPRS and the SIPS were scored by a doctoral level clinician within the context of the structured psychiatric interview, in order to provide a measure of psychiatric symptoms such as depression, anxiety, hallucinations, unusual behavior, and prodromal symptoms, respectively. In order to provide concurrent validation of our BPRS measure of symptoms of psychosis, we used the scores on the Positive Symptoms Subscale of the SIPS as the measure of prodromal/psychotic symptoms for the correlational analyses.

In order to assess which subjects would most likely convert to schizophrenia in the near future, we used three BPRS items to categorize subjects with 22q11DS according to presence or absence of positive psychotic symptoms: hallucinatory behavior, suspiciousness, and unusual thought content. Positive symptoms of psychosis were considered present if at least one of these items was rated with a severity score equal to or greater than 3. Those individuals were considered 'at high risk for developing psychosis' (Schneider et al. 2014) (Lencz et al. 2003), and are referred to in this study as having a 'high score on the BPRS-psychosis subscale' (N=9). It should also be noted that two patients in this subgroup fulfilled the criteria for a diagnosis of schizophrenia.

The study was approved by the SUNY Upstate Institutional Review Board. All subjects signed informed consent prior to participation in the study.

2.2. Diffusion-weighted imaging and image post processing

Scans were acquired on a 1.5 Tesla Philips Interra scanner equipped with a Sense Head coil to improve signal strength and signal-to-noise ratio. The dMRI images were obtained using a multi-slice, single-shot EPI (SENSE factor = 2.0), spin echo sequence to acquire 70 axial slices, 2.5 mm nominal isotropic resolution (no gaps between slices). The following scanning parameters were used TR/TE = 8197/76 ms, FOV = 240 × 240, data matrix = 96 × 96, zero-filled and reconstructed to 256 × 256. Diffusion weighting was applied along 15 directions with a $\boldsymbol{b}$ factor=800 s/mm^2. One minimally weighted volume (b_0) was acquired within each dMRI dataset. The total scan time per one dMRI dataset (15 DW and 1 b_0 images) was 2 min, 11 s. Within the same scanning session four dMRI datasets were acquired for each subject, and combined for the analysis. We used an in-house script to correct for eddy current distortions and head motion. Each diffusion-weighted volume was registered to the baseline volume using FSL linear registration software "flirt". An affine transformation was used, but the motion parameters were not recorded as we used our in-house measures to correct for both eddy current distortions and head movement.

2.3. Data Analysis

Voxel-based group comparisons of FA, MD, AD, and RD in whole brain white matter were carried out using TBSS software (Smith et al. 2006), and standard processing steps were followed as described in the guidelines (http://www.fmrib.ox.ac.uk/fsl/tbss/index.html). In short, scalar FA images were created from diffusion-weighted dMRI images using an in-house script and brain masks were generated using Brain Extraction Tool (BET) (Smith 2002). All subjects' FA images were then aligned into a common space using nonlinear registration. For this step, TBSS offers two standard options, either to register to the provided TBSS target image or to automatically select the most representative image from the current dataset. Due to the young age of our participants, we opted for the second option, because the target image provided by TBSS is for older subjects. Next, the mean FA image of all coregistered subjects was created and thinned to a white matter skeleton. The skeleton was thresholded to contain voxels with FA >0.2. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics. The number of permutations was set at 5000 and the clusters were visualized at a significance level of $p<0.05$, corrected for multiple comparisons using Threshold-free cluster enhancement (TFCE). Group comparisons of the other scalars, including MD, AD, and RD, were obtained from the nonlinear warps of the FA registrations and the projections of the other diffusion scalar volumes onto the FA skeleton.

Clusters with significant group differences were segmented into white matter tracts. The white matter tracts were defined using the Johns Hopkins University (JHU) ICBM-DTI-81 white matter labels atlas. Mean dMRI values were calculated for each WM tract within the cluster.

2.4. Statistical analysis

The Statistical Package for Social Sciences (IBM-SPSS-version-21) was used to perform independent samples T-tests of the demographic data. The statistical package STATA (Stata Corporation) was used to perform analyses testing the associations between extracted dMRI values and positive symptoms on the SIPS and BPRS. A zero-inflated Poisson (ZIP) analysis was conducted to account for a large number of cases with the score of 0 on the SIPS and BPRS scale. Effect size, Cohen’s d, was estimated based on the mean and standard deviation. We used the Effect Size Calculator, available on the internet (http://www.uccs.edu/~faculty/lbecker/).

3. Results

Abnormalities in white matter were evaluated between the groups using a whole brain voxel-by-voxel approach, the TBSS method. DMRI measures of FA, MD, AD, and RD were compared between groups: first, between the control and the 22q11DS group, and, second, between the 22q11DS subgroups with low and with high score on the BPRS-psychosis subscale.

The first TBSS analysis compared the entire 22q11DS group (N=50) with healthy subjects (N=47). We observed significant reductions ($p_{TFCEcorrected}<0.05$) in MD, AD, and RD in the

22q11DS group (**Fig. 1**). However, FA, the most widely reported dMRI measure in the 22q11DS literature, did not show any group differences. The decreases in the three dMRI measures (MD, AD, RD) showed a similar pattern and were localized to the same white matter tracts. The changes were distributed symmetrically in both brain hemispheres (**Fig. 2**). Major anatomical white matter regions with decreases in MD, AD and RD in adolescents with 22q11DS included parts of the CC (body and splenium), superior longitudinal fasciculus (SLF) and corona radiata (**Table 2**). While wide-spread reductions in all three dMRI measures were found, no brain regions showed statistically significant increases in FA, MD, AD or RD in 22q11DS.

The localization of abnormalities in white matter in 22q11DS participants at high risk for developing psychosis was explored by performing a second TBSS analysis. We compared 22q11DS subjects with low scores on BPRS-psychosis subscale (N=41) with those subjects with a high score on BPRS-psychosis subscale (N=9). Statistically significant decreases in AD were observed in subjects with a high score on the BPRS-psychosis subscale and were significant at $p<0.05_{TFCEcorrected}$ (**Fig. 3**). Similarly, decreases in MD were observed at trend level of $p<0.055_{TFCEcorrected}$ in subjects with high score on the BPRS-psychosis subscale (**Fig. 3**). Again, areas with reduced AD and MD were consistent over the same fiber tracts. There were no statistically significant differences for RD or for FA between the 22q11DS subgroups. The decreases in AD in subjects with high scores on the BPRS-psychosis subscale were localized to the right SLF, the CC (splenium and body), the right superior corona radiata, and the right internal capsule (retrolenticular part, posterior limb and anterior limb) (**Fig. 4**). It should be noted that many of the white matter regions that we observed to be abnormal in the non-prodromal group of individuals with 22q11DS are also abnormal in the prodromal group, but the extension within the tract and the distributions over the hemispheres vary. That is, in comparisons between 22q11DS and healthy subjects, the fiber tracts of both hemispheres were impacted (**Fig. 2**), whereas in comparisons between the two 22q11DS subgroups, only the tracts in the right hemisphere were impacted (**Fig. 4**).

Lastly, we examined the association between abnormalities in white matter and a dimensional measure of prodromal/psychotic symptoms. We performed correlations between the measurements from white matter, the AD, and scores on the SIPS subscale in all subjects with 22q11DS. AD was extracted from cluster showing group differences in the initial TBSS analysis (TBSS analysis comparing healthy and the entire 22q11DS group). We focused on AD because this dMRI measure showed statistically significant group differences in white matter in subjects with a high score on the BPRS subscale compared with those with low scores. There was one single cluster that included the fiber tracts of the subdivisions of the corpus callosum, the right and the left SLF, the superior and the anterior corona radiata (**Table 2**). The ZIP regression was applied in order to account for the fact that the majority of subjects with 22q11DS had a score of zero on the SIPS subscale. We observed negative associations between the SIPS Positive Symptoms and the AD in genu, body and splenium of the corpus callosum (all p values less than or equal to 0.004), while the other six regions tested did not correlate statistically significantly with scores on SIPS (**Table 3**). Statistical significance was considered when p was 0.0062 or lower in order to account for multiple comparisons ($p< 0.05/8$ regions=0.0062). These findings suggest that

decreases in AD in the corpus callosum were associated with an increase in positive prodromal symptoms in individuals with 22q11DS. Since many of our participants with prodromal symptoms were taking anti-psychotic medication or mood stabilizers, we sought to determine the extent to which medication usage might be driving these results. Accordingly, we ran ZIP regression analyses and included a term for medication usage (yes vs. no) in the model. We found that although the strength of associations between our DTI metrics and scores on symptoms of psychosis were slightly reduced when medication usage was added to the model, the associations remained significant **(Table 3)**. We further conducted the same set of analyses using the BPRS-psychosis subscale as our dependent variable (in order to confirm our findings with the SIPS), and our results remained consistent **(Table 3)**. In summary, decreases in AD in the corpus callosum were associated with increases in positive prodromal symptoms (BPRS and SIPS) in individuals with 22q11DS and these associations remained significant when medication usage (anti-psychotics and / or mood stabilizers) was included.

In order to explore whether white matter changes in the 22q11DS group are driven by the group with high score on the BPRS subscale, we completed group-wise comparisons by performing TBSS analysis among all the study groups. In addition to the group analyses mentioned above, namely comparison of healthy subjects versus the entire group with 22q11DS, and comparison of 22q11DS subjects with low versus high scores on BPRS-psychosis subscale, we performed two additional TBSS analyses. These included comparisons between the healthy subjects (N=47) and the 22q11DS subjects with low scores on BPRS-psychosis subscale (N=41), as well as a comparison between the healthy subjects (N=47) and the 22q11DS subjects with a high score on BPRS-psychosis subscale (N=9). Each of the two last analyses resulted in statistically significant reductions in MD, AD and RD in brain white matter in either of the two groups with 22q11DS (data not presented) and showed the same pattern as the analysis between the healthy and the 22q11DS subjects. This analysis shows that abnormalities in white matter are present even in subjects with 22q11DS and low scores on BPRS subscale.

4. Discussion

In this study we explored, first, the location and nature of brain white matter abnormalities in subjects with 22q11DS, compared to healthy volunteers. Second, we investigated whether individuals with 22q11DS and prodromal/psychotic symptoms differ from those without clinical symptoms. Lastly, we tested whether or not such changes are associated with positive symptoms on the SIPS subscale.

Relative to control subjects, individuals with 22q11DS have wide spread reductions in MD, AD, and RD (**Fig. 1 and 2**). This is consistent with previous reports showing that individuals with 22q11DS have decreased AD values (Radoeva et al. 2012; Kikinis et al. 2012), decreased AD and RD (Jalbrzikowski et al. 2014) and also decreased white matter volumes in comparison to controls (Kates et al. 2004; Kates et al. 2001; Sundram et al. 2010; da Silva Alves et al. 2011), and confirms that abnormalities in white matter are present in 22q11DS.

The changes in MD, in AD, and in RD, were localized to the same regions of brain white matter (**Fig.1 and 2**). We did not observe changes in FA, the most often reported dMRI measure. Moreover, we did not detect any statistically significant increases in MD, AD, or RD anywhere in the brain. Reductions in all three dMRI indices, MD, AD and RD, have not been reported in patients with schizophrenia. Diffusivity increase is usually observed with increasing neurodegeneration, as reported in demyelinating diseases (Senda et al. 2012; Della Nave et al. 2004), but also in schizophrenia and bipolar disorder (Anderson et al. 2013; Clemm von Hohenberg et al. 2014). Reductions in MD, AD, and RD are usually observed in typically developing children and adolescents over the course of the first two decades of life (Lebel and Beaulieu 2011; Lebel et al. 2012), which may suggest that changes in the dMRI measures observed here in 22q11DS might be a consequence of abnormal development, rather than the pathology observed in full blown psychosis.

When we compared whole brain white matter between the subgroups of 22q11DS with high and low scores on BPRS-psychosis subscale, we found a statistically significant reduction in AD and a reduction at trend level in MD for subjects with high scores on the BPRS-psychosis subscale (**Fig. 3**). No statistically significant reductions were found for RD or FA and no increases in any of the dMRI measures were detected. The major white matter areas with reductions in AD were located in the corpus callosum and the SLF of the right hemisphere (**Fig. 4**). Similar right-hemisphere pathology has also been reported in individuals at clinical high risk for psychosis in white matter (Clemm von Hohenberg et al. 2014) and in cortical thinning of gray matter (Cannon et al. 2015). A similar lateralization pattern has also been reported in first episode (Guo et al. 2012), but not in chronic schizophrenia patients, suggesting that lateralized patterns of abnormalities may be typical for early stages of disease.

Interestingly, findings of reduced MD, AD and RD, without changes in FA, are not reported in previous studies on 22q11DS. In fact, studies in school age children with 22q11DS report reduced FA and increased RD in the fornix (Deng et al. 2015) and in the superior longitudinal fasciculi, the inferior longitudinal fasciculi, the splenium of the corpus callosum, and the corticospinal tract (Villalon-Reina et al. 2013), which might be interpreted as abnormal myelination in 22q11DS in early childhood. In another study, where subjects of older age and a wider age range were included (10 thorough 26 years old), increased FA and reduced AD and RD were reported in several tracts in 22q11DS (Jalbrzikowski et al., 2014). These findings suggest that the nature and direction of changes in dMRI associated with 22q11DS may vary as a function of age. Our study is also unique with respect to the age of the subjects. The subjects' age range is between 16 and 20 years, which is a very narrow age range compared to many other studies. Interestingly, this is also the age range just prior to the onset of most cases of schizophrenia. At this period in time, normally developing adolescents evince an FA trajectory that shows a change from increasing (during childhood) to decreasing (in adulthood) (Lebel et al. 2012). It is thus possible that we are capturing processes of transition between developmental, with increased FA in 22q11DS, and pathological, decreased FA that is likely more characteristic of schizophrenia onset. Further longitudinal studies are, nonetheless, needed to study this transitional period in more detail.

The interpretation of the observed changes in dMRI measures with respect to pathological changes of white matter remains speculative. Reductions in RD and AD, as well as increases in white matter volumes have been reported in normally developing children during the first **three** decades of life (Lebel and Beaulieu 2011; Lebel et al. 2012). These findings suggest an ongoing maturation of white matter. We thus speculate that decreases in RD and AD in 22q11DS subjects, which we report here, likely point to **premature** development **of** white matter **in 22q11DS when compared to** normally developing adolescents. To confirm our speculation of **early** maturation of white matter in 22q11DS, future studies are needed to explore whether or not the volume of brain white matter increases at this age in 22q11DS subjects. Future studies using animal models of the 22q11.2 chromosomal deletion will also be important to determine whether or not **early** maturation of brain white matter and reductions in RD and AD occurs **in 22q11DS.**

As abnormalities in white matter may affect behavior or present risk for developing psychosis, we investigated the relationship between scores on the SIPS, respectively BPRS, Positive Symptom Subscale and AD values in brain areas of differences between the control and the 22q11DS group. This analysis was conducted on the sample of individuals with 22q11DS only. We found significant negative associations between the SIPS, respectively BPRS, positive symptoms and the genu, body and splenium of the corpus callosum, showing that decreases in AD were associated with an increase in positive psychotic symptoms. Abnormalities in the corpus callosum, the largest interhemispheric connection of the human brain, have been reported in first episode and chronic schizophrenia patients (Henze et al. 2012; Knochel et al. 2012; Kubicki et al. 2005; Samartzis et al. 2014) and associated with psychotic symptoms (Whitford et al. 2010). Similar to our findings, greater severity of positive symptoms was associated with lower AD in young subjects with 22q11DS (Jalbrzikowski et al. 2014). The localization of white matter pathology associated with clinical symptoms, however, was different, with bilateral reductions in inferior fronto-occipital fasciculus (IFOF) in the study by Jalbrzikowski et al., 2014, and corpus callosum here. While the sources of such discrepancies are not clear, it is possible that they could be partially explained by differences in age distributions between the two studies.

Further, our previous study by Perlstein et al. (2014) and by Kates et al. (2015), showed evidence of reduced FA in anterior limb of the internal capsule and the uncinate fasciculus, as well as reduced FA in the cingulum bundle, respectively. In these studies the tracts were preselected and tractography measures were used to determine whether or not these tracts were affected. In contrast, in the current study there were no a priori assumptions made with respect to which tracts might be affected. Instead, TBSS was used to investigate whole brain white matter tracts between groups using a voxel-by-voxel approach. Thus it is not surprising that the three tracts investigated in the previous studies were not the tracts that were most significantly different between groups using TBSS, i.e., corpus callosum, SLF and corona radiata. It is also not surprising that clinical correlations differed between studies given that different brain regions with different locations and functions were identified.

Finally, the effect of medication on changes observed in subjects cannot be fully excluded, but we believe that it does not confound our findings. The effect of antipsychotic and mood stabilizer medication was reported previously in cingulum bundle in this data set and had a

reparative outcome: It was observed that the subgroup of youth with 22q11DS that was given a low dose of antipsychotic or mood stabilizer medication currently or in the past, had the same FA and AD values in the cingulum bundle as the controls, while the non-medicated subjects with 22q11DS had significantly lower values in FA and AD (Kates et al. 2015). While in our current analysis, the subjects with the high score on BPRS-psychosis symptoms were more medicated than those with a low score, the AD values were lowest in the subjects with high score on BPRS-psychosis symptoms. We have not detected any 'reparative' outcome in corpus callosum and suggest that the medication does not confound our results. In addition, we have re-run our ZIP models, including medication usage (ie., anti-psychotics and / or mood stabilizers) to the model. We found that the associations between alterations in white matter of the corpus callosum and presence of prodromal symptoms remained significant even when medication usage was included in the model. Accordingly, we conclude that medication usage was not driving the association of AD and prodromal symptoms in the corpus callosum.

It should be noted that a whole brain analysis has been already performed (albeit using different methodology) and published on a subpopulation of this cohort (Radoeva et al. 2012). That study compared subjects with 22q11DS and their siblings and found reductions of AD and RD in individuals with 22q11DS in similar tracts that we report in the current study. That study, however, did not explore the nature or location of differences between 22q11DS subjects with low versus high scores on the BPRS-psychosis subscale, which is done here.

The main limitation of our study is the small number of subjects with high scores on the BPRS-psychosis subscale in this age group (N=9). Despite the small number, the number of subjects was sufficiently large to find statistically significant group differences using TBSS. Effect sizes for group differences for the extracted AD of several tracts from the TBSS cluster were Cohen's d= 0.88 and larger, which is considered a large effect size according to Cohen's convention (d≥0.8) (Cohen 1988)). Further, the sample of patients with high scores on positive symptoms on the BPRS subscale (3 or higher) included two subjects who met the criteria for a diagnosis of schizophrenia. One might expect that these two subjects with schizophrenia would have the lowest dMRI values and possibly even drive the differences between the groups. However, these two subject's AD values were not outliers and as such concerns regarding possible confounds are eliminated (data not shown). Lastly, we expected about 30% of the subjects of the 22q11DS cohort to have a high score on the BPRS-psychosis subscale, but at the time of this study only approximately 20% had high scores. This low prevalence might be due to the relatively young age of the 22q11DS participants and the follow up of this longitudinal sample, which is in process, might better reflect both more symptoms and the expected conversion rates to schizophrenia.

In this study, we used dMRI to explore changes in white matter in adolescents with 22q11DS and those with positive symptoms whom we designated as being at high risk to develop schizophrenia. Reductions in dMRI measures (MD, AD and RD) were found in 22q11DS subjects that point to the presence of abnormalities at the age of schizophrenia onset. 22q11DS individuals with high score on BPRS-psychosis subscale also showed reduced values in AD when compared to subjects with low score. The AD values further

correlated with scores on the SIPS/BPRS Positive Symptoms subscale. In this study we demonstrate that abnormalities of the white matter are present in subjects with high scores on psychosis-subscale, even prior to a clinical diagnosis of schizophrenia.

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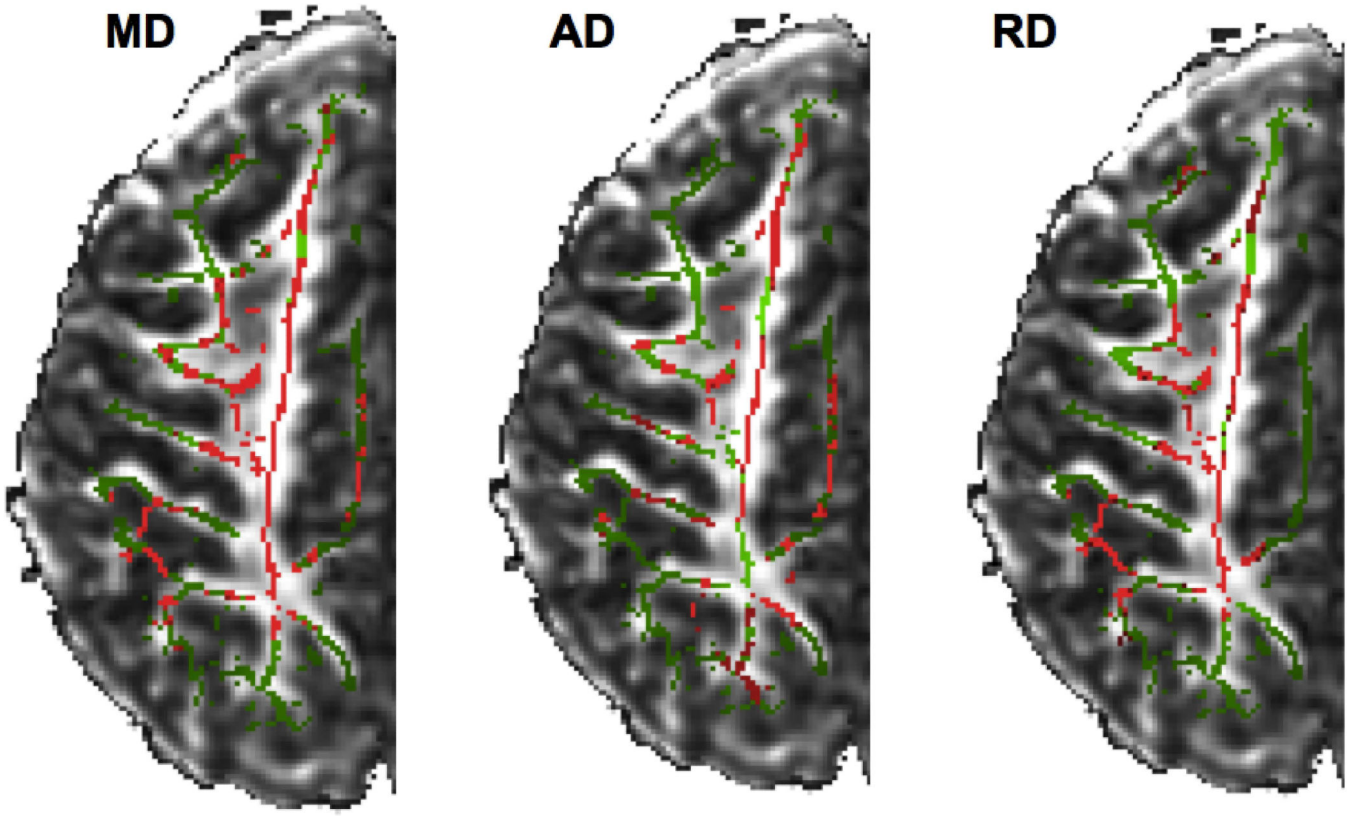

Fig.1. Results of voxel-wise analysis of brain white matter differences between the 22q11DS group and the healthy subjects group

Axial views of the right brain hemisphere are shown at the level of the superior cingulum, corpus callosum and superior longitudinal fasciculus. Decreases in voxel intensities in mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) in the 22q11.2DS group are indicated in red and represent voxels visualized at p-values of $p_{TFCE}<0.05$ (threshold-free cluster enhancement corrected for multiple comparisons). The results are overlaid on the FA image of one of the subjects and FA is presented in shades of gray and white; the mean FA skeleton is represented in green.

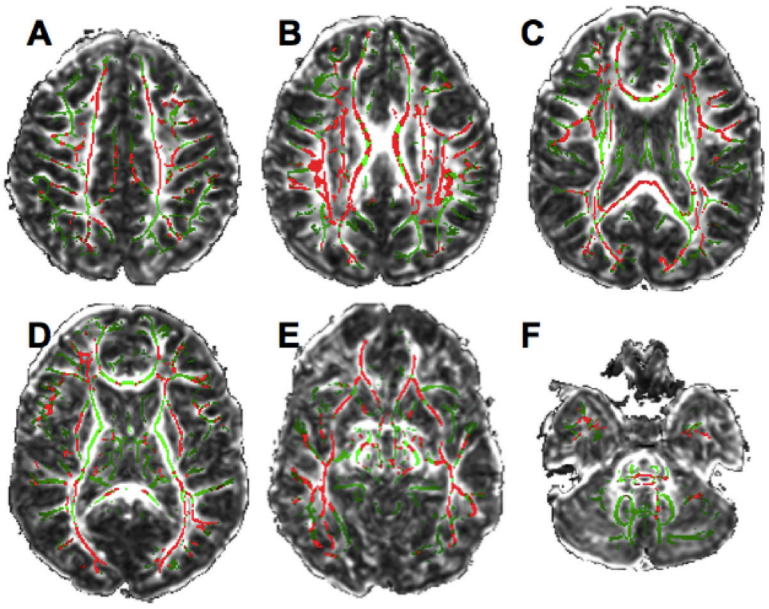

Fig.2. Differences in axial diffusivity across the brain between the 22q11DS group and the healthy subjects group

Decreases in voxel intensities of axial diffusivity (AD) in the 22q11.2DS group are indicated in red and represent voxels visualized at p-values of $p_{TFCE}<0.05$. The voxels are localized the following tracts: corpus callosum (CC) and cingulum (panel A); superior longitudinal fasciculus (SLF), body of CC, and superior corona radiata (panel B); splenium of CC and anterior corona radiata (panel C); anterior corona radiata (panel D). The FA image of one of the subjects is presented as background and FA is presented in shades of gray and white; the mean FA skeleton is in green.

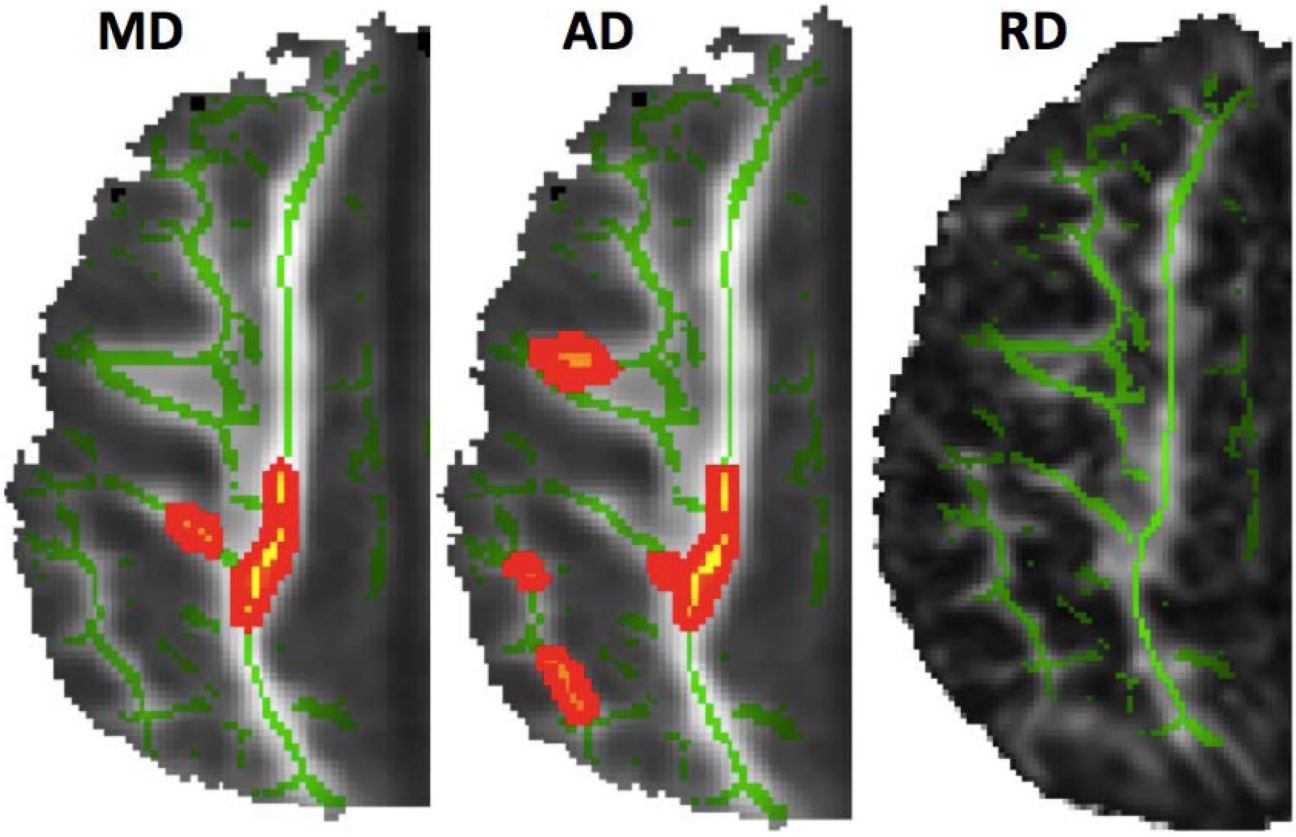

Fig.3. Results of voxel-wise analysis of brain white matter differences between 22q11DS subjects with low and high score on positive symptoms of the BPRS scale

Axial views of the right brain hemisphere are shown at the level of the superior cingulum, corpus callosum and superior longitudinal fasciculus. Decreases in voxel intensities, of the axial diffusivity (AD) in the 22q11.2DS group with high score on BPRS subscale are indicated in red and yellow and represent voxels visualized at p-values of $p_{TFCE}<0.05$ (threshold-free cluster enhancement corrected for multiple comparisons), decreases in mean diffusivity (MD) are shown at $p_{TFCE}<0.055$. To better visualize the relatively small regions of group differences, the clusters are presented here as 'thickened' in red/yellow. The results are overlaid on the FA image of one of the subjects and FA is presented in shades of gray and white; the mean FA skeleton is represented in green.

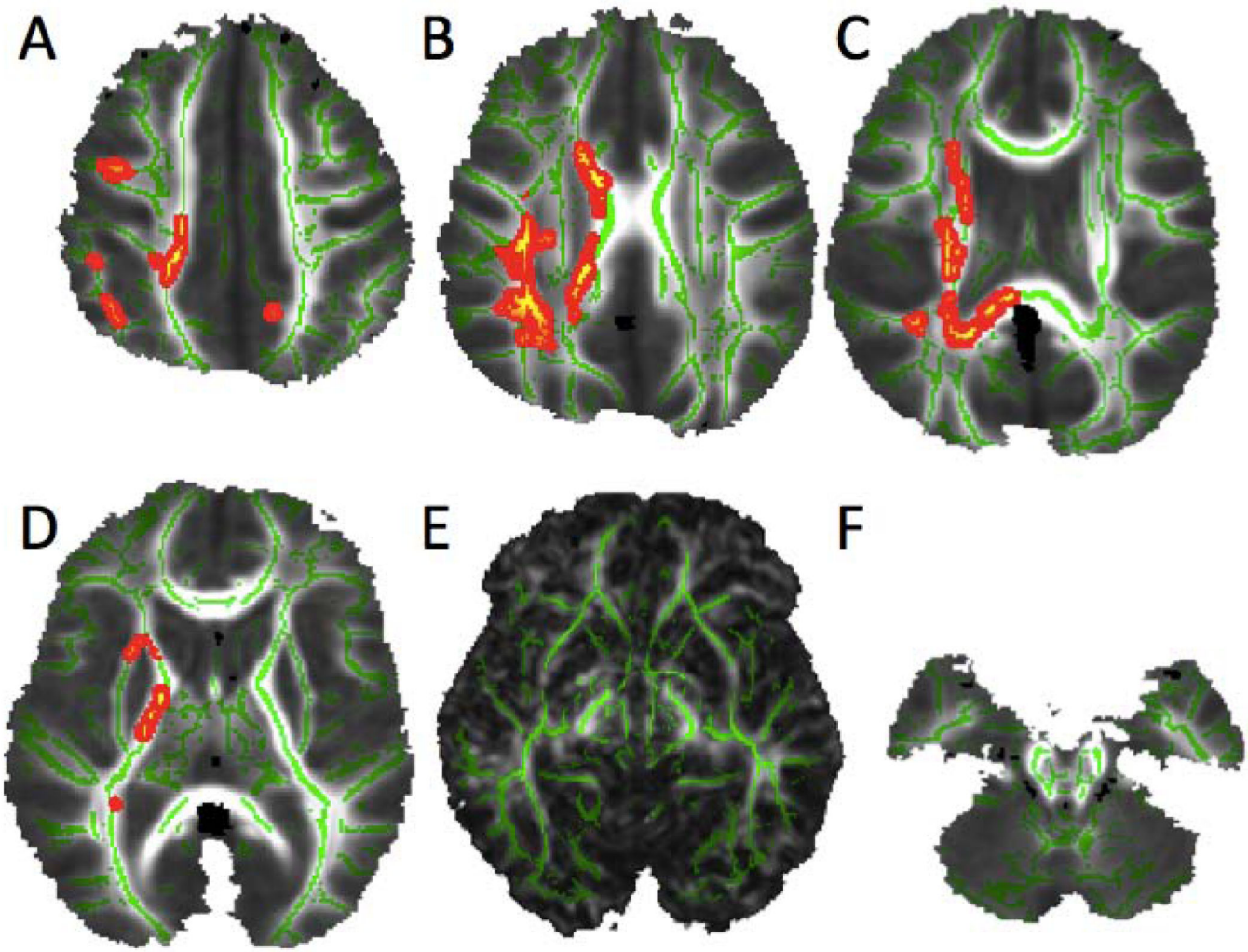

Fig. 4. Differences in axial diffusivity across the brain between the 22q11DS group with low and high score on BPRS-psychosis subscale

Decreases in voxel intensities of axial diffusivity (AD) in the 22q11.2DS group with high score on BPRS subscale are indicated in red/yellow and represent voxels visualized at p-values of $p_{TFCE}<0.05$. The voxels are localized the following tracts: right superior longitudinal fasciculus (rSLF) and body of corpus callosum (CC) (panel A, B); splenium of CC and superior corona radiata (panel C); internal capsule (panel D). The FA image of one of the subjects is presented as background and FA is presented in shades of gray and white; the mean FA skeleton is in green; the anatomically right hemisphere is presented on the left.

Table 1

Demographic and diagnostic characteristics of study groups

	healthy controls (N=47)	22q11DS (N=50)	p-value	22q11DS low BPRS (N=41)	22q11DS high BPRS (N=9)	p-value
Gender (N,%female)	22 (46%)	28 (56%)	n.s	24 (58%)	4 (44%)	n.s
Age (in years; mean +/−SD)	18.0 (1.6)	18.1 (2.3)	n.s	17.9 (2.2)	18.8 (2.8)	n.s
Handedness (Righ handed, %)	44 (94%)	39 (78%)	n.s	31 (76%)	8 (89%)	n.s
Full scale IQ index (+/−SD)	108 (17)	72 (17)	< 0.001	71.8 (17)	70.7 (17)	n.s
Medication						
Antipsychotic (current and/or past)	0	8 (16%)		2 (5%)	6 (67%)	< 0.001
Mood Stabilizer (current and/or past)	0	6 (12%)		1 (2%)	5 (56%)	< 0.001
Anti-depressant/anxiety (current)	3 (6%)	7 (14%)		7 (17%)	0 (0%)	< 0.001
Stimulant/Alpha 2 Adrenergic current)	5 (11%)	11 (22%)		8 (20%)	3 (33%)	
No medication	39 (85%)	32 (63%)		29 (71%)	3 (33%)	
Number of subjects with BPRS Psychosis Subscale*	0 (0%)	9 (18%)		0	9	
Psychiatric Diagnosis of Schizophrenia (in % N)	0 (0%)	2 (4%)		0	2	

N: number of subjects per group

p: statistical significance between the two groups (independent T-test, 2-tailed)

IQ index is based on scores from WAISIII (participants of 17 years or older) or WISCIII (for participants under 17 years of age)

BPRS: Brief Psychiatric Rating Scale

* Items on the BPRS Psychosis Subscale include suspiciousness, hallucinatory behavior and unusual thought content. A participant had to have a score of 3 or above on any of these three items to be categorized with prodromal psychosis.

Table 2

MNI coordinates of clusters of significant group differences ($p<0.05$ threshold-free cluster enhancement corrected) from TBSS analysis

Groups compared	Cluster number	dMRI measure	p	Cluster size (voxel)	MNI coordinates of peak voxel			white matter tracs overlapping with the cluster (voxel)*
					x	y	z	
healthy versus 22q11DS	1	AD	0	42509	109	78	97	Body of corpus callosum (1853) Superior longitudinal fasciculus R (1327) Splenium of corpus callosum (1175) Superior longitudinal fasciculus L (1154) Superior corona radiata R (1226) Superior corona radiata L (1214) Anterior corona radiata R (1063) Anterior corona radiata L (1065) Unclassified (25632)

MNI, Montreal Neurological Institute; AD, axial diffusivity;

White matter tracts were defined using the Johns Hopkins University White Matter Label Atlas; L=left hemisphere; R=right hemisphere;

*white matter tracts with an area of 2% and more of the cluster are listed.

Table 3

Correlations of DTI measures and positive prodromal/psychotic symptoms

	SIPS*		BPRS**		SIPS: Inclusion of medication usage in model***		BPRS: Inclusion of medication usage in model***	
	z-score	p	z-score	p	z-score	p	z-score	p
white matter tracts overlapping with the cluster								
Genu of corpus callosum	**−3.06**	**0.002**	**2.72**	**0.006**	2.21	0.027	**3.41**	**0.001**
Body of corpus callosum	**−3.48**	**0.001**	**−4.86**	**0.0001**	1.81	0.070	2.59	0.010
Splenium of corpus callosum	**−2.86**	**0.004**	**−2.79**	**0.005**	**3.05**	**0.002**	**4.02**	**0.0001**
Superior longitudinal fasciculus R	−0.07	0.944	−1.09	0.276	−1.87	0.061	−2.68	0.0070
Superior longitudinal fasciculus L	1.46	0.146	1.12	0.262	−0.3	0.767	−1.35	0.1780
Anterior corona radiata R	−1.18	0.238	−0.48	0.63	−1.03	0.303	−0.45	0.6550
Anterior corona radiata L	−1.02	0.307	−0.99	0.32	−2.21	0.027	−1.65	0.0990
Superior corona radiata R	1.24	0.214	−0.18	0.853	1.88	0.06	−0.37	0.7100
Superior corona radiata L	1.06	0.288	−1.77	0.077	1.14	0.254	−1.64	0.101

Zero-inflated Poisson (ZIP) regression was performed to account for the fact that most subjects had a score of 0 on the SIPS scale and z-scores and p-values are given.

Statistically significant results are considered for $p < 0.006$ due to correction for multiple comparison for 8 regions ($p < 0.05/8$ regions=0.006) and are highlighed in bold.

*Results of correlations between the scores on positive symptoms on the SIPS and the AD values assigned to each fiber tract of the cluster are given.

**Results of correlations between scores on the BPRS-Psychosis Subscale and the AD values for white matter tracts that were associated with the cluster

***Results of analyses when medication usage (ie., antipsychotic and/or mood stabilizer in the past or current) was included in the regression model.