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White matter microstructural deficits in 22q11.2 deletion syndrome

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Abstract

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Diffusion tensor imaging (DTI) studies in 22q11.2 Deletion Syndrome (22q11DS), a neurogenetic condition associated with psychosis, report brain white matter (WM) microstructure aberrations. Several studies report that WM disruptions in 22q11DS are similar to deficits in idiopathic schizophrenia. Yet, DTI results in 22q11DS are inconsistent. We used DTI to compare WM structure in 22q11DS individuals to healthy controls (HC) and explored WM differences in 22q11DS with (+) and without (–) psychosis spectrum symptoms. We examined 39 22q11DS individuals and 39 age, sex and race equivalent HC. DTI was performed at 3T using a 64-direction protocol. Fractional anisotropy (FA) was lower, while radial diffusivity was higher in 22q11DS within the cingulum bundle. Mean diffusivity was lower in the inferior longitudinal fasciculus, while axial diffusivity (AD) was lower in the cingulum bundle, forceps major, and several posterior to anterior fasciculi. 22q11DS+ had lower FA in the cingulum bundle and lower AD in the uncinate fasciculus compared to 22q11DS–. Overall, we found aberrant WM microstructure in individuals with 22q11DS compared to age and sex matched HC and exploratory analysis indicated subtle WM deficits associated with psychosis. The findings highlight the dysfunction of WM microstructure in 22q11DS and its potential importance in elucidating WM abnormalities in psychosis.

Keywords

22q11.2 deletion syndrome; diffusion tensor imaging; psychosis; fractional anisotropy; cingulum bundle

1.0 Introduction

The 22q11.2 deletion syndrome (22q11DS) is the most common known genetic microdeletion in humans (McDonald-McGinn et al., 2015). 22q11DS is associated with craniofacial, cardiovascular, cognitive, endocrine, immune, and gastrointestinal disorders (McDonald-McGinn et al., 2015). Notably, 22q11DS is also associated with an increased risk for psychiatric disorders (Gothelf et al., 2007; Murphy et al., 1999; Pulver et al., 1994; Schneider et al., 2014; Tang et al., 2014), including psychosis (Bassett et al., 1998; Shprintzen et al., 1992). Individuals with 22q11DS who develop psychosis show similar symptoms to individuals with idiopathic schizophrenia (Murphy et al., 1999), and approximately 1–2% of cases of idiopathic schizophrenia have 22q11.2 deletions (Bassett et al., 2010). Thus, understanding brain dysfunction in 22q11DS may elucidate critical neural mechanisms in psychosis.

Structural brain abnormalities, including lower gray matter volume (Schneider et al., 2014; Tan et al., 2009), cortical thickness (Bearden et al., 2007; Schaer et al., 2008), surface area (Jalbrzikowski et al., 2013) and gyral complexity (Schaer et al., 2008; Schaer et al., 2006; Schmitt et al., 2015), are common in 22q11DS. Neural dysfunction in 22q11DS extends into structural connectivity of the brain, which can be measured using diffusion tensor imaging (DTI). DTI facilitates the *in vivo* study of brain white matter (WM) microstructure (Mori et al., 2008), and typical DTI measures include fractional anisotropy (FA), mean (MD), axial (AD) and radial diffusivity (RD). Alterations in these metrics are reported in 22q11DS (Barnea-Goraly et al., 2003; da Silva Alves et al., 2011; Deng et al., 2015; Kates et al., 2015;

Kikinis et al., 2012; Martin et al., 2014; Ottet et al., 2013; Padula et al., 2015; Radoeva et al., 2012; Scariati et al., 2016; Sundram et al., 2010; Villalon-Reina et al., 2013), and some of the patterns observed are similar to deficits in SZ (Kyriakopoulos et al., 2008; Roalf et al., 2015; Thomason and Thompson, 2011), adolescents with psychosis (Davenport et al., 2010; White et al., 2007) and youth at risk for developing psychosis (Epstein et al., 2013; Lee et al., 2013). In contrast to structural gray matter findings, DTI results in 22q11DS are more inconsistent. The most common findings are lower FA and AD, but several studies report the opposite pattern and indicate conflicting deficits (See Supplemental Table 1). Accordingly, additional large scale studies that compare WM microstructure in 22q11DS to healthy individuals are warranted.

The overlap in brain structural abnormalities between individuals with 22q11DS and schizophrenia has led to intensive examination of the links between brain development, genetic defects and the development of psychotic symptoms (Kates et al., 2015). Patients with 22q11DS who develop schizophrenia have similar symptoms compared to patients with idiopathic schizophrenia (Murphy et al., 1999). Indeed, both 22q11DS and idiopathic schizophrenia share brain morphological changes (Eliez et al., 2001; Eliez et al., 2000; Glahn et al., 2008; Jalbrzikowski et al., 2013; Schaer et al., 2006), including alterations in WM structure and organization (Asami et al., 2014; Epstein et al., 2013; Kyriakopoulos et al., 2008; Lee et al., 2013; Roalf et al., 2013b). Thus, direct comparison of WM differences between 22q11DS patients with and without psychotic symptoms may elucidate deficits specific to psychosis.

The goals of this study were to 1) evaluate WM microstructural abnormalities in a large age, gender and race equivalent sample of participants with 22q11DS and healthy controls (HC) and 2) compare diffusion metrics in 22q11DS with and without psychotic symptoms. We hypothesized that: A) participants with 22q11DS will have lower FA and lower AD compared to HC throughout brain white matter; and B) 22q11DS participants with psychotic or prodromal symptoms will show lower FA and AD in white matter as compared to 22q11DS participants without psychotic-like symptoms.

2.0 Methods and Materials

2.1 Subjects

Individuals with 22q11DS (n=54; Table 1) were recruited for a prospective study *Brain-Behavior and Genetics Studies of the 22q11DS* at the University of Pennsylvania and Children's Hospital of Philadelphia (CHOP). This sample overlaps with a previous report of abnormal brain structure in 22q11DS (Schmitt et al., 2014). Briefly, inclusion criteria included age ≥ 8 years, proficient in English, estimated IQ >70 by available records and the Wide Range Achievement Test IV (Wilkinson, 1993), and medically stable. 22q11DS participants were between 13–30 years of age. Exclusion criteria included pervasive developmental disorder or IQ < 70 , medical disorders that may affect brain function (e.g., uncontrolled seizures, head trauma, CNS tumor and infection) or visual deficits (e.g., blindness). Deletion status was confirmed using multiplex ligation dependent probe amplification (Jalali et al., 2008). The University of Pennsylvania and the CHOP

Institutional Review Boards approved all study procedures. Informed consent/assent was obtained from minors and accompanying parent at the time of initial evaluation.

Psychopathology was assessed using the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS)(Kaufman et al., 1997), Structured Interview for Prodromal Syndromes (SIPS)(Miller et al., 2003), and the psychotic and mood diagnoses modules of the Structured Clinical Interview for DSM-IV (Modules C and D)(First and Gibbon, 2004). As in previous reports, positive, negative and disorganized SIPS symptoms were rated on a 7-point scale (0 - “absent,” 1 - “questionably present,” 2 - “mild,” 3 - “moderate,” 4 - “moderately severe,” 5 - “severe but not psychotic,” and 6 - “severe and psychotic”)(Schmitt et al., 2014). Individuals with at least one positive symptom rated 3 or at least two negative and/or disorganized symptoms rated 3 were considered at heightened psychosis risk (e.g. prodromal). Seventeen individuals were considered psychosis-spectrum based upon only the positive symptoms. Ten individuals were considered psychosis-spectrum individuals based upon negative/disorganized symptoms.

Age and gender matched healthy individuals from the follow-up study to the Philadelphia Neurodevelopmental Cohort (PNC; (Gur et al., 2012; Roalf et al., 2016; Satterthwaite et al., 2015) served as a comparison group. Matching was conducted in a similar manner as a previous study (Tang et al., 2016) using an optimizing algorithm (Konsake and Bergstrahl, 2004) in SAS programming language. Variable selected to match included age, gender and then race. Note that all analyses were conducted using a larger sample (n=141) of individuals who returned as part of the PNC; these analyses are presented in the Supplement (See “Diffusion Tensor Imaging Results using 141 healthy comparison participants from the Philadelphia Neurodevelopment Cohort”). HC had no DSM-IV Axis I psychotic disorder, no subthreshold prodromal symptomatology, no history of psychosis in a first-degree biological relative, and no personal Axis II Cluster A diagnosis. Participants were excluded for any history of neurological disorder, head trauma with loss of consciousness, lifetime history of substance dependence, substance abuse within the preceding 6 months, any medical condition that might affect brain function or any contraindication for MRI. In addition, the Global Assessment of Functioning (GAF) (Hall, 1995) scale was administered to assess overall daily functioning and the Penn Computerized Neurocognitive Battery(CNB(Gur et al., 2001) examined neurocognitive functioning. CNB performance in 22q11DS has previously been reported(Gur et al., 2014) and here we present overall performance accuracy, speed and variability (Roalf et al., 2013a; Roalf et al., 2014).

2.2 Neuroimaging

Neuroimaging was performed on all participants without contraindications for MRI. A standard protocol was followed to familiarize individuals with MRI scanning procedures. All participants underwent mock scanning prior to MRI scanning. This procedure was completed using a decommissioned GE MRI scanner with similar audio/video projection equipment. The environment mimicked the actual MR environment including the use of earplugs, headphones, and foam padding cushions. MRI scanner noise was simulated, head-motion was monitored and feedback was provided. All MRI scans were acquired on the

same 3T Siemens Tim Trio whole-body scanner, used the same 32-channel head coil and acquisition protocol at the Hospital of the University of Pennsylvania.

2.2.1 Diffusion Weighted Imaging Acquisition—DTI scans were obtained using a twice-refocused spin-echo (TRSE) single-shot EPI sequence (TR=8100 ms, TE =82 ms, FOV = 240mm²/240mm²; Matrix= RL: 128/AP:128/Slices:70, in-plane resolution (x & y) 1.875mm²; slice thickness=2 mm, gap=0; FlipAngle=90°/180°/180°, volumes=71, GRAPPA factor =3, bandwidth = 2170 Hz/pixel, PE direction = AP; 11 minutes) (Roalf et al., 2016; Satterthwaite et al., 2014a). The complete sequence consisted of 64 diffusion-weighted directions with b = 1000 s/mm² and 7 interspersed scans where b = 0 s/mm² (Satterthwaite et al., 2014a). In addition, a B0 field map was acquired and used in the pre-processing (Roalf et al., 2016).

2.2.2 DTI quality control and image processing—DTI quality control (QC), pre- and post-processing are published in detail elsewhere (Roalf et al., 2016) and in the Supplemental Methods. Briefly, images were first checked for data quality using manual and automated methods (Roalf et al., 2016). QC metrics include temporal signal-to-noise (TSNR), mean relative motion, mean and maximum outlier counts.

Following QC, diffusion data were skull stripped by generating a brain mask for each subject by registering a binary mask of a standard image (FMRIB58_FA) to each subject's brain using FLIRT (Smith, 2002). When necessary, manual adjustments were made to this mask. Next, eddy currents and movement were estimated and corrected using FSL's eddy tool (Andersson and Sotiropoulos, 2016; Graham et al., 2016; Roalf et al., 2016). Eddy is an improvement upon the typical eddy/motion correction used as part of FSL's Diffusion Tool Box (Behrens et al., 2003). This tool simultaneously models the effects of diffusion eddy current and head movement on DTI images in order to reduce the amount of resampling and is a vast improvement of the standard FSL eddy correct tool (Andersson and Sotiropoulos, 2016; Graham et al., 2016). Next, the diffusion gradient vectors were rotated to adjust for motion using the 6-parameter motion output generated from eddy. Then, the B0 field map was estimated and distortion correction was applied to the DTI data using FSL's FUGUE (Smith, 2002). Finally, the diffusion tensor was modeled and metrics (FA and MD) were estimated at each voxel using FSL's DTIFIT.

Registration from native space to a template space was completed using DTI-TK (Zhang et al., 2014; Zhang et al., 2006). First, the FA and MD output of DTIFIT was converted to DTI-TK format. Next, template was generated from the tensor volumes using 14 representative diffusion data sets that were considered "Excellent" from the PNC sample. One individual from each of the 14 ages (age range 8–21) was randomly selected. These 14 DTI volumes were averaged together to create an initial template. Next, data from the 14 subjects were registered to this template in an iterative manner. Unlike standard intensity-based registration algorithms, this process utilizes the full tensor information in an attempt to best align the underlying white matter tracts using iterations of rigid, affine and diffeomorphic registration leading to the generation of a successively refined template. Ultimately, one high-resolution refined template was created and used for registration of the remaining diffusion datasets. All DTI maps were then registered (rigid, affine, diffeomorphic) to the high-resolution

study-specific template using DTI-TK. Whole brain analysis was performed using a customized implementation of tract-based spatial statistics (TBSS) (Bach et al., 2014). FA, MD, AD, and RD were compared along a study specific white matter skeleton. Then, standard regions of interest (ROI; ICBM-JHU White Matter Tracts; Harvard-Oxford Atlas) were registered from MNI152 space to the study-specific template using ANTs registration (Avants et al., 2011). Mean diffusion metrics were extracted from these ROIs using FSL the ‘fslmeans’ command.

2.3 Statistical Analysis

Demographic and clinical differences between groups were examined with chi-square and t-tests, which were corrected for unequal variance using the Welch approximation. Prior work has demonstrated that brain development is not a linear process (Giedd et al., 1999), including white matter development (Peters et al., 2014). Thus, group-level analyses of DTI data were flexibly modeled using penalized splines within a general additive model (GAM; (Wood, 2004, 2011). The GAM is a commonly used statistical approach (Satterthwaite et al., 2014b; Satterthwaite et al., 2016) that assesses a penalty for increasing nonlinearity to avoid over-fitting. The GAM was employed for both whole brain analysis in randomise (5000 permutations) using threshold-free cluster estimation (TFCE). Only F-statistics could be generated for the voxelwise GAM. Thus follow-up ROI analyses were completed. All models included factors for sex, race and TSNR (Roalf et al., 2016). A significance threshold of $p < 5.0 \times 10^{-3}$ was used to control for Type-I error probability across both the whole brain TBSS analysis and the analyses of 17 ROIs. All ROI statistics were performed using R (3.1.2) statistical software (R-Core-Team, 2012). The relationships between DTI metrics and clinical measures were examined within each group using Pearson correlations.

3.0 Results

3.1 Participant Characteristics, Clinical and Cognitive Scores

22q11DS and HC were similar in age, gender, race, maternal and paternal education (Table 1). HC had higher education attainment [$t(55.91)=3.75$, $p < 4.10 \times 10^{-4}$]. As expected, 22q11DS participants had higher positive, negative, and disorganized symptoms, and had lower overall functioning assessed by the GAF (Table 1).

3.2 Diffusion Tensor Imaging

3.2.1 Quality Control Metrics—Overall 22q11DS individuals had poorer QC metrics as compared to HC (Figure 1). 22q11DS had lower TSNR [$t(49.23)=6.49$, $p < 3.96 \times 10^{-8}$], higher motion [$t(43.71)=4.23$, $p < 1.16 \times 10^{-4}$], average intensity outliers [$t(42.46)=3.61$, $p < 7.86 \times 10^{-4}$] and maximal intensity outliers [$t(56.26)=3.82$, $p < 3.35 \times 10^{-4}$]. Subsequently, TSNR was included as a factor in subsequent analyses.

3.2.2 Whole brain analysis—Group differences in AD and MD were found in the whole brain TBSS analysis (Figure 2). The groups differed in AD within one cluster centered and the juncture between the CST and SLF. Differences in MD were found in a large cluster including the SLF, Forceps Major, Forceps Minor and ILF. Post-hoc follow-up indicated diffusivity values were lower in 22q11DS as compared to HC. No group differences in FA or

RD reached significance at the voxel level. As the TBSS approach was limited to comparison along only the white matter skeleton, complementary ROI analyses were completed to further probe potential white matter differences since these ROI more thoroughly measure the extent of white matter microstructure.

3.2.3 Region-of-Interest Analysis—Diffusion metrics are displayed in full for each region of interest in Supplemental Table 2 and plots are shown for all regions in Supplemental Figures 1–4.

3.2.3.1 Fractional Anisotropy (FA): 22q11DS participants had lower FA in the CGC ($p < 2.86 \times 10^{-3}$) and CGH ($p < 2.98 \times 10^{-6}$; Figure 3) as compared to HC. Lower TSNR was associated with lower FA in the ATR ($p < 4.41 \times 10^{-4}$) and ILF ($p < 1.44 \times 10^{-3}$). There were no effects of age, sex or race.

3.2.3.2 Mean Diffusivity (MD): 22q11DS participants had lower MD in the ILF ($p < 2.86 \times 10^{-3}$) as compared to HC (Figure 3). Lower TSNR values were associated with higher MD in the ATR ($p < 4.50 \times 10^{-3}$) and IFO ($p < 3.31 \times 10^{-3}$). Higher MD values in the CGH were associated with younger age ($p < 3.90 \times 10^{-3}$). There were no effects sex or race.

3.2.3.3 Axial Diffusivity (AD): Axial diffusivity was lower in 22q11DS in the CGC ($p < 2.34 \times 10^{-4}$), Forceps major ($p < 4.36 \times 10^{-3}$), IFO ($p < 4.08 \times 10^{-5}$), ILF ($p < 1.73 \times 10^{-4}$), and SLF ($p < 7.70 \times 10^{-5}$) as compared to HC (Figure 3). There were no effects of age, sex, race or TSNR.

3.2.3.4 Radial Diffusivity (RD): Radial diffusivity was higher in 22q11DS in the CGH ($p < 8.20 \times 10^{-5}$) as compared to HC. (Figure 3). Lower TSNR was associated with higher RD in the ATR ($p < 1.88 \times 10^{-3}$) and IFO ($p < 4.26 \times 10^{-3}$). There were no effects of age, sex or race.

3.2.3.5 Exploratory analysis of DTI in 22q11DS with psychotic symptoms: We considered, in an exploratory manner, that 22q11DS psychosis spectrum participants ($n=27$; 22q11DS+), who included individuals with a psychotic disorder ($n=4$) and prodromal individuals ($n=23$), may exhibit subtle differences from 22q11DS without psychotic symptoms ($n=12$; 22q11DS-). Thus, we repeated the above analysis on only 22q11DS individuals and, given the exploratory nature, used an uncorrected statistical threshold due to small sample size ($p < 0.05$). The subsamples did not differ in age, education, maternal or paternal education, sex or race distribution. 22q11DS+ had higher positive, $F(1,35)=19.153$, $p < 1.0 \times 10^{-4}$, negative $F(1,35)=24.19$, $p < 2.0 \times 10^{-5}$, and disorganized $F(1,35)=8.16$, $p < 7.0 \times 10^{-3}$ symptoms, and lower GAF $F(1,32)=20.53$, $p < 7.72 \times 10^{-5}$ than 22q11DS-.

Diffusion metrics are displayed in full for each region of interest in Supplemental Table 3. 22q11DS subgroups did not differ on DTI QC metrics (all $p > 0.65$). Whole brain TBSS analysis did not reveal any significant differences. But, exploratory regional analysis indicated that 22q11DS+ had lower mean FA in the CGC ($p=0.02$) and lower mean AD in the UF ($p=0.02$) compared to 22q11DS- (Figure 4). Indeed, 22q11DS- showed similar mean FA within the CGC (0.534 ± 0.028) to HC (0.548 ± 0.035), while 22q11DS+ had lower mean FA than both (0.512 ± 0.032). 22q11DS+ and 22q11DS- did not differ in mean MD or

mean RD in any region. There were no associations with clinical or cognitive symptoms. It should be noted that many investigations of 22q11DS limit criteria of psychosis-spectrum symptoms to individuals with SIPS Positive Symptom Scores > 3. This is based on the notion that negative symptoms in 22q11DS are predominant features of the overall behavioral phenotype associated with the syndrome. The CGC effects remain in the same direction and trends accordingly when only positive symptoms were used (22q11DS- > than 22q11DS+ (p=0.13); See “Exploratory analysis of psychosis spectrum symptoms” in the Supplement for more detail).

4.0 Discussion

Overall, we find aberrant WM microstructure in individuals with 22q11DS compared to age and sex matched healthy individuals. Along the whole brain white matter skeleton we find lower in AD in the ILF and in MD in the SLF, ILF, and the Forceps Major and Minor. Regionally, we report 1) lower FA in the CGC and CGH; 2) lower AD in the CGC, Forceps major, IFO, ILF and SLF; 3) lower MD in the ILF; and 4) higher RD in the CGH in 22q11DS compared to healthy individuals. Intriguingly, our exploratory analysis of 22q11DS with (+) and without (-) psychosis symptoms indicated lower FA in the CGC and lower AD in the UF in 22q11DS+, albeit this result would not have survived statistical correction for multiple comparisons.

Our results confirm and extend previous DTI studies in 22q11DS. Overall, all previous studies report alterations in white matter FA, but the direction of FA effects is inconsistent (See Supplemental Table 1), which may be the result of relatively small sample sizes, heterogeneity of deficits in 22q11DS, or a failure to account for potential data confounds. Here, we include a large sample of individuals with 22q11DS and employ a strategy to mitigate the influence of data quality. Ultimately, we only report significantly *lower* FA within the CGC and CGH, lower MD in the ILF, and lower AD within the CGC, Forceps major, IFO, ILF, and SLF, while also finding *higher* RD in the CGH in 22q11DS. Similar results—specifically alterations in portions of the cingulum bundle (Jalbrzikowski et al., 2014; Kates et al., 2015; Kikinis et al., 2012), IFO (Kikinis et al., 2012), ILF (Kikinis et al., 2012) and SLF (Kikinis et al., 2012) have been reported in 22q11DS. Lower FA within the cingulum bundle (Kelly et al., 2017; Roalf et al., 2013b) and SLF aligns with patterns of disruption seen in schizophrenia, including in the recent results from the ENIGMA-DTI consortium (Kelly et al., 2017). Below, we expand upon several of the specific findings and their relevance for 22q11DS.

White matter alterations in the cingulum bundle are commonly reported in 22q11DS (Jalbrzikowski et al., 2013; Kates et al., 2015; Simon et al., 2005). In addition, the cingulum bundle has been intensely studied in schizophrenia due to its role in emotion processing and executive functioning, and has received recent attention in 22q11DS (Kates et al., 2015). Here, we found lower FA and AD in the cingulate gyrus of the cortex (CGC), and lower FA and complementary higher RD in the cingulum bundle proximal to the hippocampus (CGH). Lower FA and AD in the CGC aligns with a recent study of 47 22q11DS participants (Kates et al., 2015). The cingulum bundle is a major fiber tract that connects limbic and cortical brain regions, has connections with several regions including the thalamus, amygdala,

hippocampus, and dorsolateral and dorsomedial prefrontal cortex (Croxson et al., 2005; Di Rosa et al., 2008; Goldman-Rakic et al., 1984), and is critical for memory and executive functioning—two abilities disrupted in 22q11DS (Gur et al., 2014). Disruption within the cingulum white matter, a midline structure, correlates with anatomic imaging and connectomic data (Vaáša et al., 2016) that localize many 22q11DS deficits to the midline. Moreover, our exploratory comparisons of 22q11DS with (+) and without (–) psychosis symptoms indicated lower FA in the CGC. While this difference was small and would not have survived stringent multiple comparison correction, it suggests that this disruption may be associated with features associated with psychosis. Lower FA of the cingulum bundle in psychosis is linked to lower attention, poorer executive function (Nestor et al., 2007) and greater inconsistency in neurocognitive performance (Roalf et al., 2013b). In addition, the cingulum bundle is associated with conflict monitoring (Bush et al., 2002), providing feedback to guide prospective decisions (Carter et al., 2001), and is important for other neurocognitive tasks (Carter et al., 2001; Peters et al., 2012). These results further suggest disorganization of critical axons that connect the anterior cingulate with the limbic and motor cortices (Nestor et al., 2008; Nestor et al., 2007; Roalf et al., 2015; Roalf et al., 2013b; Takei et al., 2009) in 22q11DS and, moreover, that this deficit may be related to psychosis.

We also found significantly lower AD in several long-range white matter tracts in 22q11DS. Lower AD in the IFO, ILF, and SLF corroborate several recent reports (Bakker et al., 2016; Kates et al., 2015; Kikinis et al., 2012; Villalon-Reina et al., 2013) and suggest that specific aspects (e.g. myelination or axonal diameter) of the white matter microstructure may be disrupted. Importantly, these large association white matter fibers connect rostral and caudal brain regions. For example, the SLF connects aspects of the parietal lobe with frontal cortex, including the DLPFC. As such, disruption of the SLF is associated with poorer working memory, an ability often affected in 22q11DS (Bava et al., 2011; Montojo et al., 2014). Moreover, one previous study found lower AD in 22q11DS (Kikinis et al., 2012), but no associations with cognition were reported. The IFO, another region with significantly lower AD in 22q11DS, forms the main connection between the fusiform and lingual gyri and the prefrontal cortex (Martino et al., 2010). Disruption of the right IFO is associated with deficits in semantic processing (Duffau et al., 2005) and recognition of facial expressions, including emotional content (Philippi et al., 2009; Thomas et al., 2008). Finally, it appears that lower AD is a more common finding in 22q11DS than in schizophrenia (Kikinis et al., 2012) and it was the most common finding in the current study. Importantly, our diffusivity results in 22q11DS align with the results of a recent direct comparison of 22q11DS and ultra high risk psychosis (UHR) patients (Bakker et al., 2016). In this study, the most pronounced alterations were found in AD, but in different directions for 22q11DS (lower) and UHR (higher). While it is tempting to speculate that lower AD is specifically associated with changes in axonal diameter in 22q11DS, it is incomplete information and mapping the outcome of complex diffusion analyses onto specific microstructural features is extremely difficult, if not impossible (Wheeler-Kingshott and Cercignani, 2009). Nonetheless, the current findings illuminate significant neuroanatomical deficits in white matter structural connectivity in 22q11DS and in individuals with 22q11DS and psychosis features.

Our exploratory findings in 22q11DS+ individuals suggest that the use of 22q11DS as a model for understanding psychosis is likely useful, but significantly larger samples of 22q11DS+ participants are needed to confirm these findings. Moreover, lower FA and AD and higher radial diffusivity in other white matter regions align with some whole brain findings in 22q11DS (Bakker et al., 2016; Barnea-Goraly et al., 2003; da Silva Alves et al., 2011) and psychosis (Asami et al., 2014; Epstein et al., 2013; Kyriakopoulos et al., 2008; Lee et al., 2013; Roalf et al., 2013b). While it is tempting to draw conclusions as to how white matter alterations in 22q11DS can inform us about structural changes in psychosis, more research is necessary to elucidate the specific features that overlap and those that are distinct to each disorder.

4.1 Limitations

While our study benefitted from a large sample, rigorous attention to data quality, and nonlinear analytics, several limitations should be noted. First, only high functioning 22q11DS participants without a neurological diagnosis and with IQ > 70 were included in the sample and some individuals did not qualify for MRI due to contraindications. This may have precluded the sicker individuals from participating, and as such our results may underestimate white matter deficits in 22q11DS. Notably, high functioning individuals with 22q11DS are anxious and have learning disabilities (Tang et al., 2014). These factors may have increased the rate of questionable data within this sample, which was considerably higher than the exclusion rate in a much larger sample of typically developing youth (~10%) (Roalf et al., 2016) collected on the same scanner, by the same investigators, using the same DTI acquisition protocol. However, procedures were in place to minimize anxiety as much as possible, including the use of a prescribed protocol to familiarize individuals with MRI scanning procedures. Secondly, we employ an uncommon, but powerful statistical approach (GAM) (Wood, 2004, 2011) that did not assume a linear trajectory with age. This approach differs from most analysis of DTI data in 22q11DS, yet we believe that this is a significant strength of the current approach. We do not report the effects of medication in the 22q11DS group. However, previous reports have not consistently shown a relationship between DTI metrics and medications (Kanaan et al., 2009; Kyriakopoulos et al., 2011), but at least one report in 22q11DS suggests a reparative effect (Kates et al., 2015). Finally, discrepancies between our whole brain and ROI approach is not surprising given that when a significant cluster is quite large and spans multiple anatomical regions, it is difficult to make inferences about a specific anatomical region with confidence, as one can only infer that there is significant signal somewhere within the expansive cluster. While TFCE is more robust to this issue than other cluster based approaches, it still suffers from low spatial specificity when clusters are large (Woo et al., 2014). Hence, ROI based analyses aid in the regional interpretation of potential differences based upon group.

Finally, we offer a note of caution regarding data quality. Our results provide a specific example of the confounding effects of poor data quality on DTI analysis. While not the focus of the current study, it should be noted that data quality is an important factor to consider when comparing individuals with and without 22q11DS. We reported lower overall data quality in 22q11DS, as measured by TSNR, head motion, and image intensity outliers. As a result, we included TSNR as a covariate in all regional analyses. Nonetheless, lower

TSNR was associated with significant differences in FA and diffusivity metrics. These issues are certainly not specific to 22q11DS, but indicate a systemic problem in the use of DTI in clinical populations. Importantly, *not all group differences could be explained by data quality issues*, and as such real differences in white matter are likely a true reflection of aberrant neuronal processes in 22q11DS.

In conclusion, we find individuals with 22q11DS to have consistent alterations in white matter microstructure, some of which are specifically relevant for psychosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- WM microstructure in individuals with 22q11DS is aberrant compared to age and sex matched healthy individuals.
- The general pattern of DTI dysfunction was lower FA, MD, and AD, while also finding higher RD in 22q11DS
- White matter microstructure within the cingulum bundle was lower in 22q11DS with psychosis symptoms

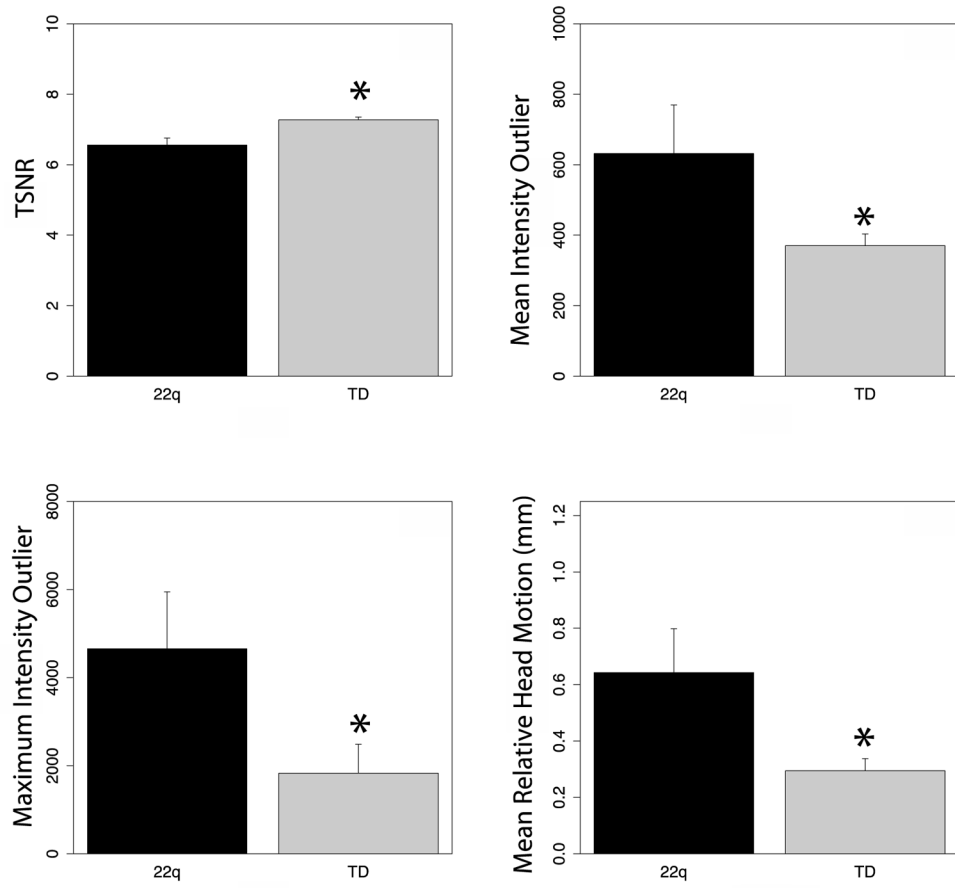


Figure 1. Diffusion Tensor Imaging data quality

Data quality was lower in 22q11DS than healthy comparison participants. Hence, data quality (TSNR) was included in statistical analysis of group differences in diffusion metrics. * $p < 0.05$.

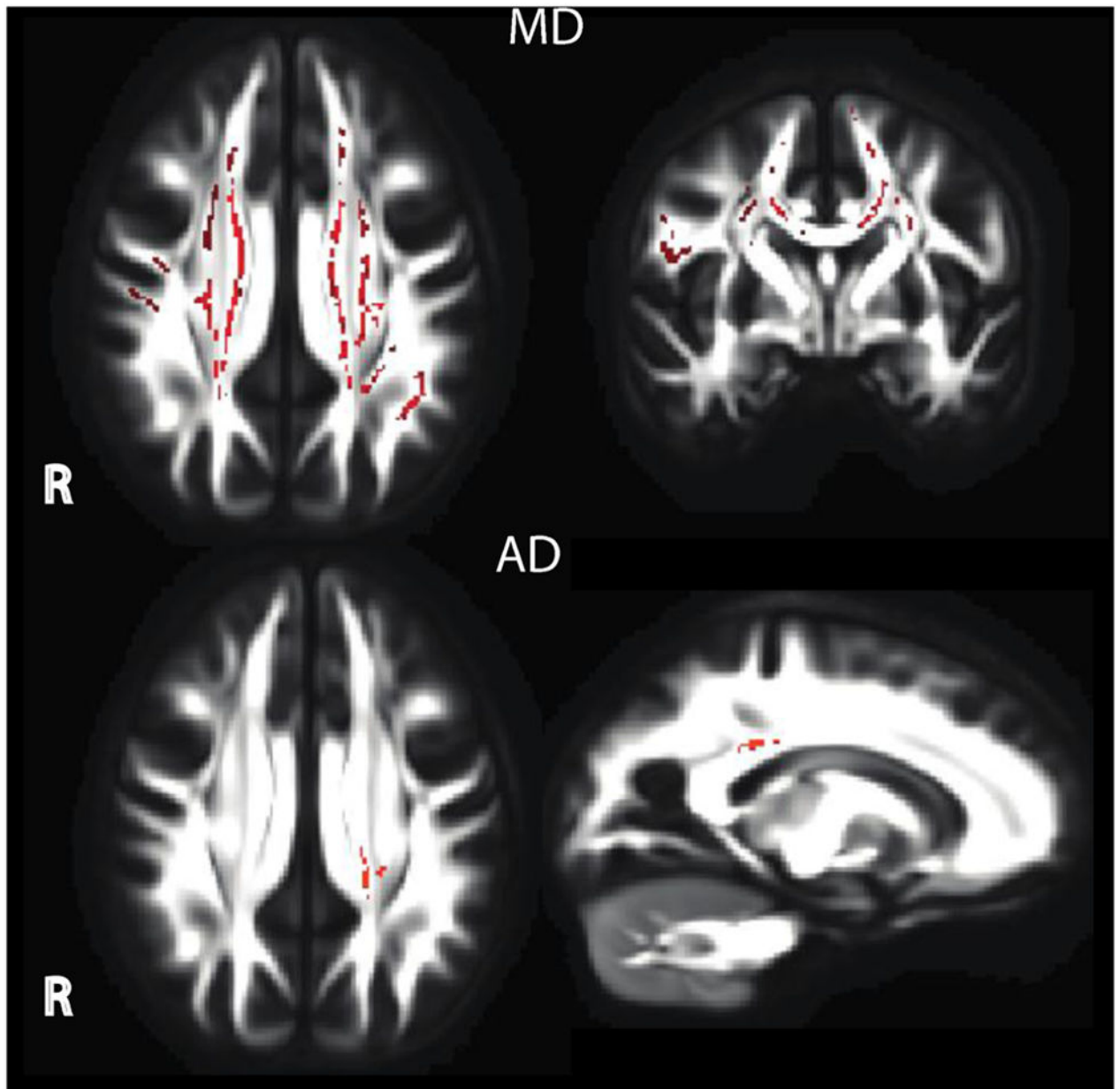


Figure 2.

Whole brain comparison using tract-based spatial statistics. Healthy comparison differed from 22q11DS in both whole brain MD and AD. Lower AD was found in one cluster centered near the SLF and CST. Lower MD in 22q11DS was found in a large cluster including the SLF, Forceps Major, Forceps Minor and ILF.

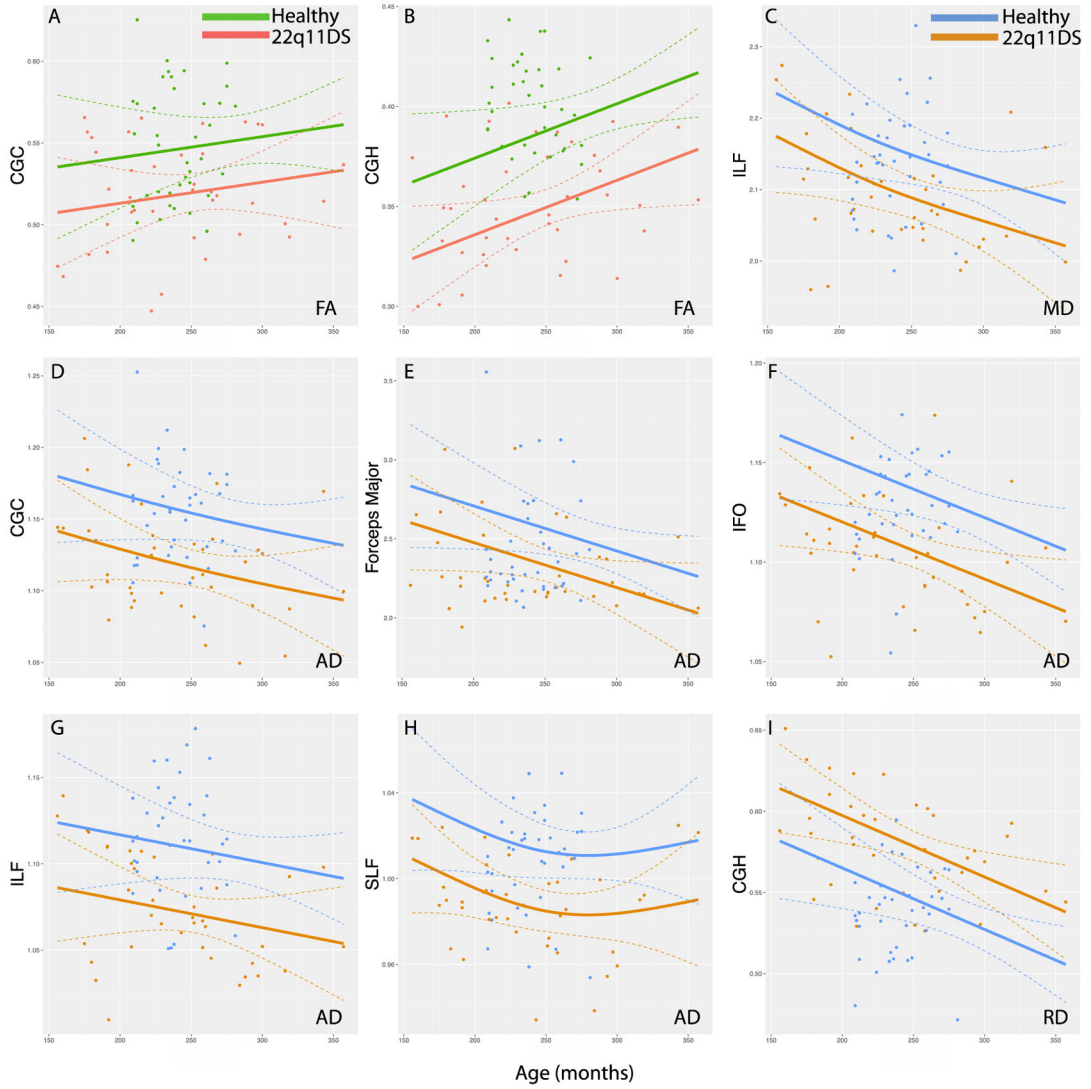


Figure 3. Significant differences in mean FA, MD, AD and RD between 22q11DS and healthy comparison participants are displayed across the age spectrum (in months). Linear and non-linear associations with age were analyzed using a general additive model. Significant group mean FA differences across age are displayed in A–B; significant group mean MD results in C; significant group mean AD results in D–H; and significant group mean RD results in I. All analyses are corrected for temporal signal-to-noise ratio. Significance threshold was $p < 5.0 \times 10^{-3}$. Complete display of all ROI plots are available in the Supplement. (Color)

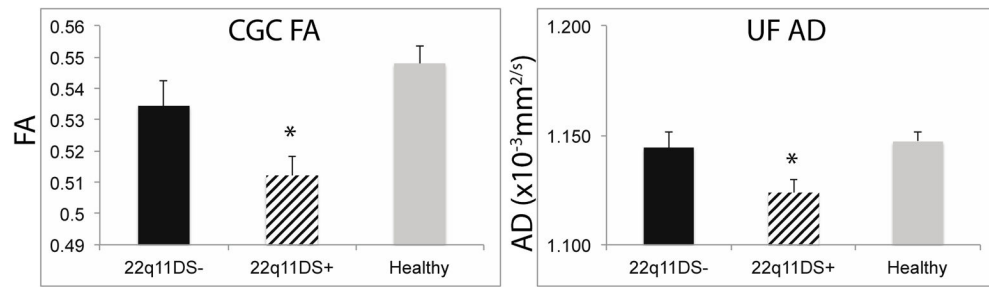


Figure 4.

Exploratory analyses between 22q11DS+ and 22q11DS-. 22q11DS+ had lower FA in the CGC and lower AD in the UF as compared to 22q11DS-. Healthy comparison participants are shown for comparison. Mean \pm SEM are reported. * $p < 0.05$.

Table 1

Sample demographics, clinical and cognitive measures for Healthy Comparison (HC) and 22q11DS. This information is also shown for 22q11DS with (+) and without (–) psychosis symptoms

	Full Sample		22q11DS subsamples	
	HC (n=39)	22q11DS (n=39)	22q11DS+ (n=27)	22q11DS– (n=12)
Sex, n				
Male	20	20	15	5
Female	19	19	12	7
Race, n				
Non-Caucasian	6	6	6	0
Caucasian	33	33	21	12
Age (years)	19.99 (1.73)	19.83 (4.25)	19.25 (4.50)	21.17 (3.42)
Education (years)	13.05* (1.59)	11.05 (2.84)	10.50 (2.92)	12.36 (2.20)
Maternal Education (years)	14.30 (3.83)	14.65* (2.13)	14.42 (2.12)	14.09 (2.18)
Paternal Education (years)	14.43 (2.57)	14.02 (2.30)	14.00 (2.50)	14.09 (1.87)
Global Functioning (GAF)	85.79* (7.24)	60.44 (17.13)	53.92 (15.08)	77.40 (8.22)
Medication APS/ADS/Stim/Other	-	3/13/6/6	2/13/2/2	1/0/4/4
Clinical Aymptoms				
SIPS Positive	1.12* (2.00)	7.87 (6.19)	10.25 (5.82)	2.50 (2.57)
SIPS Negative	1.07* (1.89)	10.53 (8.25)	13.92 (7.62)	2.91 (2.53)
SIPS Disorganized	0.31* (0.61)	5.43 (5.78)	7.04 (6.21)	1.83 (1.95)
Cognitive Performance				
Accuracy (z-score)	0.52* (0.44)	-1.28 (0.66)	-1.28 (0.68)	-1.27 (0.65)
Speed (z-score)	0.35* (0.37)	-0.22 (0.74)	-0.27 (0.78)	-0.09 (0.63)
Accuracy Variability	0.67* (0.18)	1.08 (0.32)	1.17 (0.32)	0.90 (0.26)
Speed Variability	0.71* (0.47)	1.09 (0.63)	1.14 (0.69)	0.91 (0.40)

APS= Antipsychotic medication; ADS= Antidepressant medication; Stim=Stimulant; Other = Other CNS medication. Cognitive scores are global indices of performance across all tasks.

* denotes $p < 0.05$ between groups.

Table 2**ICBM-JHU White Matter Tracts**

Abbreviations for regions used in DTI analysis.

Abbreviation	Region-of-Interest
ATR	Anterior Thalamic Radiation
CST	Corticospinal Tract
CGC	Cingulate Gyrus-Cingulum Bundle
CGH	Cingulate Gyrus proximal to the Hippocampus
Forceps Major	Forceps Major
Forceps Minor	Forceps Minor
IFO	Inferior Fronto-Occipital Fasciculus
ILF	Inferior Longitudinal Fasciculus
SLF	Superior Longitudinal Fasciculus
UF	Uncinate Fasciculus

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