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White matter microstructural abnormalities of the cingulum bundle in youths with 22q11.2 deletion syndrome: Associations with medication, neuropsychological function, and prodromal symptoms of psychosis

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ABSTRACT

Background: The 22q11.2 deletion syndrome (22q11.2DS) is regarded as an etiologically homogenous model for understanding neuroanatomic disruptions associated with a high risk for schizophrenia. This study utilized diffusion tensor imaging (DTI) to analyze white matter microstructure in individuals with 22q11.2DS. We focused on the cingulum bundle (CB), previously shown to be disrupted in patients with schizophrenia and associated with symptoms of psychosis.

Methods: White matter microstructure was assessed in the anterior, superior, and posterior CB using the tractography algorithm in DTIStudio. Neuropsychological function, presence of prodromal symptoms of psychosis, and medication history were assessed in all participants.

Results: Relative to controls, young adults with 22q11.2DS showed alterations in most DTI metrics of the CB. Alterations were associated with positive prodromal symptoms of psychosis. However, when individuals with 22q11.2DS were divided by usage of antipsychotics/mood stabilizers, the medicated and non-medicated groups differed significantly in axial diffusivity of the anterior CB and in fractional anisotropy of the superior CB. DTI metrics did not differ between the medicated group and the control group.

Conclusions: Results suggest that the microstructure of the CB is altered in individuals with 22q11.2DS, and that those alterations may underlie positive prodromal symptoms of psychosis. Our findings further provide preliminary evidence that antipsychotic/mood stabilizer usage may have a reparative effect on white matter microstructure in prodromal 22q11.2DS, independent of the potential effects of psychosis. Future studies of white matter pathology in individuals with 22q11.2DS should test for potential effects of medication on white matter microstructure.

1. Introduction

Chromosome 22q11.2 deletion syndrome (22q11.2DS; also known as velo-cardio-facial syndrome or DiGeorge syndrome) is a genetic neurodevelopmental disorder that occurs from an interstitial deletion of 40–50 genes on the long arm of chromosome 22. Individuals with 22q11.2DS often experience cardiac and craniofacial anomalies, as well as learning difficulties and emotional dysregulation (Swillen et al., 1997; Simon et al., 2002). Additionally, at least 25% of individuals with this syndrome go on to develop psychotic disorders, including schizophrenia, in young adulthood (Murphy et al., 1999), making 22q11.2DS the most common genetic basis for schizophrenia next to having two parents or a monozygotic twin with the disorder. Given the significant findings related to schizophrenia in 22q11.2DS, researchers have been exploring the links between the genetic defect, brain development, and the development of psychotic symptoms.

Early studies typically focused on gray matter changes, and most reported an overall significant reduction in total brain tissue and gray matter volumes in individuals with 22q11.2DS (Campbell et al., 2006;

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Dufour et al., 2008; Gothelf et al., 2011). Studies have also demonstrated white matter abnormalities, particularly volumetric deficits, in children (Kates et al., 2001; Campbell et al., 2006), adolescents (Baker et al., 2011), and adults (vanAmelsvoort et al., 2001; da Silva Alves et al., 2011) with 22q11.2DS. A meta-analysis by Tan et al. (2009) concluded that 22q11.2DS is associated with global brain volumetric reduction affecting both gray and white matter, with specific cortical volumetric white matter reductions in temporal, parietal, and occipital lobe areas. Longitudinal studies have demonstrated that these volumetric white matter reductions persist into young adulthood (Gothelf et al., 2007, 2011).

Researchers have more recently begun to use diffusion tensor imaging (DTI) to examine white matter microstructure in individuals with 22q11.2DS. DTI allows us to probe the underlying microstructure of white matter anatomy by measuring the magnitude and direction of water diffusion in brain tissue in three dimensions. DTI provides several scalar parameters from which differences can be detected. The most commonly used parameter is fractional anisotropy (FA), which measures the extent to which diffusion is directionally restricted. The FA level usually decreases in damaged white matter, but it remains unknown what type of damage has occurred (e.g., axon loss/membrane breakdown, demyelination, or gliosis/inflammation). Accordingly, other parameters obtained through DTI include radial diffusivity (RD), thought to be associated with the modulation of myelin in white matter, and axial diffusivity (AD), purportedly associated with axonal loss or disorganization (Song et al., 2002; Budde et al., 2009).

DTI studies in 22q11.2DS have shown abnormal white matter connectivity among individuals with 22q11.2DS, including reduced fractional anisotropy (FA) in interhemispheric connections, increased FA in frontal and parietal connections, and reduced FA in anterior–posterior projecting tracts (see Dennis and Thompson, 2013 for a review; Ottet et al., 2013). More specifically, Barnea-Goraly et al. (2003) reported decreased FA values in fronto-frontal and fronto-temporal tracts in individuals with 22q11.2DS. These areas also show aberrant connectivity in individuals with schizophrenia. Other significant DTI findings in 22q11.2DS include abnormalities within fibers of the visual ventral stream and a significant correlation between FA values in left parietal areas and arithmetic subtest scores (Barnea-Goraly et al., 2005; Kikinis et al., 2013). In addition, children with 22q11.2DS have higher parietal FA values that are related to poorer performance on an attentional counting task, thereby suggesting a different developmental trajectory related to disruption in parietal connectivity via the superior longitudinal fasciculus (SLF; Simon et al., 2008). Moreover, in an atlas-based study from our group, Radoeva et al. (2012) found significantly lower axial diffusivity (AD) in individuals with 22q11.2DS, including tracts terminating in parieto-occipital (posterior corona radiata), fronto-parietal/occipital (inferior frontal occipital fasciculus [ILF], SLF), fronto-temporal, cingulum bundle (CB) and cerebellar areas, suggesting a widely distributed set of disrupted tracts in 22q11.2DS. Finally, Villalon-Reina et al. (2013) studied white matter tractography in 22q11.2DS, Turner Syndrome, and Fragile X Syndrome. Girls with 22q11.2DS showed more inferior longitudinal fasciculus (ILF) involvement in the right hemisphere, in more fronto-parietal areas, as opposed to the more temporo-parietal involvement seen in Turner Syndrome (Villalon-Reina et al., 2013). These findings provide a potential neuroanatomical background for the previously reported neuropsychological impairments in visuospatial ability, mathematics, and attention among children with 22q11.2DS (Swillen et al., 1997; Barnea-Goraly et al., 2005; Antshel et al., 2006).

Researchers have also investigated possible links between white matter tract integrity and psychiatric symptoms in 22q11.2DS. Sundram et al. (2010) reported a significant correlation between high schizotypy scores and decreased white matter FA in the right posterior limb of the internal capsule, and concluded that the microstructural abnormalities seen in individuals with 22q11.2DS may partially explain their schizotypic behaviors. Most recently, Perlstein et al. (2014) reported alterations in the anterior limb of the internal capsule (ALIC), fornix, and uncinate, and also observed associations between DTI metrics in ALIC and positive prodromal symptoms as measured by the Structured Interview for Prodromal Symptoms.

These studies, taken together, demonstrate the importance of studying white matter tract differences in helping to understand various neuropsychological and psychiatric impairments in individuals with 22q11.2DS. Although some studies speculate about the underlying nature of the white matter tract integrity differences (i.e., axonal loss, myelination, or inflammation; Kikinis et al., 2012; Radoeva et al., 2012), the use of FA in most studies leaves the exact cause of the differences unknown. In addition, most studies have included small sample sizes, and do not control for the potential effects of medication. Although results of DTI studies have not consistently shown a relationship between white matter volumes and medication (Kanaan et al., 2009; Kyriakopoulos et al., 2011), MRI research has demonstrated that antipsychotic medications – particularly atypical antipsychotics – may have a promyelinative effect. Specifically, their use has been associated with increased frontal white matter volume and intracortical myelin in individuals with schizophrenia (Bartzokis et al., 2007, 2009). Accordingly, studies that incorporate potential effects of medications on white matter volumes and microstructure are warranted.

To date, few studies have examined the volume or white matter microstructure of the cingulate in individuals with 22q11.2DS. A volumetric study demonstrated bilateral volumetric reductions in cingulate gyrus cortical volume gray matter in 22q11.2DS compared to controls (Dufour et al., 2008). Furthermore, the authors observed a significant reduction in right cingulate gray matter volume in a low-performing executive functioning group (Dufour et al., 2008). As noted above, we have recently used a whole brain, atlas-based method to investigate white matter microstructure, and found that the anterior cingulum bundle (CB) (among other tracts) showed reductions in axial diffusivity (Radoeva et al., 2012). In a whole-brain voxel-based study of white matter, Simon et al. (2005) reported increased FA in a cluster of voxels that encompassed the anterior to posterior cingulate and splenium of the corpus callosum. Accordingly, studies that focus specifically on the white matter microstructure of the CB in 22q11.2DS are warranted, particularly since the cingulate is known to be disrupted in schizophrenia as well as associated with psychotic symptoms of the disorder (Walterfang et al., 2011; see Samartzis et al., 2014 for a review).

The cingulate has been a region of interest for neuroimaging studies of schizophrenia spectrum disorders due to its role in the processing of emotional stimuli, expression of emotion, mood regulation, and executive functioning, all of which are among the areas of impairment associated with the disorder (see Baiano et al., 2007; Williamson and Allman, 2012 for reviews). DTI studies of individuals with schizophrenia have demonstrated decreased FA and increased diffusivity within the prefrontal and temporal lobes, as well as abnormalities within fiber bundles connecting those regions, including the CB bundle (CB; Kubicki et al., 2007; Walterfang et al., 2011). More specifically, studies have shown a smaller mean area of and lower mean FA in the CB among individuals with schizophrenia (Kubicki et al., 2003), particularly the right anterior CB (Yan et al., 2012). Bilaterally decreased FA of both the dorsal and pregenual regions of the CB has also been reported, as well as a significantly higher mean diffusivity (MD) in the bilateral dorsal area of the CB in individuals with schizophrenia (Takei et al., 2009). Associations between DTI scalars and executive function (Kubicki et al., 2003; Nestor et al., 2004), memory (Nestor et al., 2004) and cognitive control (Takei et al., 2009) in individuals with schizophrenia have also been reported.

Taken together, all of this evidence points to the importance of investigating white matter microstructure of the CB in individuals diagnosed with 22q11.2DS, including potential associations between DTI scalars and medication usage, neuropsychological function and prodromal symptoms of psychosis. Based on the extant literature