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## Toddlers later diagnosed with autism exhibit multiple structural abnormalities in temporal corpus callosum fibers

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## ABSTRACT

Interhemispheric functional connectivity abnormalities are often reported in autism and it is thus not surprising that structural defects of the corpus callosum (CC) are consistently found using both traditional MRI and DTI techniques. Past DTI studies however, have subdivided the CC into 2 or 3 segments without regard for where fibers may project to within the cortex, thus placing limitations on our ability to understand the nature, timing and neurobehavioral impact of early CC abnormalities in autism. Leveraging a unique cohort of 97 toddlers (68 autism; 29 typical) we utilized a novel technique that identified seven CC tracts according to their cortical projections. Results revealed that younger (<2.5 years old), but not older toddlers with autism exhibited abnormally low mean, radial, and axial diffusivity values in the CC tracts connecting the occipital lobes and the temporal lobes. Fractional anisotropy and the cross sectional area of the temporal CC tract were significantly larger in young toddlers with autism. These findings indicate that water diffusion is more restricted and unidirectional in the temporal CC tract of young toddlers who develop autism. Such results may be explained by a potential overabundance of small caliber axons generated by excessive prenatal neural proliferation as proposed by previous genetic, animal model, and postmortem studies of autism. Furthermore, early diffusion measures in the temporal CC tract of the young toddlers were correlated with outcome measures of autism severity at later ages. These findings regarding the potential nature, timing, and location of early CC abnormalities in autism add to accumulating evidence, which suggests that altered inter-hemispheric connectivity, particularly across the temporal lobes, is a hallmark of the disorder.

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## 1. Introduction

A leading hypothesis regarding autism neurophysiology suggests that the disorder is characterized by atypical anatomical and functional connectivity. This hypothesis has been supported by numerous Diffusion Tensor Imaging (DTI) studies that have assessed the microstructure of white matter fibers (Alexander et al., 2007; Ameis & Catani, 2015; Barnea-Goraly et al., 2004; Ben Bashat et al., 2007; Solso et al., 2016; Thomas, Humphreys, Jung, Minshew, & Behrmann, 2011; Travers et al., 2012; Wolff et al., 2012) and by functional magnetic resonance imaging (fMRI) studies that have assessed functional synchronization across brain areas during different tasks (e.g., Just, Cherkassky, Keller, & Minshew, 2004; Müller et al., 2011) as well as during rest or sleep (e.g., Anderson et al., 2011; Di Martino et al., 2014; Dinstein et al., 2011).

Among the different forms of connectivity, inter-hemispheric anatomical and functional connectivity is of particular interest to autism research for several reasons. First, anatomical studies have reported that one or more subregions of the corpus callosum (CC) are smaller in older children, adolescents, and adults with autism (Egaas, Courchesne, & Saitoh, 1995; Frazier & Hardan, 2009; Travers et al., 2015, but also see; Haar, Berman, Behrmann, & Dinstein, 2014). Second, fMRI studies have reported that toddlers, children, adolescents, and adults with autism exhibit decreased inter-hemispheric functional connectivity during rest/sleep in comparison to controls (e.g., Anderson et al., 2011; Di Martino et al., 2014; Dinstein et al., 2011). Third, DTI studies have reported that adolescents and adults with autism exhibit smaller CC volumes, reduced fractional anisotropy (FA) and increased Mean Diffusivity (MD) values in comparison to controls (Alexander et al., 2007; Catani et al., 2016; Thomas et al., 2011). Fourth, up to 45% of children who are born without a CC (agenesis of the CC) exhibit behavioral symptoms that are consistent with a formal autism diagnosis (Lau et al., 2013; Paul, Corsello, Kennedy, Adolphs, 2014). Similarly, BTBR mice, a strain where the corpus callosum is entirely absent (Wahlsten, Metten, & Crabbe, 2003), exhibit several autism-like behaviors (Bolivar, Walters, & Phoenix, 2007) and are a popular animal model for autism research (Blanchard et al., 2012; McFarlane et al., 2008; Silverman, Yang, Lord, & Crawley, 2010). Finally, studies of affect demonstrate that the integrity of the CC is important for higher-order social cognitive tasks (Mike et al., 2013; Symington, Paul, Symington, Ono, & Brown, 2010), a key area of impairment in autism. Taken together, it is tempting to speculate that alterations in inter-hemispheric connectivity may represent an important neural phenotype of at least some individuals who develop autism.

How early and where exactly do interhemispheric connectivity abnormalities emerge? Since autism is a disorder of early neural development (Courchesne, Campbell, & Solso, 2011; Stoner et al., 2014; Willsey et al., 2013), it is particularly important to examine inter-hemispheric connectivity at very young ages when the behavioral symptoms of autism first emerge (Courchesne et al., 2007; Pierce et al., 2011). Only a few DTI studies have done so and all have reported that the CC at young ages in autism exhibits abnormally increased FA values (Ben Bashat et al., 2007; Solso et al., 2016; Travers et al., 2015;

Weinstein et al., 2011; Xiao et al., 2014). This finding stands in sharp contrast to findings in mature children, adolescents and adults where nearly every study has reported *reduced* CC FA values in autism (Alexander et al., 2007; Barnea-Goraly et al., 2004; Jou et al., 2011; Travers et al., 2012; Vogan et al., 2016). Studies have suggested that the FA values transition from abnormally high to abnormally low values very early in development, apparently sometime between the ages of 2 and 4 years (Ben Bashat et al., 2007; Solso et al., 2016; Travers et al., 2015; Weinstein et al., 2011). These findings are in line with the transient early overgrowth hypothesis, which suggests that some infants and toddlers with autism have excess cortical neurons and display early accelerated brain growth followed by later arrested neuronal growth and axonal and synaptic development (Chow et al., 2012; Courchesne et al., 2001; Courchesne, Campbell, et al., 2011; Courchesne, Mouton, et al., 2011).

All of the DTI studies performed to date in toddlers with autism have subdivided the CC roughly into two or three segments without determining the cortical projections of the fibers in each segment. Thus, each segment likely contained a mixture of fibers that projected to multiple cortical areas. A more detailed examination of CC development, which takes into account the projection of CC fibers into specific occipital, parietal, temporal, and frontal areas is, therefore, important for determining which inter-hemispheric connections develop abnormally in autism and for revealing the nature and timing of abnormalities in each fiber group.

In the present study of prospectively identified toddlers with autism, we examined diffusion properties in seven different CC segments that were defined according to the cortical regions that were connected by their corresponding fibers. This allowed us to separate tracts that connected occipital, parietal, temporal, and frontal regions and sub-regions in each participant. We then examined the diffusion properties within a 10 mm mid-sagittal segment of each tract, (i.e., the segment where tracts cross the mid-line) and compared the results across autism and control toddlers who were 1 to 4 years old at the time of MRI scanning. An important advantage of our intentional focus on midsagittal CC segments is that these segments do not contain crossing or kissing fibers (Jeurissen, Leemans, Tournier, Jones, & Sijbers, 2013), which are known to alter diffusion measures (Assaf & Pasternak, 2008; Mori & van Zijl, 2002). This means that potential differences in diffusion measures across groups are more likely to represent true differences in underlying axonal microstructure rather than differences in the number of crossing fibers.

## 2. Materials and methods

### 2.1. Subjects and recruitment

Toddlers were recruited through community referral and a population based screening approach called the 1-Year Well Baby Check-Up Approach (Pierce et al., 2011) at the University of California, San Diego. Ninety-seven toddlers participated in this study: sixty-eight with autism (mean age: 31 months old, range: 13–51 months) and twenty-nine typically developing controls (mean age: 29 months old, range: 13–48). There was no significant group difference in age ( $p > .05$ , two-tailed t-test for

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