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Disrupted fornix integrity in children with chromosome 22q11.2 deletion syndrome

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ABSTRACT

The fornix is the primary subcortical output fiber system of the hippocampal formation. In children with 22q11.2 deletion syndrome (22q11.2DS), hippocampal volume reduction has been commonly reported, but few studies as yet have evaluated the integrity of the fornix. Therefore, we investigated the fornix of 45 school-aged children with 22q11.2DS and 38 matched typically developing (TD) children. Probabilistic diffusion tensor imaging (DTI) tractography was used to reconstruct the body of the fornix in each child's brain native space. Compared with children, significantly lower fractional anisotropy (FA) and higher radial diffusivity (RD) was observed bilaterally in the body of the fornix in children with 22q11.2DS. Irregularities were especially prominent in the posterior aspect of the fornix where it emerges from the hippocampus. Smaller volumes of the hippocampal formations were also found in the 22q11.2DS group. The reduced hippocampal volumes were correlated with lower fornix FA and higher fornix RD in the right hemisphere. Our findings provide neuroanatomical evidence of disrupted hippocampal connectivity in children with 22q11.2DS, which may help to further understand the biological basis of spatial impairments, affective regulation, and other factors related to the ultra-high risk for schizophrenia in this population.

1. Introduction

Chromosome 22q11.2 deletion syndrome (22q11.2DS), also known as DiGeorge syndrome (Kirkpatrick and DiGeorge, 1968) and velocardiofacial syndrome (Shprintzen et al., 1978; Shprintzen, 2008), results from a microdeletion within chromosome 22 at band q11.2 (Carey et al., 1992; Driscoll et al., 1992). The prevalence of the 22q11.2DS in the general population is one in 2000–4000 live births (Botto et al., 2003; Shprintzen, 2008). Youth with 22q11.2DS have increased risk of schizophrenia, with up to 45% displaying the prodrome (Baker and Skuse, 2005; Stoddard et al., 2010) and up to 30% developing psychotic disorders when they reach adulthood (Bassett and Chow, 1999; Murphy et al., 1999; Arnold et al., 2001; Kates et al., 2011). In children with 22q11.2DS, nonverbal cognitive and behavioral impairments, especially in visuospatial processing and memory, have been consistently reported (Moss et al., 1999; Swillen et al., 1999a, 1999b; Wang et al., 2000; Bearden et al., 2001; Simon et al., 2005a, 2005b, 2008a; Bish et al., 2007; Karayiorgou et al., 2010). Brain-imaging studies report consistent neuroanatomical changes in individuals with 22q11.2DS (for review, see Karayiorgou et al., 2010), including structural alterations (Eliez et al., 2000; Kates et al., 2001, 2004; Bish et al., 2004; Shashi et al., 2004; Simon et al., 2005c; Campbell et al., 2006; Machado et al., 2007; Beaton et al., 2010), reduced cortical thickness (Bearden et al., 2007, 2009) and gyral complexity (Schaer et al., 2006, 2009; Srivastava et al., 2011); altered connectivity in major white matter fiber tracts (Simon et al., 2005c; Machado et al., 2007; Sundram et al., 2010; Radoeva et al., 2012), some of which correlate with functional

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impairments (Barnea-Goraly et al., 2003, 2005; Simon et al., 2008b; Radoeva et al., 2012). Notably, many of these brain anomalies are in the midline (Simon et al., 2005c; Campbell et al., 2006; Machado et al., 2007; Beaton et al., 2010), and similar patterns of neural alteration are also reported in people with schizophrenia (for review, see Shenton et al., 2001), though their relationship to the actual psychotic symptomatology remains unclear.

The hippocampal formation plays a critical role in the representation of space and memory, and has been shown to modulate emotional processing (Gray and McNaughton, 2000). In typical developing (TD) children, the volume of the hippocampus appears to be positively associated with verbal and full-scale IQ (Schumann et al., 2007). Impairments in the above cognitive domains, and borderline IQ scores are characteristics of children with 22q11.2DS. Reduced hippocampal volume has been consistently reported in this population (Eliez et al., 2000; Kates et al., 2001, 2004, 2006; Simon et al., 2005c; Campbell et al., 2006; Debbané et al., 2006; Deboer et al., 2007) and was significantly correlated with lower verbal IQ (Deboer et al., 2007). Alterations of the hippocampal formation are considered to be a biomarker for schizophrenia and tend to show a similar pattern of functional relationships to that described above (for review, see Shenton et al., 2001).

Despite the important role that the hippocampus plays in core cognitive, affective and behavioral aspects of the 22q11.2DS phenotype, its connectivity to other brain regions has attracted surprisingly little analytical attention. One key tract to consider is the fornix, a bidirectional fiber tract that connects the hippocampal formation (mainly the subiculum) to the septal nuclei and mammillary bodies in the hypothalamus. It also carries a number of afferent fibers to the hippocampal formation from diverse regions including the septal region, the supramammillary region and the locus coeruleus and raphe nuclei. While not likely its primary function, the fornix has been proposed to be involved in affective function, primarily the regulation of anxiety levels and expression of fear-related behaviors in both rodents and humans (Gray and McNaughton, 2000). If this were to be the case, then it would make this circuit particularly relevant to 22q11.2DS given the high levels of anxiety reported and the recently described relationship between anxiety and adaptive functioning (Green et al., 2009; Angkustsiri et al., 2012). Also of considerable relevance is recent evidence demonstrating the modulating role that anxiety plays in attention and executive functioning (Pérez-Edgar and Fox, 2007; Roy et al., 2008; Bishop, 2009; Krug and Carter, 2010; Pérez-Edgar et al., 2011), which are key components of the schizophrenia endophenotype. Similarly, emotional content significantly impacts memory formation (LeDoux, 2000) and thus can further impact affective dysregulation as in the case of atypical fear extinction and generalization as is common in those with elevated levels of anxiety (Lau et al., 2008; Lissek et al., 2008).

To our knowledge, no detailed study of fornix integrity has ever been reported in children with 22q11.2DS. This may be partly due to the difficulty of registering individual brains to a template that is created by the significant but widely varying midline anomalies that are common in this population (Bish et al., 2004; Antshel et al., 2005; Simon et al., 2005c; Campbell et al., 2006; Machado et al., 2007; Beaton et al., 2010; Karayiorgou et al., 2010). Therefore, in this study, we applied probabilistic diffusion tensor imaging (DTI) tractography to each child's high-resolution DT images in their own native brain space, thereby obviating the complexity of whole brain registration. Our goal was to investigate fornix integrity in children with 22q11.2DS and its relationship with the volume of the hippocampal formation. We hypothesized that fornix fiber integrity is reduced in children with 22q11.2DS, when compared with typically developing children. Moreover, this disrupted fornix integrity would correlate with the volume reductions in the hippocampal formation.

2. Methods

2.1. Participants

Forty-five 7- to 14-year-old children with 22q11.2DS and 38 age-, gender-, and handedness-matched TD children were recruited at the MIND Institute at the University of California, Davis. Children with 22q11.2DS were confirmed by fluorescence in situ hybridization (FISH) testing during recruitment. Their demographics and medication history are summarized in Table 1 and the Supplementary material. The study was approved by the University of California Davis Institutional Review Board. All participants gave written informed assents, and parental consents were also obtained.

2.2. MRI acquisition and preprocessing

Before magnetic resonance imaging (MRI) was performed, all participants underwent acclimation and head motion suppression training in a mock MRI scanner. MRI scans were acquired on a 3 T Siemens Trio MRI System (Siemens Healthcare, Erlangen, Germany) running version VA25A SyngoMR operating software with an eight-channel head coil (Invivo Corporation, Gainesville, FL) at the University of California, Davis Imaging Research Center. For each child, head motion was minimized by placing padding around the head and securing a strap across the forehead. High-resolution T1-weighted images were acquired using a 3D magnetization-prepared rapid gradient echo (MPRAGE) pulse sequence, with the following parameters: 192 sagittal slices; slice thickness = 1 mm, echo time (TE) = 4.82 ms, repetition time (TR) = 2170 ms, flip angle = 7°, field of view (FOV) = 256 mm × 256 mm, matrix size = 256 × 256; receiver bandwidth = 140 Hz/Px; echo spacing = 11.1 ms; voxel size = 1.00 × 1.00 × 1.00 mm^3. DTI data were acquired using the Siemens diffusion-weighted spin-echo echo-planar imaging (EPI) pulse sequence (ep2d_diff) with the following parameters: 40 axial slices; slice thickness = 3.0 mm; slice gap = 0.0 mm; TE = 99 ms; TR = 6700 ms; flip angle = 90°, FOV = 220 mm × 220 mm; matrix size = 128 × 80 based on Partial Phase Fourier = 5/8; Receiver Bandwidth = 1502 Hz/Px; EPI factor = 128; echo spacing = 0.84 ms; voxel size = 1.72 × 1.72 × 3.0 mm^3. Diffusion gradients were applied in 12 directions (specified in the sequence by Siemens) with $b = 1000$ s/mm^2.

All DTI preprocessing steps were conducted using the Stanford open-source VISTASOFT package (http://white.stanford.edu/newlm/index.php/Software) running on MATLAB version 2010a (The Mathworks, Inc., Natick, MA, USA). The details are fully described in other publications (Sherbondy et al., 2008a, 2008b; Yeatman et al., 2011, 2012). Briefly, the steps involve removing eddy current distortions and motion artifacts in the diffusion-weighted images using a 14-parameter constrained nonlinear co-registration procedure based on the expected pattern of eddy-current distortions given the phase-encode direction of the acquired data (Rohde et al., 2004). Each diffusion-weighted image was registered to the non-diffusion-weighted ($b = 0$) images using a two-stage coarse-to-fine approach that maximized the normalized mutual information.

T1 images were skull-stripped and horizontally linearly aligned from the anterior commissure to posterior commissure (referred to as AC − PC aligned). After the linear transformation, the AC − PC aligned brains were resampled to 1-mm isotropic voxels using a 7th-order b-spline algorithm based on code from Statistical Parametric Mapping

Table 1
Participant demographics in typically developing (TD) and 22q11.2DS groups.

	TD ($n = 38$) Mean (S.D.)	22q11.2DS ($n = 45$) Mean (S.D.)	Statistics		
			T	d.f.	*p*-Value
Age (in months)	121.2 (27.5)	130 (22.8)	−1.56	72.05	0.12
Gender (M/F)	19/19	22/23	N/A		0.90
Handedness, right handed, *n* (%)	34 (89.5%)	36 (80%)	N/A		0.51
Verbal IQ	115.3 (13.0)	80.1 (12.8)	11.8	68.4	< 0.001
Performance IQ	115.3 (11.1)	76.5 (13.0)	14.1	73.7	< 0.001
Full Scale IQ	116.2 (10.3)	74.0 (12.4)	16.3	74.1	< 0.001

Note: Welch Two-Sample *t*-test or Chi-squared test.