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Adults with attention-deficit/hyperactivity disorder — A diffusion-tensor imaging study of the corpus callosum

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ABSTRACT

The objective of the present study was to investigate the microstructure and the macrostructure of the corpus callosum (CC) in adults with Attention-Deficit/Hyperactivity Disorder (ADHD) by means of magnetic resonance imaging (MRI). Twenty-nine participants with ADHD and 37 controls were included from the Norwegian ADHD project in Bergen. We measured the fractional anisotropy (FA) values, as well as the size of different subdivisions of the CC, using diffusion tensor imaging (DTI) and anatomical MRI. The isthmus/splenium part of the CC in the ADHD group showed reduced FA values compared to the control group, whereas the size of the CC did not differ across groups. Our findings thus demonstrate a divergence between microstructural and macrostructural measures in the CC of adults with ADHD. This contrasts with findings in children demonstrating callosal abnormalities in both microstructure and macrostructure. Our results may indicate that adults with ADHD in part have succeeded in passing by an earlier developmental delay of the CC, resulting in a normalization of callosal macrostructure into adulthood. However, microstructural differences are still present in adults, which may point to an abnormal lateralization in adults with ADHD, or could be a sign of a persisting impairment.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder with symptoms of inattention, impulsivity, and hyperactivity (American Psychiatric Association, 2000). According to a worldwide estimation, 5.3% of children and adolescents are diagnosed with ADHD (Polanczyk et al., 2007), but great variations in prevalence are reported (Skounti et al., 2007). Approximately 65% of children with ADHD show persistent symptoms and impaired function into adulthood (Faraone et al., 2006), even if the estimates vary (Mannuzza et al., 2003). The maturation of the cerebral cortex is delayed in children with ADHD (Shaw et al., 2006, 2007), but children who improve clinically, show partial normalization of cortical thickness (Shaw et al., 2006). However, the majority of affected children continue to have symptoms into adulthood, leading to functional impairment (Biederman and Faraone, 2005; Biederman et al., 2006). Adults with ADHD may represent a subgroup with neurobiological dysfunctions other than late maturation of the cortex, such as dysregulation of the dopamine system (Staller and Faraone, 2007; Genro et al., 2010), or a hypoglutamatergic prefrontal condition (Carlsson, 2001).

The corpus callosum (CC) is the main commissural white matter bundle interconnecting the two cerebral hemispheres in a dynamic and flexible interaction (Innocenti, 2009). The number of callosal fibers is determined prenatally, but throughout childhood and adolescence the CC area changes due to axonal myelination, redirection, and pruning (LaMantia and Rakic, 1990; Luders et al., 2010; Westerhausen et al., 2011b). The size of the CC increases into the late twenties, along with an age-related decrease of T1 image signal intensities, which may reflect a maturation of the axonal cytoskeleton with a decrease in the microtubular density (Pujol et al., 1993; Keshavan et al., 2002). Transcallosal conduction time seems to increase in larger brains, and this interhemispheric transfer delay may relate to hemispheric specialization (Ringo et al., 1994; Aboitiz and Montiel, 2003). Forebrain volume correlates inversely to the midsagittal size of the CC in both children and adults (Ringo et al., 1994; Jancke et al., 1999), supporting the theory of increased lateralization in larger brains. Lateralization processes may be of importance in the pathophysiology of ADHD (Roessner et al., 2004), and impaired development of the normal cortical

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asymmetry is reported in a longitudinal study of children with ADHD (Shaw et al., 2009).

Two meta-analyses suggest that a reduction of the posterior region including the splenium of the CC (Seidman, 2005; Valera et al., 2007) is one of the most replicated structural neuroimaging findings in the CC in children with ADHD. Subsequent studies have revealed inconsistent results (Luders et al., 2009; Cao et al., 2010; McNally et al., 2010). The results, however, may be difficult to compare because of methodological differences. The only structural magnetic resonance imaging (MRI) study of the CC in adults with ADHD (Rüsch et al., 2007) found a reduction of the region including the isthmus. This study included women with ADHD and a concurrent borderline personality disorder, and it is thus impossible to estimate the impact of ADHD itself.

When exploring the role of the CC in a psychiatric disorder, it is relevant to examine microstructural characteristics besides its macroanatomical features. Diffusion tensor imaging (DTI) is an MRI technique using the properties of water diffusion within white matter tracts to obtain information about the microstructural architecture of these tracts (Mori and van Zijl, 2002; Jones, 2008; Mori et al., 2009). Different diffusion parameters have been developed to characterize the diffusion process and to quantify micro-architectonical properties of the brain white matter. Fractional anisotropy (FA) indicates the directionality of the diffusion process, and can be taken to indicate the alignment and density of axons within a fiber tract. Three DTI studies with focus on the CC in children with ADHD have so far been published. One article found no group differences in FA in the CC (Hamilton et al., 2008), whereas the two others observed reduced FA in the genu (Chao et al., 2009) and isthmus (Cao et al., 2010) in children with ADHD compared with healthy controls. To our knowledge, no studies have earlier studied FA values in the CC of adults with ADHD. The only DTI study of adults with ADHD (Rusch et al., 2010) did not examine FA values, but used measures of tractography, reconstructing the fiber bundles, and reported a decreased number of reconstructed fiber tracts through the anterior region of the CC in adults with ADHD. Moreover, this study included only women, and all participants with ADHD had a comorbid borderline personality disorder, which makes it impossible to draw firm conclusions concerning the impact of microstructural features of the CC in adults with ADHD only.

Few studies have focused on the morphometry of the CC in adults with ADHD, and to our knowledge, no reports exist that combine structural MRI and measures of FA values in adults with ADHD. We thus compared the CC in adults with ADHD with a group of healthy controls using anatomical MRI and DTI. Based on earlier studies of children, we expected a reduction of the CC size in the ADHD group compared with the controls as our first hypothesis. Secondly, because FA may be an expression of fiber density or thickness, reflected by the size of the CC, we expected a reduction of FA values in the ADHD group.

2. Materials and methods

2.1. Participants

Twenty-nine participants with ADHD and 37 controls were selected from the Norwegian ADHD project in Bergen. The recruitment procedure is described in detail in other publications (Johansson et al., 2008; Halleland et al., 2009; Halmoy et al., 2009). The Norwegian ADHD project in Bergen included participants with ADHD diagnosed according to ICD-10 or DSM-IV criteria for hyperkinetic disorder/ADHD by psychiatrists or psychologists, whereas controls were recruited from the database of the Medical Birth Registry of Norway.

An experienced psychiatrist (M.D.) interviewed all participants with the ADHD module of the Kiddie-SADS (Kaufman et al., 1997) adjusted to adults, to verify the diagnoses in our study. The profile of symptoms reported in childhood according to the Kiddie-SADS, determined the ADHD subtypes in participants with ADHD, resulting in 19 subjects with combined type, seven with inattentive type, and three with hyperactive/impulsive type. Current ADHD symptoms were measured with the Adult ADHD Self-Report Scale (ASRS-18) (Kessler et al., 2005). The ASRS-18 consists of two subscales, one measuring inattention, the other hyperactivity and impulsivity.

The ADHD group consisted of 15 men and 14 women with mean age of 32.9 years (SD = 7.1, age range 21–48 years). The control group included 14 men and 23 women with mean age of 30 years (SD = 6.4, age range 21–41 years). The groups did not differ significantly in their gender composition ($\text{Chi}^2 = 1.27$, $\text{dF} = 1$, $p = 0.26$). Participants across the two groups did not differ significantly in their mean age ($t(64) = -1.72$, $p = 0.09$). Participants in the ADHD group, however, were older than the controls on a trend level.

Mean IQ on the Wechsler Abbreviated Scale of Intelligence (WASI) in the ADHD group was 110.6 (SD = 14.3, IQ range 78–128), and in the control group 116.7 (SD = 9.2, IQ range 96–136). Twenty-three participants in the ADHD group were right-handed, and six were left-handed, whereas 32 participants in the control group were right-handed and five were left-handed. Handedness was determined by the hand the subject preferred to draw and write with.

Exclusion criteria were current serious psychiatric disturbance or substance abuse, epilepsy, or other neurological or physical disease that significantly impaired their neurocognitive function. We also excluded participants with a lifetime history of developmental delay, premature birth before 34 weeks of gestational age, or an IQ below 70, as measured by the WASI. Further exclusion criteria for the controls were lifetime history of ADHD, first-degree relatives (parents, children, siblings) with ADHD, or current ADHD symptoms (score > 36 on the ASRS-18, or score > 20 on one of the two ASRS subscales).

We included patients with ADHD that were medication-naïve, as well as those that were medicated, to assure representativeness of the groups. Sixteen patients were medicated with stimulants or atomoxetine. Participants on medication were instructed to withhold their medication 48 h prior to testing. Nine managed to follow this instruction, five reduced the dosage in the last 48 h, and two continued their ordinary medication. Thirteen of the participants with ADHD had not used stimulants or atomoxetine during the past 6 months.

2.2. Magnetic resonance imaging (MRI)

MRI scans were acquired on a 3.0 Tesla GE-Signa system (General Electric Medical Systems, Milwaukee, WI) with an eight-channel headcoil. For all participants T1-weighted images were acquired using a Fast Spoiled Gradient Recall sequence (FSPGR, echo time = 14 ms, repetition time = 400 ms, inversion time = 500 ms) collecting 188 sagittal slices of 1 mm thickness (no interslice gap; scan matrix: 256×256; field of view of 256×256 mm) to achieve a reconstructed voxel size of $1 \times 1 \times 1$ mm. DTI was obtained with a diffusion-weighted imaging sequence based on a single-shot echo-planar imaging sequence (TE = 89 ms, flip angle = 90°). Sensitizing gradients were applied in 30 directions with a weighting factor of b = 1000 s/mm^2 and six (unweighted) b0 images were acquired. The measurement consisted of 45 axial slices of 2.4 mm thickness (no gap, scan matrix: 128×128; field of view of 220×220 mm^2) and reconstructed to voxel size of $1.72 \times 1.72 \times 2.4$ mm.

2.3. Processing of the MRI data

2.3.1. Measurement of the corpus callosum

To measure the cross-sectional area of the total CC, the mid-sagittal slice of the T_1-weighted images was identified and reoriented so that it was located in plane with the longitudinal fissure, using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Second, we obtained a horizontal orientation of the mid-sagittal CC, relative to a line