Manuscript Title:

Associations between Corpus Callosum Size and ADHD Symptoms in Older Adults: The PATH Through Life Study

Short Title:

Corpus Callosum and ADHD Symptoms

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Abstract

Neuroimaging studies of attention-deficit / hyperactivity disorder (ADHD) have revealed deviations of the corpus callosum in children and adolescents. However, little is known about the link between callosal morphology and symptoms of inattention or hyperactivity in adulthood, especially later in life. Here, we investigated in a large population-based sample of 280 adults (150 males, 130 females) in their late sixties and early seventies whether ADHD symptoms correlate with callosal thickness. In addition, we tested for significant sex interactions, which were followed by correlation analyses stratified by sex. Within males, there were significant negative correlations with respect to inattention and hyperactivity in various callosal regions, including the anterior third, anterior and posterior midbody, isthmus, and splenium. A thinner corpus callosum may be associated with fewer fibers or less myelination of fibers. Thus, the observed negative correlations suggest impaired inter-hemispheric communication channels necessary to sustain motor control and attention, which may contribute to symptoms of hyperactivity, impulsivity and/or inattention. Interestingly, within females, callosal thickness was positively related to hyperactivity in a small area within the rostral body, suggesting a sexually dimorphic neurobiology of ADHD symptoms. Altogether, the present results may reflect a lasting relationship between callosal morphology and ADHD symptoms throughout life.

1. Introduction

Converging evidence suggests a neurobiological basis for attention-deficit / hyperactivity disorder (ADHD). While its precise etiology remains unclear, one of the most replicated structural alterations in ADHD is a significantly smaller corpus callosum (Seidman et al., 2005). Meta-analytic findings suggest the callosal splenium (Valera et al., 2007) as well as the forceps minor (van Ewijk et al., 2012) to be particularly affected. However, ADHD-related callosal abnormalities have also been reported for the isthmus (Lyoo et al., 1996), the anterior midbody (Cao et al., 2010), the rostral body (Baumgardner et al., 1996; Giedd et al., 1994), the genu (Hynd et al., 1991), the rostrum (Giedd et al., 1994), as well as the corpus callosum as a whole (Hill et al., 2003). The aforementioned callosal subsections (with exception of the forceps minor, a fiber bundle crossing through the genu) refer to the well-established Witelson scheme (Witelson, 1989), as illustrated in **Figure 1**.

In contrast to an abundance of ADHD studies and callosal findings in children and adolescents (i.e., all of the studies mentioned above were conducted in pediatric samples), little is known about links between callosal morphology and symptoms of inattention or hyperactivity in adulthood. The sparseness of findings with respect to adult ADHD-related variations in callosal morphology (or brain features in general) may be largely due to the fact that ADHD, as we know it today, has only been defined relatively recently (Lange et al., 2010). More specifically, the first characterization of the disorder was added to the DSM-II in 1968, but the actual name was only implemented as “attention deficit disorder: with and without hyperactivity” in 1980 (DSM-III), followed by “attention deficit hyperactivity disorder” in 1987 (DSM-III-R). Still, a few adult studies exist and point to ADHD-related callosal abnormalities later in life: For example, Dramsdahl and colleagues examined 29 individuals with ADHD and 37 controls (mean age of 32.9 years) complementing MRI- and DTI-based measures in a region-of-interest analysis focusing on the corpus callosum. Specifically, they compared fractional

anisotropy (a measure of diffusion directional anisotropy) as well as the size of callosal subdivisions between the two groups. The study revealed a significantly reduced fractional anisotropy within the ADHD group for the isthmus/splenium but no group differences with respect to the size of the callosal subdivisions (Dramsdahl et al., 2012). A couple of years later, Chaim and colleagues examined 22 individuals with ADHD and 19 controls (mean age of 28.8 years and 28.7 years, respectively) using MRI- and DTI-based measures and applying optimally-discriminative voxel-based (ODVB) analyses. Specifically, they compared fractional anisotropy as well as trace (a measure of diffusivity) between the two groups. With respect to the corpus callosum (there were significant effects in other brain regions as well), the study revealed reductions in trace in the ADHD group within the callosal body and splenium (Chaim et al., 2014). Finally, Onnink and colleagues examined 107 individuals with ADHD and 109 controls (mean age of 35.0 years and 36.1 years, respectively) using DTI-based measures and applying tract-based spatial statistics (TBSS). Specifically, they compared fractional anisotropy as well as mean, axial, and radial diffusivity between the two groups. With respect to the corpus callosum (there were also significant effects in other brain regions), the study revealed a significantly lower fractional anisotropy in the ADHD group within the callosal body and splenium as well as a significantly higher mean and radial diffusivity within the callosal body, splenium, and genu (Onnink et al., 2015).

To further expand this understudied field of research, the current MRI-based study was designed to establish the presence and direction of possible links between ADHD symptoms and callosal morphology later in life. For this purpose, we administered the ADHD Self-Report Scale (ASRS), which was developed by the World Health Organization to enable assessment of ADHD symptoms without the necessity of a diagnosis. The ASRS was not only found to have good validity in younger samples with an ADHD diagnosis (Sonnby et al., 2015) but also demonstrated in older cohorts

to reveal significant links between ADHD symptoms and daily functioning as well as mental health, cognition, and brain anatomy (Das et al., 2014a; Das et al., 2012; Das et al., 2014b). Here, we investigated a large sample of 280 adults (mean age of 70.93 years) and applied a well-validated computational approach capturing the thickness of the corpus callosum at 100 equidistant locations across the callosal surface. We hypothesize ADHD symptoms would be negatively associated with callosal thickness. We also tested for significant sex interactions and conducted follow-up analyses stratified by sex (150 males, 130 females) as both the prevalence and the presentation of ADHD appear to differ between the sexes (Davies, 2014). In terms of the specific location of significant correlations, we set out to determine which affected callosal regions, if any, would resemble those revealed when contrasting children with ADHD (mean age of 11.7 years) and their age-matched controls in a previous study using the same callosal approach (Luders et al., 2009). Specifically, we had detected that ADHD was associated with a decreased callosal thickness in regions corresponding to the anterior third (mainly genu and rostral body), isthmus, and splenium (mainly anterior splenial section).

– Figure 1 –

2. Methods

2.1 Subjects

The study sample was drawn from the PATH Through Life Project, a large longitudinal study of mental health and aging, as detailed elsewhere (Anstey et al., 2012). The study was approved by the ethics committees of the Australian National University, Canberra and the University of New South Wales, Sydney, Australia. All participants gave written informed consent to be included in this project. The

present study focuses on the old-age cohort, which included 2,551 individuals aged 60-64 years at the start of the project. A subsample of 2,076 agreed to be contacted regarding MRI assessment, 622 randomly selected participants were offered a brain scan, and 479 completed a structural MRI scan at first assessment (Wen et al., 2009). Of those, 315 participants had a repeat structural MRI scan at the third assessment (wave three), which is the focus of this study (as the ASRS was first administered at wave three). After excluding 35 MRI scans due to movement artifacts, poor scan quality, truncation, neurological disorders and participants who did not complete the ASRS questionnaire, the final sample of the current study consisted of 280 subjects (150 males, 130 females) ranging from 68.6 to 73.8 years of age. This selected sample (n=280) did not differ from the original cohort (n=2,551) or from those only surveyed (but not scanned) at the third assessment (n=1,973) in age, sex, or race. However, they had on average a slightly (about seven months at first assessment and four months at third assessment) but significantly ($p<0.05$) higher level of education.

2.2 ADHD measures

ADHD-related measures were obtaining using the ASRS, a checklist of six questions regarding symptoms of ADHD based on the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (Hesse, 2013; Kessler et al., 2005; Kessler et al., 2007). Each item requires respondents to rate how frequently a particular symptom of ADHD occurred over the past six months on a 5-point scale (from 0 = never to 4 = very often). A summary score (ASRS) with a possible range of 0 to 24 was obtained as an equally weighted sum of response scores for all questions, with higher scores indicating increased risk of ADHD. As previously described (Das et al., 2012), the first four items of the ASRS screener capture inattention-related symptoms, while the remaining two items assess hyperactivity-related symptoms. Thus, in addition to the overall ASRS score, we also calculated an

Inattention Trait (IT) score using the equally weighted sum of the first four items, as well as a Hyperactivity Trait (HT) score using the equally weighted sum of the last two items.

2.3 Image acquisition and data preprocessing

All brain images were acquired on a Siemens 1.5 Tesla Avanto scanner (Siemens Medical Solutions) in sagittal orientation using the following scanning parameters: TR = 1160 ms, TE = 4.17 ms, flip angle = 15°, matrix size = 512 × 512, slice thickness = 1 mm, voxel size = $1 \times 0.5 \times 0.5\ mm^3$. Images were spatially aligned using six parameter (rigid body) transformations, normalized for intensity as well as corrected for B_0 inhomogeneities (Sled et al., 1998) using the MINC imaging toolbox (MINC; http://en.wikibooks.org/wiki/MINC). In addition, the intra-cranial volumes (ICV) were estimated for each subject using FreeSurfer (Fischl, 2012).

2.4 Callosal tracing and callosal thickness measurement

Using the processed images in their native dimensions, the corpus callosum was outlined manually for each subject in the midline section by one rater (D.E.O.), as described previously (Luders et al., 2007). The resulting outlines were carefully checked to ensure that they precisely followed the natural course of the callosal boundaries. Inter-rater reliability was assessed by comparing callosal traces produced by two experienced operators (D.E.O. and N.C.) using the Jaccard index (Real, 1996) . The Jaccard index is defined as the size of the intersection divided by the size of the union of the sample sets and, basically, computes the overlap between two (or more) sets of traces. In this study, the Jaccard index across duplicate traces (n=10) was 0.84 indicating a high inter-rater reliability. Using the callosal traces, highly localized measures of callosal thickness were obtained, as detailed elsewhere (Kurth et al., 2013). Briefly, we first re-sampled the upper and lower callosal boundaries at regular

intervals resulting in 100 equidistant surface points. Subsequently, we automatically created a new segment (midline) by computing the spatial average 2D curve from the 100 equidistant surface points representing the upper and lower callosal boundaries. Finally, we calculated the distances between the 100 surface points of both the upper and the lower callosal boundaries and the midline. These regional distances indicate callosal thickness with a high spatial resolution (i.e., at 100 locations distributed evenly over the callosal surface).

2.5 Statistical analyses

We investigated the Pearson correlations between point-wise callosal thickness and (a) ASRS scores, (b) IT scores, and (c) HT scores, while removing the variance associated with ICV, sex, age, and years of education. In addition to conducting these tests within the whole sample (i.e., males and females combined), we tested for significant sex interactions with follow-up correlation analyses separately within males and females if indicated. Significant partial correlations were coded in color and projected onto the mean callosal surface created from all subjects in this study (n=280). Given that, in older adults, ADHD symptoms were found to be positively associated with depressive symptomatology (Das et al., 2014b), part of the ADHD-related associations might be mediated by depressive symptoms. Thus, additional analyses were conducted to determine whether observed effects persisted after controlling for depression symptoms as measured with the Goldberg depression scale (Goldberg et al., 1988). For all analyses, permutation testing was employed to confirm significance using a two-tailed alpha level of $p \leq 0.05$, as described previously (Luders et al., 2009).

3. Results

Sample-specific descriptive statistics are provided in **Table 1**. Males and females did not differ significantly with respect to health, cognitive, and socio-demographic measures, except for education where females had a slightly lower level. ASRS scores were normally distributed across the whole sample (see **Supplemental Figure 1**).

– Table 1 –

As shown in **Figure 2** (top row), within the whole sample, there were no significant positive or negative correlations with respect to ASRS scores and HT scores. However, there was a trend for a negative correlation for the IT scores ($p_{corr.}$=0.08). More specifically, a thicker corpus callosum was related to a lower inattention measure within the callosal anterior third (at the border between genu and rostrum) as well as within isthmus and splenium (mainly the anterior splenial section). There were significant sex interactions for the ASRS scores ($p_{corr.}$<0.001) as well as for the HT scores (corrected $p_{corr.}$<0.001), but not for the IT scores.

As further shown in **Figure 2** (middle row), follow-up analyses within males revealed significant negative correlations for ASRS scores ($p_{corr.}$<0.001), for HT scores ($p_{corr.}$<0.001), as well as for IT scores ($p_{corr.}$<0.001)[1]. These correlations were located in similar callosal regions as those revealed for the IT scores within the whole sample (i.e., anterior third, isthmus, splenium) with additional effects in the anterior and posterior midbody. There were no significant positive correlations in males. In contrast, follow-up analyses within females revealed no significant negative correlations. Interestingly though,

[1] Although the preceding analysis did not reveal a significant sex interaction for IT, sex-specific exploratory analyses for the IT scores were conducted for completeness.

as shown in **Figure 2** (bottom row), females had a small area within the rostral body, where callosal thickness was positively related to hyperactivity ($p_{corr.}$=0.012).

Last but not least, controlling analyses for depression symptoms within males left the significant ASRS-related correlations essentially unchanged, but slightly decreased the extent and number of clusters pertaining to IT and HT scores, with significant negative correlations remaining within isthmus, splenium, and midbody. In addition, controlling for depression introduced a significant positive correlation between callosal thickness and IT scores within the rostral body (see **Supplemental Figure 2**). No correlations remained significant within females after controlling for depression symptoms.

– Figure 2 –

4. Discussion

In this study, we applied a well-validated approach calculating the thickness of the corpus callosum and correlating it with ADHD symptoms with a high regional specificity. One important aspect of this research is that ADHD symptomatology is not only captured as a summary measure (ASRS scores), but also as two differential measures discriminating between inattentive features (IT scores) and hyperactivity features (HT scores). Importantly, all of these measures have been previously investigated in older adults and found to be associated with cognition, mood, and general functioning (Das et al., 2014a; Das et al., 2014b). Moreover, they were reported to significantly correlate with volumetric measures of several gray matter regions (Das et al., 2014a). The current study expands this line of research by focusing on a white matter region known to be affected in ADHD: the corpus callosum.

4.1 Correspondence with previous research

For the whole sample (on a trend level) as well as in males, we revealed significant negative correlations within the callosal anterior third, isthmus, and splenium (as well as midbody in males). These negative correlations are in agreement with prior studies, albeit conducted in clinically diagnosed children and adolescents with ADHD, that revealed a reduced size of the corpus callosum (Hill et al., 2003) and of callosal subsections, such as the rostral body (Baumgardner et al., 1996; Giedd et al., 1994), anterior midbody (Cao et al., 2010), genu (Hynd et al., 1991), isthmus (Lyoo et al., 1996), and splenium or its anterior vicinity (Hynd et al., 1991; Lyoo et al., 1996; Semrud-Clikeman et al., 1994).

Perhaps even more interesting, we had applied the same callosal thickness approach (Luders et al., 2009) analyzing a pediatric sample consisting of 19 boys with ADHD (mean age ± SD: 11.8 ± 2.7 years) and 19 normally developing children matched for sex and age (mean age ± SD: 11.7 ± 2.6 years). There, significant effects (i.e., thinner corpora callosa in boys with ADHD) were evident in similar regions, such as the anterior third (mainly genu and rostral body), isthmus, and splenium (mainly anterior splenial section), as illustrated in **Figure 3**. In other words, there is a prominent correspondence between those previous findings and our current findings within the whole sample (**Figure 2**, top panel). However, since the previous study included boys only, it seems to be most appropriate to relate them to our current findings within males only (**Figure 2**; middle panel). The spatial correspondence is still striking but, interestingly, there is also an additional region (within the callosal midbody) where ADHD symptoms are negatively correlated with callosal thickness. The question arises whether re-assessing the aforementioned pediatric sample in their late sixties / early

seventies would also reveal this additional region, as it may be due to the sustained effects of ADHD pathology over decades. Unfortunately, such data are currently not available.

Another open question is whether the currently observed correlation profile is truly characteristic of adult ADHD or mainly reflects ADHD symptomatology. Note that none of the adult participants included in our study were diagnosed with ADHD as this requires an ADHD diagnosis in childhood. However, a childhood diagnosis could not have been given to them because ADHD, as we know it today, was only clinically defined at a time when study participants had already reached adulthood (Lange et al., 2010). The few other existing adult studies contrasting actual ADHD groups and controls focused on younger samples (in their mid-thirties) and also obtained different kinds of callosal measures (DTI-based) making it difficult to reasonably compare outcomes across studies. Nevertheless, it seems worth mentioning that, in at least two adult studies, structural alterations within the ADHD group were detected within the "body" of the corpus callosum (Chaim et al., 2014; Onnink et al., 2015).

– Figure 3 –

4.2 Potential etiologies

Callosal abnormalities as often reported in children and adolescents with ADHD are likely to reflect maturational delays. Given the striking correspondence between the current outcomes in an older sample and previous outcomes in a pediatric sample, our study might suggest – at least with respect to the corpus callosum – that such maturational delays do not normalize over time as proposed previously (Rubia, 2007). Instead, our current findings seem to corroborate the hypothesis that (at least some) ADHD-related abnormalities persist with age, as also supported by outcomes from an

earlier longitudinal study following 152 children and adolescents with ADHD and 139 age- and sex-matched controls (Castellanos et al., 2002). Moreover, developmental aberrations might not only persevere but also lead to additional aberrations later in life, perhaps as a secondary consequence of the ADHD symptoms. While the exact nature and origin of these processes is rather unclear, it is possible that the sustained experience of ADHD symptoms leads to intrinsic or extrinsic factors (e.g., stress) deleterious to brain health, which might ultimately manifest as thinner corpora callosa. The observed associations between callosal thickness and ADHD symptoms in older adulthood might also be reflective of age-related neurodegeneration, either alone or in combination with the aforementioned processes. Alternatively, it is possible that the ADHD symptoms themselves, when detected in old age, are the consequence of neurodegenerative processes and as such might not have existed earlier in life. Importantly though, the constructs of hyperactivity and inattention underlying the ASRS used in this study have been found not to differ between middle age and old age, while the ASRS-composite score was even decreasing from middle to old age (Das et al., 2014b). Thus, it does not seem likely that ADHD symptoms and their association with callosal thickness are solely the consequence of age-related neurodegeneration. This is further supported by the aforementioned similarity of the significance profiles indicating ADHD-related links in adults and in children.

Further research is clearly necessary, ideally following individuals with ADHD from (early) childhood into (late) adulthood and possibly extending the focus of research from the corpus callosum to other brain regions. For example, structural ADHD-related abnormalities within the adult brain were reported for numerous other white matter regions underlying the frontal, temporal, parietal, occipital and cingulate cortices as well as for the internal and external capsule, sagittal stratum, fornix, corona radiata, thalamic radiation, and the superior longitudinal, superior lateral and fronto-occipital fascicule (Chaim et al., 2014; Onnink et al., 2015). In addition, there are reports of

gray matter aberrations in adults with ADHD (Chaim et al., 2014; Montes et al., 2013) as well as correlations between gray matter and measures of hyperactivity, inattention, and ADHD severity in adult samples (Das et al., 2014a; Montes et al., 2013).

4.3 Possible functional relevance

Significant negative correlations between callosal thickness and ASRS scores as well as IT scores were most pronounced within the isthmus and anterior splenium, callosal regions suggested to contain fibers projecting to parietal regions (Hofer and Frahm, 2006; Witelson, 1989; Zarei et al., 2006). In addition, we detected significant negative correlations between callosal thickness and ASRS scores (a trend was also detected for IT scores) at the border between genu and rostrum. These findings corroborate other reports of parietal abnormalities (Durston, 2003; Krain and Castellanos, 2006; Montes et al., 2013; Seidman et al., 2005) as well as prefrontal abnormalities in ADHD subjects (Durston, 2003; Krain and Castellanos, 2006; Seidman et al., 2005; Valera et al., 2007). As discussed elsewhere (Luders et al., 2000), a thinner corpus callosum might indicate a smaller number and/or diameter of axons crossing through. Since both the parietal and the frontal cortex are involved in the control and regulation of attention (Corbetta, 1998; Han et al., 2004), the negative correlations within isthmus/splenium and genu/rostrum might point to a decreased interhemispheric connectivity and signal conduction in communication channels necessary to sustain attention (Wong, 2000). Alternatively, they may also suggest that transcallosal inhibition with respect to attentional processes might be compromised if there are fewer or less myelinated fiber tracts, possibly leading to decreased attention as well.

Intriguingly though, when correlating callosal thickness and HT scores (rather than IT scores), the same region within isthmus / splenium became most significant, at least in males. Thus, in

addition to attention, other processes perhaps related to hyperactivity, impulsivity and/or motor regulation might be impacted by callosal reductions. This assumption is further supported by an additional highly significant cluster observed within the posterior / anterior midbody. As these callosal areas have been demonstrated to contain fibers connecting premotor, supplementary motor, and primary motor cortices (Hofer and Frahm, 2006), the negative correlations might reflect an impaired transcallosal inhibition pertaining to motor function. In fact, a defective inhibition of motor programs in ADHD has been suggested previously (Buchmann et al., 2003). It should be noted, however, that ADHD symptoms in adults are associated with a complex behavioural picture which is not completely understood and which does not seem to be exclusively associated with impairment. Indeed, Das and colleagues (Das et al., 2014b) investigated the relationship between ADHD symptoms and cognitive performance in the larger cohort from which the present MRI sub-sample was selected and found that while higher IT scores were associated with lower performance on a digit-symbol substitution task, they were associated with higher performance on a verbal ability task. Moreover, higher HT scores were associated with better task-switching abilities.

4.4 Differential effects in male and female brains

In our main analysis (i.e., without controlling for depression), we observed one single region within females only, where callosal thickness was positively correlated with HT scores. The region was located within the rostral body, thus containing fibers projecting into the prefrontal lobe as well as into premotor and supplementary motor areas (Hofer and Frahm, 2006). The functional relevance and exact underlying mechanism of this observed positive correlation remains to be resolved. Nevertheless, the pronounced sex effect both with respect to the direction of the correlations (negative in males, positive in females) and their specific location on the callosal surface is intriguing

particularly because overall ADHD scores did not differ between males and females. Consequently, the sex differences observed may reflect a differential impact of the condition in males and females rather than different symptom severities.

In terms of comparable data, ADHD studies are usually skewed towards male subjects, where most of the more gender-balanced studies have removed the variance explained by sex (rather than tested for sex interactions). Still, a few ADHD studies have conducted such analyses and revealed significant gender-by-diagnosis interactions as well as different ADHD effects in males and females in various cortical and subcortical regions (Montes et al., 2013; Onnink et al., 2015). With particular respect to the corpus callosum, there seems to be only one study, which explicitly tested for sex interactions but did not find any significant differences between males and females when comparing ADHD patients and healthy controls (Dramsdahl et al., 2012). However, the statistical power might have been too low in that study as only 29 ADHD and 37 control subjects were included (compared to 280 subjects in our study). Moreover, the mean age in that study (early thirties) was relatively young (compared to the late sixties / early seventies in our study). Thus, the current observations indicating sex-specific correlations within the corpus callosum might manifest only later in life, possibly due to a long-term interaction of genetic and acquired differences between male and female brains, especially in (callosal) regions involved in the mediation of ADHD-related processes.

When controlling our analyses for depression symptoms, which have been shown to mediate associations between IT scores and cognitive performance (Das et al., 2014b), the direction and magnitude of callosal correlations were somewhat altered, with attenuated negative correlations pertaining to IT. While this might have been expected (given the aforementioned link between depression and IT), controlling for depression also introduced a positive correlation in males for the IT scores within the rostral body – a location similar to that observed in females for the HT scores, when

not controlling for depression. Interestingly, these positive correlations in females completely disappeared when controlling for depression. These latter findings came as a surprise and are difficult to interpret as, on the one hand, they may indicate mediation of ADHD symptoms by depression but, on the other hand, could also be reflective of limited statistical power. It is intriguing though that controlling for depression seems to unveil even further sex differences in the underlying biology of ADHD that go beyond merely modulating the link between symptom measures and callosal thickness.

Disclosure Statement

There are no actual or potential conflicts of interest.

Acknowledgments

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Figure Legends

Figure 1. Callosal subsections. Visualized are callosal segments according to the Witelson parcellation scheme [Witelson 1989b]. The posterior end of the corpus callosum points to the left; the anterior end points to the right.

Figure 2. Correlations between callosal thickness and ADHD symptoms**.** Shown are the outcomes within the whole sample (top row), within males (middle row), and within females (bottom row) for ADHD Self-Report Scale (ASRS) scores, Inattention Trait (IT) scores, and Hyperactivity Trait (HT) scores. The color bar encodes the uncorrected significance (p). The asterisks mark the significance maps that were confirmed by permutation testing ($p \leq 0.05$). Confirmation on a trend level is indicated by "T" ($p=0.08$) and non-significance is indicated by "n.s" ($p>0.05$).

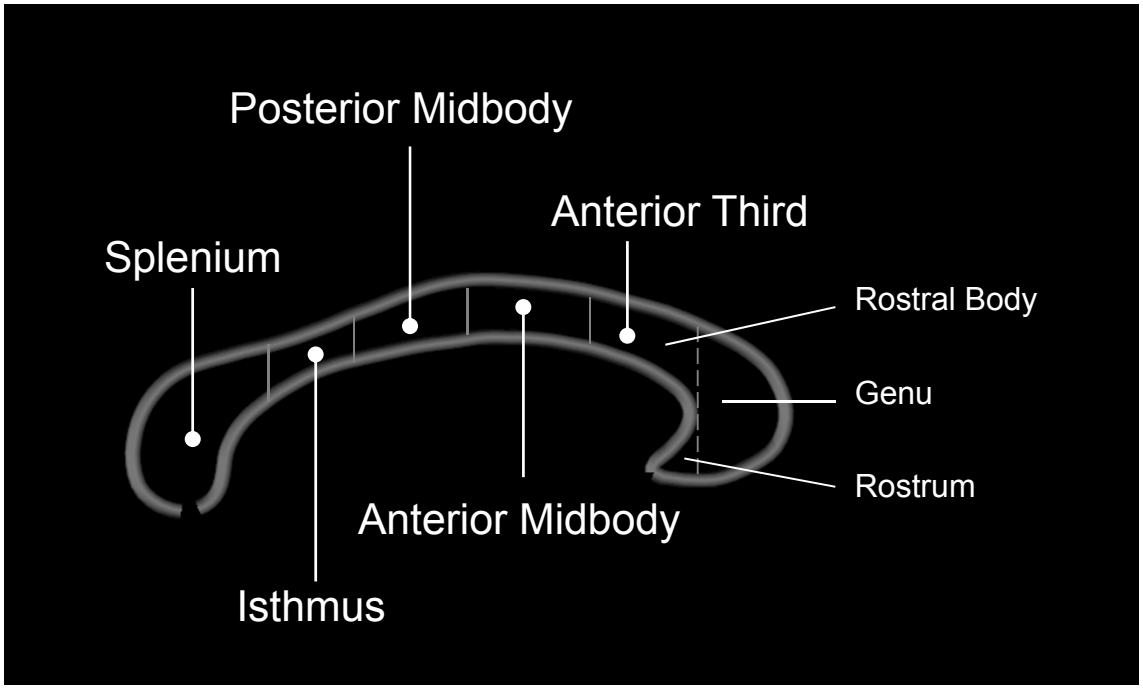
Figure 3. ADHD effects on callosal thickness as revealed in a paediatric sample using the same point-wise measurement. Illustrated are regions of significantly reduced callosal thickness in 19 boys with ADHD (mean age ± SD: 11.8 ± 2.7 years) compared to 19 normally developing boys (mean age ± SD: 11.7 ± 2.6). The color bar encodes the uncorrected significance (p) but outcomes are corrected for multiple comparisons (permutation corrected $p=0.04$). ADHD was associated with a decreased callosal thickness in regions corresponding to the anterior third (mainly genu and rostral body), isthmus, and splenium (mainly anterior splenial section). Original figure adapted with permission from Luders et al., 2009 (Biological Psychiatry. doi: 10.1016/j.biopsych.2008.08.027).

Table

Table 1. Descriptive Statistics

	Whole Sample (n=280)	Males (n=150)	Females (n=130)
Age (mean ± SD)	70.9 ± 1.4 years	70.9 ± 1.4 years	71.0 ± 1.4 years
Education (mean ± SD)	14.3 ± 2.6 years	15.1 ± 2.2 years**	13.4 ± 2.6 years**
MMSE (mean ± SD)	29.34 ± 0.85	29.28 ± 0.90	29.42 ± 0.78
BMI (mean ± SD)	26.46 ± 4.43	26.41 ± 3.47 kg/m^2	26.51 ± 5.33 kg/m^2
Depression (mean ± SD)	1.46 ± 1.82	1.45 ± 1.90	1.48 ± 1.72
Diabetes (n [%])	41 [15%]	24 [16%]	17 [13%]
Hypertension (n [%])	223 [80%]	121 [81%]	102 [79%]
ASRS score (mean ± SD)	6.90 ± 3.18	6.87 ± 3.32	6.94 ± 3.02
IT score (mean ± SD)	4.71 ± 2.27	4.77 ± 2.43	4.63 ± 2.09
HT score (mean ± SD)	2.20 ± 1.66	2.10 ± 1.57	2.31 ± 1.76

MMSE = Mini–Mental State Examination; BMI = Body Mass Index; ASRS = Adult ADHD Self-Report Scale; IT = Inattention Trait; HT = Hyperactivity Trait; **p<0.01 significant sex difference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Splenium
Rostral Body
Genu
Rostrum
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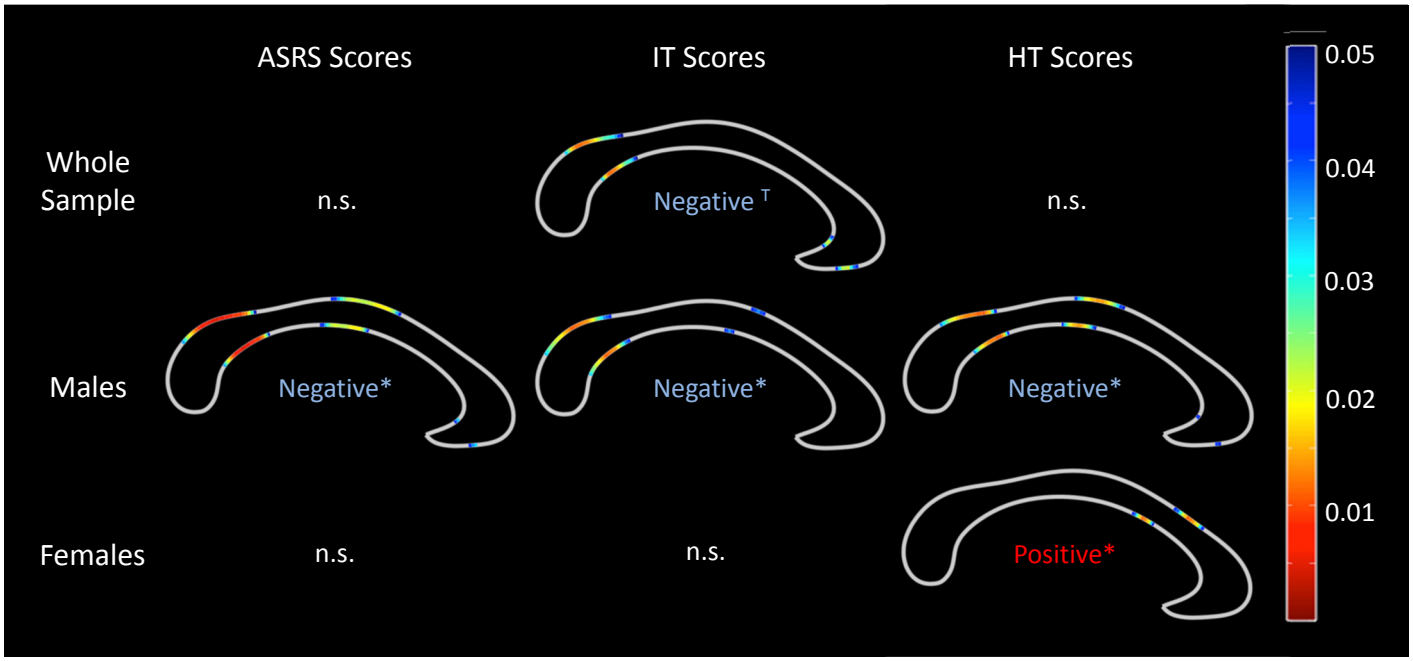
ASRS Scores
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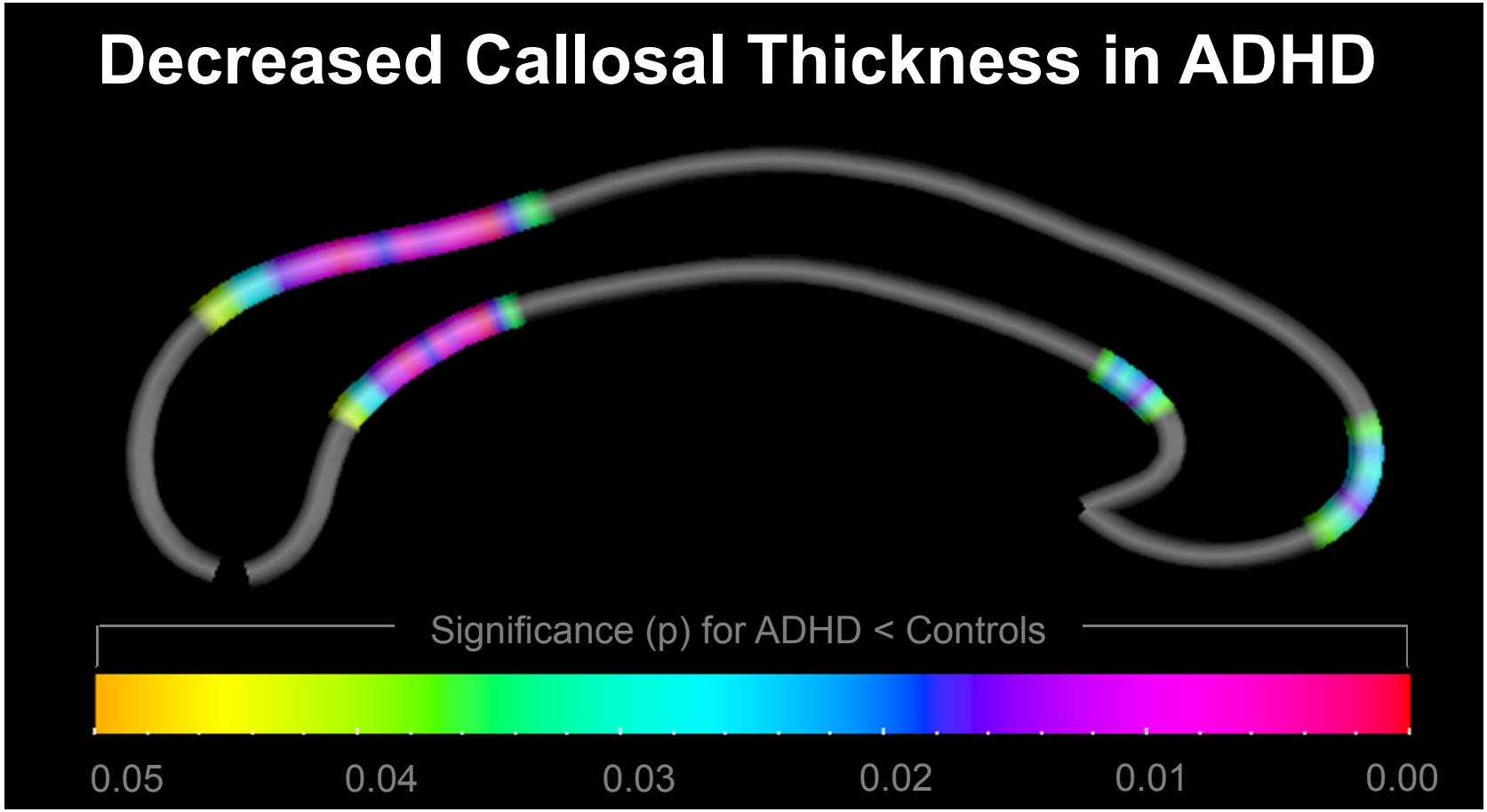
Decreased Callosal Thickness in ADHD
Significance (p) for ADHD < Controls
0.05
0.04
0.03
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