Corpus Callosum Morphology in Children and Adolescents With Attention Deficit Hyperactivity Disorder: A Meta-Analytic Review

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Several studies have examined corpus callosum (CC) morphology in children and adolescents with attention deficit hyperactivity disorder (ADHD). A meta-analysis of atypical brain morphology in children and adolescents with ADHD by Valera, Faraone, Murray, and Seidman (2006) reported a reduction in the splenium of the CC in this group compared with healthy controls. This meta-analysis undertook a more detailed examination of callosal morphology by also considering comorbid conditions and gender differences. The data from 13 studies were analyzed. Consistent with Valera et al. (2006), the splenium was smaller in children and adolescents with ADHD than in healthy controls. However, this result appears to be the result of a smaller splenium in females with ADHD. In addition, boys exhibited a smaller rostral body. There were no significant differences in CC measurements of studies that included ADHD samples with comorbid conditions. However, comorbidities were not consistently reported, making it difficult to accurately evaluate the impact of comorbidity on CC size. Additional research is needed to investigate whether gender differences reflect different ADHD subtypes. In addition, it is not known if these CC differences persist into adulthood.

Keywords: ADHD, corpus callosum, meta-analysis, comorbidity, gender differences

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differences (Castellanos et al., 1996; Overmeyer et al., 2000). It is possible that methodological differences between these studies, such as the participants' demographics (e.g., age, gender, sample size), the presence of comorbidities (e.g., learning disorders, conduct disorder), the use of medications, and differences in the segmentation schemes that are used to divide the CC into subregions, may have contributed to these inconsistent findings. Direct comparisons of the findings among these studies are therefore difficult.

A recent meta-analysis reviewed the findings of studies that have examined differences in brain morphology via structural imaging in children and adolescents with ADHD compared to controls (Valera et al., 2006). This review included the CC among the many brain structures that it examined, and reported that only the splenium was significantly smaller in children and adolescents with ADHD, when compared to healthy controls. In this meta-analysis, studies were grouped according to two of the three different methods that are used to parcellate the CC into subregions. The goal of the current study was to extend the analysis of Valera et al. (2006) in a number of ways. Thus, in addition to considering the possible influence of comorbid disorders and gender, we also separately examined data according to the three methods that have been used to divide the CC into subregions in ADHD samples. The method that is most commonly used to subdivide the CC is that of Witelson (1989), which divides the CC into seven subregions: the rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus, and the splenium (see Figure 1). A second method divides the CC into five equal regions (Baumgardner et al., 1996) (see Figure 2). Finally, the CC can also be divided into five equal sections using a procedure outlined by O'Kusky et al. (1988) (see Figure 3). These three methods were considered separately when calculating effect sizes for each region of the CC to ensure that the measurements being synthesized were equivalent.

Using Witelson’s (1989) divisions of the CC, it has traditionally been thought that the anterior regions of the CC, namely the rostrum and genu, connect the prefrontal cortical areas of the brain. Posterior to these regions, the rostral body connects homologous prefrontal regions, and homologous premotor and supplementary motor regions of the frontal lobes (Giedd et al., 1994; Pandya & Seltzer, 1986). The anterior midbody connects the motor cortices, and the posterior midbody connects somatosensory and posterior...
parietal areas. The isthmus connects the superior temporal and posterior parietal lobes. Finally, the splenium, the most posterior section of the CC, connects the occipital and inferior temporal lobes (Giedd et al., 1994; Pandya & Seltzer, 1986). However, a recent diffusion tensor imaging (DTI) study, which reexamined the cortical connections of the human CC in healthy adults, suggests that Witelson’s divisions may not reflect connectivity as previously assumed (Hofer & Frahm, 2006). They recommend different divisions of the CC into five regions that better reflect the origin of those fibers (see Figure 4). Specifically, they define the most anterior region of the CC as the area that contains fibers that project to prefrontal regions. The second region, which makes up the rest of the anterior half of the callosum, contains fibers projecting to the premotor and supplementary motor regions. The third region contains fibers projecting to the primary motor cortex, while fibers crossing the callosum in the fourth region project to the primary sensory cortex. Finally, the most posterior part of the CC projects to the parietal, temporal, and occipital cortex. This posterior section could not be further differentiated because the fibers projecting to each of these regions overlap.

Given the relatively distinct cortical projections of the CC, compromise to the CC would be expected to cause different cognitive problems depending on the location of the compromise. Hofer and Frahm (2006) provide a framework by which to identify which brain regions send projections through different regions of the callosus. If one assumes that the prefrontal and parietal regions are involved in the anterior and posterior attentional systems, respectively (Posner, Inhoff, Friedrich, & Cohen, 1987), then we would expect to see differences in the anterior portion and splenium of the corpus callosum between children and adolescents diagnosed with ADHD and healthy controls. The findings of Valera et al. (2006) are consistent with such a suggestion. We also included studies in our meta-analysis in which the participants with ADHD had comorbid conditions such as Tourette syndrome, velocardiofacial syndrome (a genetic disorder caused by a deletion on chromosome 22q11.2), and neurofibromatosis (an autosomal dominant genetic disorder). In addition to examining group differences, we also examined gender differences. No specific predictions were made about the impact of comorbidities or gender on CC size due to the lack of research in these areas in ADHD.

Method and Materials

Literature Search and Inclusion Criteria

A comprehensive search of the PubMed and PsycINFO electronic databases between January 1980 and October 2006 was undertaken in order to identify published journal articles that used magnetic resonance imaging (MRI) with children and adolescents who were diagnosed with ADHD. The key search terms included terms for ADHD (attention deficit hyperactivity disorder, ADHD, attention deficit disorder, ADD) and imaging (neuroimaging, magnetic resonance image, MRI). Corpus callosum was not included as a search term in order to conduct a broad search and identify a maximum number of potentially relevant articles. The bibliographies of all relevant papers were also examined for additional references. In order to be selected for the current meta-analysis, a study had to meet the following criteria: (1) the inclusion of participants with ADHD together with a control group, (2) imaging was performed and the CC was measured, (3) the provision of statistical data that would enable the calculation of Cohen’s $d$ effect sizes was provided (Cohen, 1988) (e.g., means and standard deviations, results of t tests or one-way F tests), and (4) the studies were published in English.

This literature search yielded a total of 1,066 potentially relevant studies, 11 of which met all of the inclusion criteria. Of the studies that did not meet one or more of the inclusion criteria, 1,022 either did not include participants with ADHD and/or did not measure the CC, 22 were not published in English, 7 were unpublished dissertations, and 4 did not provide specific measurements of the CC that would enable the calculation of effect sizes. In addition, two of the publications that met the inclusion criteria contained data for separate samples (Antshel, Conchelos, Lanzetta, Fremont, & Kates, 2005; Baumgardner et al., 1996). In each case, data were provided for cases of ADHD that were compared with unaffected controls, as well as data for children who had ADHD comorbid with another clinical condition (e.g., Tourette syndrome or velocardiofacial syndrome) who were compared with controls who had the other clinical condition without ADHD. Each of these publications was treated as two studies because data were provided for independent samples. Therefore, a total of 13 studies were included in the final meta-analysis. Finally, Lyoo et al. (1996) provided results for children who were diagnosed with ADHD on the basis of a clinical chart review as well as results for a subset of these children who were also diagnosed using the Child Version of the Diagnostic Interview Schedule for Children (DISC). The meta-analysis conducted by Valera et al. (2006) only included data from this latter subset of children. However, the current meta-analysis included results for the whole sample because the diagnostic criteria used by Lyoo et al. (1996) (with or without the DISC) were equivalent to those employed by the other studies included in this meta-analysis. This is the only difference between those studies that compared children and adolescents with ADHD and healthy controls that were included in Valera et al. (2006) and those included in the current study. However, whereas Valera et al. (2006) only used two methods of partitioning the CC to group their findings (Baumgardner et al., 1996; Witelson, 1989), the current meta-analysis used three methods (Baumgardner et al., 1996; Hynd et al., 1991; Witelson, 1989). The most commonly used method was that of Witelson (1989), which was used by seven

Figure 4. Hofer and Frahm’s proposed corpus callosum divisions. Reprinted from Neuroimage, 32, Hofer, S., Frahm, J. Topography of the human corpus callosum revisited—comprehensive fiber tractography using diffusion tensor magnetic resonance imaging, 989–94, Copyright (2006), with permission from Elsevier.
studies (see Figure 1). Five studies (Antshel et al., 2005; Baumgardner et al., 1996; Mostofsky, Wendlandt, Cutting, Denckla, & Singer, 1999) used a method that divided the CC on the midsagittal slice into five regions (see Figure 2). Finally, one study (Hynd et al., 1991) divided the CC into five regions using a procedure outlined by O’Kusky et al. (1988) (see Figure 3). Separate effect sizes were calculated for each of the regions of the CC that were measured by these three methods.

**Statistical Analysis**

Cohen’s $d$ effect sizes (Cohen, 1988) were calculated for each region of the CC that was measured by a study. A small effect size is defined as $d = .2$, a medium effect as $d = .5$, and a large effect as $d = .8$. Each effect size was then weighted by the inverse of the variance using the method outlined by Lipsey and Wilson (2001). This weighting takes into account the effect that sample size has on the reliability of an effect size but is more precise than simply weighting effect sizes by sample size. The effect sizes from all studies that measured a particular region were then aggregated to calculate a mean effect size, standard deviation, and minimum and maximum mean effect size for each region. The CC measurements of the control group were subtracted from those of the ADHD group when calculating effect sizes. Therefore, a negative effect size indicates that the CC was smaller for children and adolescents with ADHD compared to healthy controls. Whereas mean effect sizes measure the extent (and direction) of the difference between ADHD and controls, the standard deviation ($SD$) shows the degree of variation in the effect sizes for each region of the CC.

Percent overlap (%OL) statistics are also reported. This measures the degree of overlap in the measurements of the two groups (Zakzanis, 2001). These %OL scores vary inversely with mean effect sizes, such that larger effect sizes are associated with less overlap in the CC measurements. For example, an effect size of 0 is associated with 100% overlap, indicating that the CC measurements of the two groups are indistinguishable. A $d$ of 1.0, is associated with 45% overlap and, if the effect size is 3.0, the overlap between the CC measurements of the two groups is less than 5%, indicating that the groups are almost clearly distinguishable from each other (Zakzanis, 2001). The 95% confidence intervals (95% CIs) were also calculated in order to determine the statistical significance of an effect size. If a confidence interval does not span zero, the difference in the CC measurements of the ADHD and control groups differ significantly from zero, indicating that there is a statistically significant difference between the size of the CC for the two groups.

It is also possible that studies with statistically significant results are more likely to be published and, therefore, more likely to be included in a meta-analysis. The failure to include unpublished studies with nonsignificant results increases the risk of a Type I error, which may result in an effect size being overestimated (Zakzanis, Leach, & Kaplan, 1999). A fail safe $N$ ($Nfs$) was therefore calculated using the method described by Rosenthal (1995) to address this possible source of bias. This statistic estimates the number of unpublished studies, with nonsignificant group differences (i.e., small effect sizes), that would be required in order to call the current findings into question. The higher the number, the more confident one can be in a finding.

The potential influence of participants’ age on the CC measurements was also examined. The mean age of participants was calculated for each study for this purpose. This was done by combining the age data from the ADHD and control groups for that study (e.g., $M_{ADHD} - M_{Control} \pm SD_{age}$) and weighting it by the sample sizes of the ADHD and control groups. In addition, a weighted mean effect size was calculated for the callosal measurements from each study. The mean age for each study was then correlated with the weighted mean effect size for that study using Pearson’s $r$. It was also intended that IQ be examined in this way. However, only five studies reported this information, therefore precluding a reliable assessment of the relationship between IQ and callosal size.

### Table 1

**Demographic Details for the ADHD and Control Groups**

<table>
<thead>
<tr>
<th></th>
<th>ADHD</th>
<th>Controls (all types combined)</th>
</tr>
</thead>
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<tr>
<td>$N$ studies</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>$N$ participants</td>
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</tr>
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<td>Max</td>
<td>57</td>
<td>55</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>IQ</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Gender</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>229 (204 males)</td>
<td>218 (177 males)</td>
</tr>
</tbody>
</table>

*Note. The $N$ differs between variables because not all studies provided data for each variable.*

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1 Antshel et al. (2005) and Baumgardner et al. (1996) each provide data that were treated as two studies, therefore only three references are provided for the five studies.
performance or even brain morphology that is related to ADHD. Therefore, IQ was not statistically controlled for in the current meta-analysis. Chi-square tests indicated that there were significantly more males than females in both the ADHD and control groups. In addition there were significantly more females in the control group than in the ADHD group ($p < .05$ level). Therefore, if gender differences are found in the morphology of the CC, they may be confounded by this significant difference in the composition of the samples. However, any differences in CC size are unlikely to be attributable to age differences, as the ADHD and control groups did not significantly differ in this regard. Whole brain size was measured in most studies and was often included as a covariate in order to ensure that differences in CC size were not simply due to a reduction in whole brain size. Only one study did not take this issue into account. The removal of the results from this study did not change the overall findings of this meta-analysis. Therefore, it was included in the analysis.

**Diagnostic Criteria, Comorbidities, and Medication**

All studies based the diagnosis of ADHD on criteria from various editions of the Diagnostic and Statistical Manual (DSM) of Mental Disorders (APA, 1980, 1987, 1994). ADHD was assessed through a range of parent, teacher, and child questionnaires, and clinical interviews. Therefore, despite changes to the DSM criteria over time, all studies applied comparable rigor to the diagnosis of participants. The ADHD subtypes (i.e., ‘combined,’ ‘predominantly inattentive,’ and ‘predominantly hyperactive’ subtypes) were introduced to the fourth edition of the DSM (APA, 1994). This information was only provided for two studies, so it was not possible to determine whether there are differences in CC morphology for the different subtypes. In addition, there were some inconsistencies in terms of the inclusion or exclusion of comorbid psychiatric conditions. For example, five studies included participants with ADHD and comorbid conduct disorder (Castellanos et al., 1996; Giedd et al., 1994; Hynd et al., 1991; Lyoo et al., 1996; Overmeyer et al., 2000) and two studies excluded participants with ADHD and comorbid conduct disorder (Hill et al., 2003; Semrud-Clikeman et al., 1994). This information was not provided for the remaining six studies (Antshel et al., 2005; Baumgardner et al., 1996; Kayl, Moore, Slopis, Jackson, & Leeds, 2000; Mostofsky et al., 1999). Moreover, some studies excluded participants with certain comorbid psychiatric disorders, such as depression and anxiety, learning disabilities, neurological disorders, and developmental delay (Castellanos et al., 1996; Giedd et al., 1994; Hill et al., 2003; Lyoo et al., 1996; Overmeyer et al., 2000; Semrud-Clikeman et al., 1994). However, seven studies did not provide detailed information about the inclusion or exclusion of comorbid psychiatric conditions (Antshel et al., 2005; Baumgardner et al., 1996; Hynd et al., 1991; Kayl et al., 2000; Mostofsky et al., 1999). Due to the inconsistent reporting of inclusion and exclusion criteria, it was not possible to accurately determine whether the inclusion or exclusion of these participants influenced the CC measurements.

Similarly, the amount of information provided about the medications used for the treatment of ADHD varied. Seven studies did not report information about current use of medications (Antshel et al., 2005; Baumgardner et al., 1996; Giedd et al., 1994; Lyoo et al., 1996; Mostofsky et al., 1999). Four studies indicated that the participants were all taking medications prior to the study but did not indicate whether participants were taking medications at the time of the study (Castellanos et al., 1996; Hynd et al., 1991; Overmeyer et al., 2000; Semrud-Clikeman et al., 1994). One study indicated that participants either had no prior use of stimulants or received a physician’s consent to stop taking medications 16 hours prior to participating in the study (Hill et al., 2003) and one study indicated that two thirds of the ADHD participants were taking medications to treat the disorder (Kayl et al., 2000). Due to these inconsistencies, it was not possible to reliably examine the impact of medications on the CC findings.

**Corpus Callosum Morphology in ADHD**

The weighted effect sizes ($d_{r}$) for subregions of the CC (mean, $SD$, 95% CIs), measured in children and adolescents with ADHD and healthy controls are provided in Table 2. The $Nfs$ and the percentage overlap between groups (%OL) are also provided, as are the number of studies, number of participants, and the study references. These statistics were all considered when interpreting the current results.

The effect sizes for the different regions of the CC ranged from a minimum of $-0.06$ for the midbody, equating to 92% overlap between the measurements for the two groups (Baumgardner et al., 1996 method), to a maximum of $-0.94$ for region 4 (a region anterior to the splenium), with 48% overlap between ADHD and controls (Hynd et al., 1991 method). The latter result equates to a large difference (Cohen, 1988). In terms of the statistical significance of the effect sizes, as indicated by confidence intervals that do not span zero, only the measurement for the splenium (using Witelson’s method) of the ADHD and control groups differed significantly from zero. Thus, there do not appear to be reliable group differences in any region of the CC, other than the splenium. The splenium yielded an effect size of $-0.54$ indicating that, on average, there is a half a standard deviation difference in the mean measurements between the two groups. Moreover, the $Nfs$ for the splenium indicates that seven unpublished findings with nonsignificant findings would be necessary to challenge this result. This is unlikely given the small number of studies that have measured the CC in participants with ADHD.

**Corpus Callosum Morphology With Specific Comorbid Conditions**

Five additional studies compared the CC size of children with ADHD who also had a specific comorbid condition to that of children with the comorbid condition but without ADHD. These studies were not included in the previous calculations but were considered separately. Two of these studies (Baumgardner et al., 1996; Mostofsky et al., 1999) examined CC area in children and adolescents with ADHD and comorbid Tourette syndrome, and compared area measurements with a group of children and ado-
lescents with Tourette syndrome without ADHD, in order to determine whether these conditions had distinct or common differences in CC morphology. This research yielded small (0.02) to moderate (−0.35) effect sizes but these were all nonsignificant (see Table 1, supplemental material).

The remaining three studies looked at different comorbid conditions. First, Overmeyer et al. (2000) compared children and adolescents with ADHD with siblings of children and adolescents with ADHD, although not necessarily siblings of the ADHD participants in the study. This was done in order to examine the relationship between callosal morphology and the expression of ADHD symptoms. These results are presented in Table 2 of the supplemental material. Another study by Antshel et al. (2005) examined CC size in children with ADHD and velocardiofacial syndrome and children with velocardiofacial syndrome without comorbid ADHD (see Table 3, supplementary material). Finally, Kayl et al. (2000) researched CC size in children with ADHD and comorbid neurofibromatosis and children with neurofibromatosis without comorbid ADHD (see Table 4, supplementary material) to determine if the structural differences in ADHD extended to children with neurofibromatosis, given that ADHD occurs more frequently in these children than in the general population. Effect sizes were calculated for these studies although effect sizes based on single studies are considered to be less reliable (Rosenthal, 1995). The effect sizes from these three studies were all small and nonsignificant, indicating that the size of CC regions did not differ between the two groups. The very small Nfs for these studies also suggests limited confidence in these results. Thus, on the basis of limited available evidence, there do not appear to be any differences in CC size when the effects of comorbid conditions are controlled for.

<table>
<thead>
<tr>
<th>Region</th>
<th>N studies</th>
<th>N participants (ADHD + Controls)</th>
<th>Mean Cohen’s $d_w$</th>
<th>SD $d_w$</th>
<th>95% CI</th>
<th>Min $d_w$</th>
<th>Max $d_w$</th>
<th>Nfs</th>
<th>%OL</th>
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<td>-0.72</td>
<td>0.53</td>
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<td>-0.15</td>
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<td>-0.48</td>
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<td>-0.21</td>
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<td>-0.94</td>
<td>0.52</td>
<td>-1.96</td>
<td>0.08</td>
<td>4</td>
<td>48</td>
<td></td>
<td>Hynd et al 1991</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>17</td>
<td>-0.67</td>
<td>0.51</td>
<td>-1.66</td>
<td>0.32</td>
<td>2</td>
<td>57</td>
<td></td>
<td>Hynd et al 1991</td>
</tr>
</tbody>
</table>

Note. N = number of studies contributing to the effect size; Mean $d_w$ = mean weighted effect size; SD $d_w$ = standard deviation of weighted effect size; 95% CI = 95% confidence intervals for means; Max $d$ = maximum effect size; Min $d$ = minimum effect size; Nfs = fail safe N; % OL = percent overlap between ADHD and Control groups.

*a Effect sizes weighted by the inverse variance.*
**Moderator Variables**

In order to examine the effect of gender on CC size, effect sizes were recalculated separately for studies that included only males, only females, or a combination of male and female participants. This analysis is available as supplementary material (see Table 5). When studies were separated according to the gender of the participants, the effect size for the splenium (measured according to Witelson’s method) was no longer significant when only male samples were examined. However, significant differences in the rostral body (measured according to Witelson’s method) were found for males with ADHD compared to healthy controls. Although this effect size was based on only two studies, the fact that the confidence interval did not span zero suggests that this is a statistically significant effect. Another study examined the rostral body exclusively in females with ADHD and comorbid Tourette syndrome compared with females with Tourette syndrome only. However, there was no significant difference in rostral body size in these two groups.

The influence of age on group differences in callosal size was additionally examined using Pearson r correlation coefficients. The mean age of those studies that reported this data was correlated with the weighted mean effect sizes for these studies. A small nonsignificant correlation was observed for age ($r = -0.06, n = 11, p = .86$), indicating that age of the samples was not related to the effect sizes calculated for a study.

**Discussion**

Overall, the results of this meta-analysis indicated that children and adolescents with ADHD had a smaller splenium than those without, consistent with the findings of Valera et al. (2006). In addition, there was some indication that, for males only, children and adolescents with ADHD had a smaller anterior portion of the CC.

To put these findings in perspective, the data for this meta-analysis was obtained from 13 studies that examined the size of the CC of 284 children and adolescents with ADHD and 311 controls. Although the two groups were comparable in terms of age, participants with ADHD had a lower IQ than control participants. As discussed earlier, this may be part of the disorder (Hervey et al., 2004). Therefore, statistically controlling for differences in IQ may remove variation in cognitive performance or even brain morphology that is an integral part of ADHD (Hervey et al., 2004). In addition, IQ was not available for the majority of the studies, preventing an analysis of the impact of IQ on the findings.

In the current meta-analysis, the splenium of ADHD participants compared with healthy controls (measured using Witelson’s method) was the only difference in callosal size that was associated with an acceptable Ns, small overlap between the two groups, and a 95% CI indicating that it differed significantly from zero. Although it was associated with 67% overlap for the callosal measurements for the two groups, only small differences were expected and moreover, differences in the CC are not being proposed as a tool for the diagnosis of ADHD. The significant differences in this region are consistent with the meta-analysis performed by Valera et al. (2006).

According to Witelson (1989), the splenium has connections to temporal regions (Giedd et al., 1994; Pandya & Seltzer, 1986) and may, therefore, be associated with memory. Problems with memory have previously been reported in both children and adults with ADHD (Cutting, Koth, Mahone, & Denckla, 2003; Gallagher & Blader, 2001; Hervey et al., 2004; McLean et al., 2004; Norrelgen, Lacerda, & Forssberg, 1999). The more recent work by Hofer and Frahm (2006) based on diffusion tensor imaging, suggests that the most posterior part of the CC (which included the splenium) projects to parietal, temporal, and occipital cortex. These projections overlapped, preventing further differentiation of this region. Given these connections of the posterior region of the CC, the smaller splenium may provide a potential substrate for some of the problems experienced by persons with ADHD in the areas of sustained attention and divided attention, which are functions supported by the parietal region (Banich, 2004). In addition, the memory problems associated with ADHD may result from poor encoding of information due to attention problems.

Several studies in the current meta-analysis compared children with ADHD and a comorbid clinical disorder to children with that clinical disorder without comorbid ADHD. These studies consistently yielded only small effect sizes. It is possible that any differences in CC size were common to both ADHD and the comorbid disorder and, therefore, not evident when comparing the two clinical groups. Although these studies provide information about the ways in which ADHD and the comorbid conditions vary from one another, they do not provide clear evidence for any differences associated with ADHD compared to healthy controls.

In the current meta-analysis, effect sizes were additionally calculated for males and females separately. The effect size for the splenium (measured using Witelson’s scheme) was significant for studies that examined males or both males and females. However, this effect was rendered nonsignificant when only males were considered (such an analysis could not be done for females, as there were no studies comparing the size of the splenium in females only). These results raise the possibility that the smaller splenium associated with ADHD is more pronounced in females. However, further research is needed to confirm this gender difference because females have not been examined exclusively and females were generally underrepresented in the studies that were included here. Although these differences may have disappeared due to low power, such an interpretation is made less likely by the fact that an equal number of studies used males and females, but the difference for the splenium remained significant. In addition, a smaller rostral body was associated with males with ADHD as compared with healthy male controls. The rostral body was not significantly different in a study comparing ADHD with comorbid Tourette syndrome to Tourette syndrome only in female participants. This pattern of results suggests that the smaller rostral body is driven by the inclusion of male participants.

The possible influence of the demographic characteristics on the CC measurements was also examined. Although an analysis of age, for those studies that provided this information, indicated that this variable did not significantly influence the group differences in CC size, we cannot be sure of the impact of other variables, such as current medications, IQ and comorbid psychiatric conditions, as they were not consistently reported. Therefore, there is the potential for significant but unreported variation in the samples under investigation. Our inability to account for the influence of these variables may have obscured additional differences in the size of callosal regions between ADHD children and control groups.

Despite significant findings, there are a number of caveats to the current study. First, several studies included samples of ADHD with comorbid conditions. These comorbidities may obscure or
confound relevant group differences. For example, learning disabilities, conduct disorder, and mood disorders are commonly comorbid with ADHD (for a review see Daley, 2006). There is also some evidence for larger CC volume in adults with antisocial personality disorder (Raine et al., 2003), which is the adult manifestation of conduct disorder. If conduct disorder is also associated with a larger CC volume, this might offset reductions in CC size associated with ADHD. In addition, major depressive disorder is often found in children and adolescents with ADHD (Busch et al., 2002). A recent study has shown that people with familial major depressive disorder had larger regions of the CC compared to healthy controls (Lacerda et al., 2005). Therefore, larger CC regions associated with major depressive disorder may be offset by smaller CC regions associated with ADHD in children and adolescents with both conditions. Therefore, comorbid psychiatric disorders may have the potential to obscure differences in callosal size driven by ADHD. Unfortunately, comorbidity is not consistently reported, which makes it difficult to disentangle the effects on callosal size that may be driven by ADHD as compared with other disorders. Such information should be included in future publications of primary research on ADHD to allow an accurate and detailed evaluation of the research findings.

Second, the implications of moderate differences in the size of the splenium in ADHD are unclear. From an anatrophic perspective, one could assume that a larger callosum is associated with more nerve fibers. If so, then the reduction in callosal size in the splenium of individuals with ADHD might indicate that there are fewer fibers connecting the parietal regions. Another possible interpretation is that there is reduction in the brain regions that typically send those fibers, that is, parietal regions. Although a reduction in parietal volume has been reported (Castellanos et al., 2002), other studies have failed to find significant differences (Durston et al., 2004; Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002). Although reductions for any given parietal region might not be large enough to reach statistical significance, subtle differences across a variety of parietal regions may add up to be reflected in callosal size if they send fibers through similar regions. Still another possibility is that ADHD and controls have equal number of fibers passing through the splenium, but that these are more myelinated in controls, leading to larger callosal size (Banich & Shenker, 1994). This may result in individuals with ADHD not being able to coordinate processing between the hemispheres in as integrated a manner as controls.

Finally, our meta-analysis was restricted to samples of children and adolescents because CC size has not yet been examined in adults with ADHD. Therefore, it is not known whether any differences, such as a smaller splenium, persist into adulthood or whether the size differences resolve with further development. The CC begins to develop between the 10th and 25th week of gestation (Moutard et al., 2003) and myelination continues throughout childhood (Barnea-Goraly et al., 2005). In addition, there is evidence that the posterior CC continues to change throughout adolescence, whereas anterior regions reach adult levels earlier in childhood (Giedd et al., 1999; Thompson et al., 2000). Although it would be ideal to examine differences in children and adolescents separately, most of the studies included both children and adolescents in their samples. Further research is needed to determine whether differences persist into adulthood, given the developmental changes in myelination of the CC.

In summary, the findings of this meta-analysis suggest that the splenium of the CC of children and adolescents with ADHD is smaller than that of healthy controls. In addition, the rostral body may be smaller in males with ADHD. Further research is necessary to determine whether these differences persist into adulthood and the mechanisms by which such differences are related to the symptoms observed in children with ADHD.

References


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