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## A Meta-Analysis of the Corpus Callosum in Autism

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### Abstract

**Background**—Several previous MRI studies have reported reductions in corpus callosum (CC) total area and CC regions in individuals with autism. However, studies have differed concerning the presence, magnitude, and/or region contributing to CC reductions. The primary aim of the present study was to determine the significance and magnitude of reduction in CC total and regional area measures in patients with autism.

**Method**—PubMed and PsycInfo databases were searched to identify MRI studies examining corpus callosum area in autism. Ten studies contributed data from 253 patients with autism (Mean age=14.58, SD=6.00) and 250 healthy controls (M age=14.47, sd=5.31). Of these ten studies, eight reported area measurements for corpus callosum regions (anterior, mid/body, and posterior), with six studies reported area for Witelson subdivisions. Meta-analytic procedures were used to quantify autism versus healthy control differences in total and region CC area measurements. Demographics and study characteristics were examined as moderators of total CC area.

**Results**—Total CC area was reduced in autism and the magnitude of the reduction was medium (Weighted Mean  $d=.48$ , 95% CI=.30-.66). All regions showed reductions in size with the magnitude of the effect decreasing caudally (anterior  $d=.49$ , mid/body  $d=.43$ , posterior  $d=.37$ ). Witelson subdivision 3 (rostral body) showed the largest effect, indicating greatest reduction in the region containing pre-/supplementary motor neurons.

**Conclusions**—CC reductions are present in autism and support the aberrant connectivity hypothesis. Future diffusion tensor imaging studies examining specific fiber tracts connecting the hemispheres are needed to identify the cortical regions most affected by CC reductions.

### Keywords

autism; corpus callosum; meta-analysis; magnetic resonance imaging

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Autism is a neurodevelopmental disorder characterized by deficits in social interaction, communication, and stereotyped or repetitive behaviors (1). There is strong evidence of neural system abnormalities in autism, but the extent and neurodevelopmental timing of these abnormalities remains uncertain (2). Findings from post-mortem, head circumference, and brain imaging studies have suggested increases in brain volume in autism (3-9), with the largest increase being for gray matter and outer radiate white matter (2). These observations may be related to genetic influences, as seen in Fragile X (10) and *PTEN* heterozygous mutations

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(11,12). Recent studies of biological pathways implicated in these changes might support the connection between cortical overgrowth and autism symptoms (13). However, these findings should be reconciled with the hypothesis of abnormal connectivity in autism and the evidence of decreased, and not increased, corpus callosum size.

Aberrant connectivity theory posits dysfunction in the long-distance connections between cortical brain regions in autism, resulting in impairments in complex cognitive processes such as executive functions, social cognition, and language (14). Structural white matter abnormalities (15), recent findings from studies using functional imaging (16-20), and post-mortem neuropathologic investigations (3) support the theory of aberrant connectivity in autism (17,20,21). However, examination of structural imaging studies indicates that the magnitude and direction of white matter findings varies by the region examined and methodological differences across studies. Two studies have found *increased* volume of outer radiate white matter (15,22), whereas findings for inner (deep) white matter compartments and long fiber tracts have generally indicated decreased area (17,23-28), volume (29), density (30,31), and integrity (29). Negative studies have also been reported, with no significant alterations in CC size in autism (32-34). The present study aims to bring clarity to previous inconsistencies by quantitatively summarizing results from studies examining area measurements of the corpus callosum.

The corpus callosum (CC) is the main fiber tract connecting the hemispheres and is topographically organized (35). Anterior CC regions represent fibers from pre-frontal cortices; mid/body regions are composed of fibers from pre-motor, motor, parietal, and superior temporal cortices; and the posterior region represents fibers from inferior temporal and occipital cortices (25). Given these extensive connections, study of the CC represents an important window into long-fiber, white matter connection abnormalities in autism. The majority of previous studies (7 of 10) have suggested significantly reduced total mid-sagittal area of the CC (17,23-28). However, the magnitude of total CC area reductions and the regions contributing to these reductions have varied significantly across studies.

The first aim of the present study was to determine the magnitude and significance of total CC area reductions in individuals with autism relative to healthy participants. It was hypothesized that total CC area will be significantly smaller in autism and that the magnitude of this effect will be non-trivial, falling in the medium to large range (Cohen's  $d=.50-.80$ ). The second aim was to determine the magnitude and significance of CC region differences. This was done in two ways: using broader regions (anterior, mid/body, and posterior) and Witelson (35) subdivisions. Based upon previous findings of abnormal connectivity in numerous cortical regions in autism (2), it was hypothesized that all regions would show significant reductions in area. However, given the prominence of pre-frontal structures in brain connectivity, the later development and myelination of these regions (36), and the substantial executive functioning deficits in autism (37,38), anterior CC areas were hypothesized to show larger reductions than other regions.

An additional and final aim of the present study was to examine moderators of total CC area reductions in autism. To avoid non-replicable, post-hoc findings, *a priori* hypotheses were generated for potential moderators and analyses were restricted to total CC area. The relationship between age and neurobiological abnormalities is particularly intriguing given recent reviews strongly implicating abnormal neurobiological trajectories in autism (2,39). Previous data have found reductions of white matter in autism with increasing age (5). Therefore, it was hypothesized that reductions in CC area relative to healthy controls would be larger with increasing average age of study participants. Following previous findings of increased total brain volume in autism, studies correcting for total brain or intracranial volume were anticipated to show larger CC area reductions. One study found a relationship between

lower CC volume and lower intellectual level in autism (29), therefore, it was hypothesized that lower functional level of autism participants would be correlated with larger CC area reductions. Finally, it was expected that studies using more sensitive imaging techniques, higher magnet strength, and more detailed reporting of methodology would produce larger effects.

## Method

### Search Strategy and Exclusion Criteria

PubMed/Medline and PsycInfo were searched from January 1970 to June 2008 using the terms “autism or PDD or pervasive developmental disorder” and “corpus callosum.” A specific search for Asperger’s disorder was also done but no published studies were identified. Additional studies were identified by reviewing the references of each article found. Studies were included if they reported measurement for the total corpus callosum area in patients with autism and healthy controls. A total of 20 potential studies were identified. Ten studies were excluded for the following reasons: if effect sizes could not be computed (k=2), if there was clear overlap with a more detailed report (k=1), or if they reported volume or density measurements rather than area (k=7).

### Study Coding

For each study, demographic and clinical variables were coded as follows: study publication date, sample size, average age, % male, IQ scores (if available), magnet strength, and means and SDs of CC total and region areas. If CC total or region means and SDs were not reported, inferential statistics were converted to an effect size (Cohen’s *d*; 40). If total CC area was not reported, but all CC regions were reported, values were averaged across regions to generate an estimate for total CC area. When more than one comparison group was available, healthy controls were chosen. When more than one set of values were presented for patients with autism (for example, autistic disorder and PDD NOS or autism spectrum), the values for patients with strictly defined autism were chosen. If both total brain volume corrected and uncorrected values were reported, corrected values were used. When covariates were used to adjust descriptive statistics, adjusted values were used. If studies presented a modified Witelson method, effect sizes were included if the regions reported closely mapped onto Witelson subdivisions. Figure 1 presents regions and Witelson sub-divisions. Region A, the anterior CC, represents the combination of Witelson subdivisions 1 and 2. Region B, CC body, represents Witelson subdivisions 3-6. Region P, posterior CC, is Witelson subdivision 7.

To determine the quality of study method and results reporting the following variables were coded (0 if not present/no, 0.5 partially present, 1 completely present/yes): the study was prospective; DSM diagnostic criteria were used; a gold standard diagnostic interview or observation scale was used to make the diagnosis (41,42); demographics were reported; controls were healthy; controls were screened for neuropsychiatric illness; age, gender, IQ, and total brain or intracranial volume were matched or statistically controlled; image tracing blinded; inter-rater reliability reported; MRI slice thickness  $\leq 3$ mm; imaging method clearly described; and descriptive and/or inferential statistics reported for regions. Summing these variables yields a scale (Method Index) that evaluates methodology and results reporting - rather than study quality, as quality can only be inferred from reporting. The Method Index has a possible range from 0 to 15 (Table 1).

### Statistical Analysis

Data were analyzed using both fixed and random effects models. Random effects models indicated little change in weighted mean effect sizes and negligible widening of confidence intervals relative to fixed effects models. The similarity of these approaches indicates that study

level sampling error was negligible. Therefore, only results of the fixed effects analyses are reported as recommended by Lipsey and Wilson (43). Study effect sizes (Cohen's  $d$ ) were pooled using inverse variance weighting methods (43). Pooled effect sizes, 95% confidence intervals, the  $z$ -test examining the significance of the pooled effect size, and the chi-square goodness of fit test of heterogeneity of effect sizes ( $Q$ ) were calculated for each comparison of interest: total CC area; anterior, mid/body, and posterior regions; and Witelson subdivisions (labeled W1-W7; Table 2).  $Q$  tends to be underpowered for small meta-analytic sample sizes, leading to failure to reject the null hypothesis of homogeneity of effect sizes when substantial heterogeneity is actually present. For this reason, we examined the influence of study characteristics on effect sizes using meta-regression (44). These analyses were restricted to *a priori* hypotheses regarding average age, correction for total brain volume, functional level of autism participants, magnet strength, and method index as moderators of total CC effect sizes. The file drawer problem (publication bias) was examined by creating a funnel plot and calculating the fail safe  $N$  (45). The funnel plot examines the relationship between study effect size and the standard error of the effect size. This plot is particularly useful for examining whether small or medium-sized studies (with larger standard errors) are under-represented in the region of small effect sizes, signaling publication bias toward larger  $N$  studies more likely to detect significance. The fail safe  $N$  is the number of studies needed to bring the weighted mean effect size down to a negligible value ( $d=.05$ ). Fail safe  $N$  examines the robustness of the weighted mean effect size to publication bias toward studies with significant effects.

## Results

Ten studies met inclusion criteria with each study providing one effect size (see Table 1). Of these 10 studies, two studies only provided total CC area (33,34) and two studies only provided data for broad regions but not Witelson subdivisions (24,27). One study included only enough information to evaluate W1-4 and W7 (32). Another study only included enough information to evaluate W4-7 (23).

Table 1 presents demographics and study characteristics. Studies contributed 503 total participants (253 with autism and 250 healthy controls). The average age of study participants was 14.5 ( $SD=5.7$ ) and 86% of study participants were male. Two studies examined low functioning autism (26,33), four examined mixed samples including both low and high functioning individuals (24,27,28,34), and four studies exclusively examined high functioning autism (17,23,25,32). Importantly, the body of studies included a number of methodologically rigorous reports, with 6 of the 10 studies receiving scores of 12.5 or above (out of 15) on the method index (median=12.75). Of the 7 studies reporting a significant reduction of the total CC area in autism, 3 had an unadjusted 95 % confidence interval that included zero; further supporting the need for a meta-analysis of these studies.

Table 2 presents meta-analytic statistics for total CC area, regions, and Witelson subdivisions. Consistent with expectation, total CC area was significantly reduced in autism patients ( $z = 5.17$ ,  $p<.0001$ ). This effect fell at the lower end of the predicted range (weighted mean  $d=.48$ , predicted range of  $d=.50-.80$ ). Areas for each CC region and Witelson subdivision were also significantly reduced in autism (smallest  $z = 3.07$ ,  $p<.001$ ). Figure 2 presents weighted mean effect sizes and standard errors for each region and Witelson subdivision. Consistent with expectation, area reductions in CC regions showed a very large linear trend (anterior vs. posterior  $F(1,7)=3.23$ ,  $p=.115$ ,  $d=1.36$ ), and did not reach significance probably due to the small sample ( $k=8$ ). Similarly, the correlation between Witelson subdivision (numbered 1-7 anterior to posterior) and weighted mean effect sizes was large ( $r = -.52$ ,  $d=-1.22$ ,  $df=5$ ,  $p=.23$ ), but did not reach significance. Visual inspection of Figure 2 indicates that the rostral body of the CC (Witelson subdivision 3) showed the largest difference (weighted mean  $d=.66$ ).

None of the pooled effect sizes had a significant Q statistic (see Table 2). However, because the Q statistic is under-powered in small samples and *a priori* predictions were made regarding the relationship between study characteristics and effect sizes, meta-regression was used to examine the relationship between total CC area and potential moderator variables. Meta-regression using weighted least squares indicated a significant overall prediction of weighted effect sizes, adjusted  $R^2=.89$ ,  $F(5,4)=15.76$ ,  $p=.010$ . Age was a significant predictor with increasing age indicating a larger discrepancy between participants with autism and healthy controls,  $t(4)=4.32$ ,  $p=.012$ . Magnet strength was also a marginally significant predictor,  $t(4)=-2.68$ ,  $p=.055$ , with stronger magnets showing larger discrepancies between autism and healthy controls. None of the other predictors significantly accounted for unique variance (largest  $t(4)=1.95$ ,  $p=.112$ ).

Previous data have suggested that earlier publications in a scientific field tend to yield larger findings, the relationship between publication date and total CC area effect sizes was also examined (46). Contrary to expectation, publication date was *positively* related to total CC area effect sizes and the effect was significant ( $\beta=.76$ ,  $t(8)=3.26$ ,  $p=.012$ ). This may be partly due to greater use of more sensitive imaging methods in later publications. The method index did not significantly predict total CC area effect sizes ( $\beta=.45$ ,  $t(8)=1.43$ ,  $p=.192$ ), indicating that better reporting of study methodology did not influence effect sizes, although the effect was in the expected direction.

Inspection of the funnel plot indicated a relatively even representation of small and moderate N studies across the range of effect sizes (figure available from the first author). The fail safe N (see table 2) indicates that publication bias is an unlikely explanation for the observed effect sizes. Fourteen additional studies each contributing a null effect size ( $d=.00$ ) would be needed to reduce the observed weighted mean effect size for total CC area to a small effect ( $d=.20$ ). Eighty-six new studies would be needed to reduce the observed effect size to a negligible effect ( $d=.05$ ). Similar results were observed for regions and Witelson subdivisions, indicating that publication bias is unlikely to play a substantial role in the present findings.

## Discussion

Findings from the present investigation provide strong support to previous studies suggesting involvement of CC in the pathophysiology of autism. The present meta-analytic results indicate that total CC area is smaller in autism; consistent with studies implicating the CC in emotional and social functioning (47) and higher cognitive processes such as decoding non-literal meaning, affective prosody, and understanding humor (48,49). The CC provides integrated inter-hemispheric communication between homotopic and heterotopic cortical regions (50). Disruption of CC-mediated inter-hemispheric communication may underlie many of the sensory, cognitive, and behavioral symptoms observed in children with autism spectrum disorder.

In the present study the weighted mean effect size for the CC was slightly smaller than anticipated. It is close to the medium range and does not appear to be a result of publication bias. Interestingly, the effect size was found to be large in a recent study using a 3T magnet ( $d=.73$ ) (23), suggesting that future studies applying newer imaging methodologies (e.g., diffusion tensor imaging or related novel white matter tractography methods) and higher magnet strength are likely to yield larger differentiation of individuals with autism and healthy controls. The present results clarify previous null findings (3 of 10 studies) as either underpowered or due to sampling error. Findings were concordant with studies applying other imaging methods, supporting the aberrant connectivity hypothesis in autism (15-18). These data suggest that brain connectivity is likely to be impaired in most regions as evidenced by



alterations of all CC subdivisions and is supported by several functional studies implicating multiple cortical including frontal, and parietal regions (17,19,20,51).

The greatest reduction of CC area was observed in anterior regions providing a neuroanatomical link to the prominent executive dysfunction in autism (37). Furthermore, the largest reduction at Witelson subdivision 3 (rostral body) indicates disruption of fiber tracks originating in pre-/supplementary motor regions (35). Pre-/supplementary motor regions are crucial for motor planning and disruption of these regions may be the neural substrate for impairments in fine motor skills and imitation observed in autism. Several studies have reported abnormalities in motor functioning (52,53) and imitation (54) when compared to controls. Additionally, these CC regions, while important for motor planning, have also been identified as supporting a subset of mirror neuron functions (55). Thus, the present data may suggest reduced functional output of mirror neuron regions or decreased hemispheric cross-talk between mirror neuron regions. In turn, reduced output or cross-talk of these regions may contribute to reduced attunement to others' intentions (56).

Total CC reductions were moderated by two major factors: magnet strength and participant age. Increasing magnet strength predicted larger reductions in CC area as would be expected with higher resolution (3T) imaging techniques. Larger CC reductions with advancing age are in agreement with previous white matter findings (5). Increasing reductions in CC size over time might be a downstream consequence of early abnormal cortical development, a result of ongoing neurobiological disruptions, or due to other unknown processes. One possible explanation is that early neural proliferation with abnormal cortical cytoarchitecture and densely-packed minicolumnar organization (3) may lead to poor coordination with distal brain regions. Consequently, developmental alterations of these neural networks may result in reductions over time of long fiber neurons responsible for intra-hemispheric or inter-hemispheric regional communication. Clearly, additional studies incorporating multimodal imaging techniques are needed to tease out these possibilities.

Results reported here are consistent with evidence from investigations examining individuals with agenesis of the CC, pointing to the role that this structure plays in complex brain functions. Several cognitive and social deficits observed in autism have also been described in individuals with agenesis of the CC, although not all individuals with these deficits meet full DSM-IV-TR criteria for autistic disorder. Impairments in abstract reasoning (57,58), problem solving (59, 60), and generalization (61), as well as emotional immaturity, lack of introspection, impaired social competence, and poor communication of emotions (47,62,63) have all been described in individuals with agenesis of the CC in the absence of intellectual disability. Deficits in social judgment and planning (62), decoding non-literal meaning (48), affective prosody and humor (49,64) have also been reported in both disorders. The clinical similarities between the two disorders highlight the need for a better understanding of the neurobiology of agenesis of CC. This will shed light on the genetic and pathologic contribution of CC structural alterations to cognitive and social deficits observed in neuropsychiatric disorders known to have anatomical abnormalities of the CC.

### Limitations and Future Directions

The small study sample size ( $k=10$ ) makes conclusions concerning moderating factors less certain. Similarly, as in any meta-analysis, the heterogeneity of study methods and samples complicate interpretation of moderating factors. As additional studies are being completed, meta-regression will become more powerful and may uncover additional moderators of the observed effect sizes. Several studies did not include Witelson subdivisions, reducing the ability to statistically examine finer grained differences among CC regions. It is also possible that differences in the magnitude of effects across broad regions and Witelson subdivisions are simply due to sampling error and do not represent real differences, although the pattern of

findings appeared congruent with other results in autism research. Additional imaging studies, using diffusion tensor imaging and tractography, may also be helpful for determine which fiber tracts are most responsible for CC reductions.

Despite evidence suggesting moderate reductions in CC area at the group level, not all individuals with autism exhibit reduction in the size of this structure. Coupling larger databases and statistical methods for determining the presence of unique sub-groups, such as mixture modeling, may be useful for uncovering distinct patterns of CC reduction among autism patients. Inclusion of a broader spectrum of autism patients may also be helpful for uncovering CC sub-groups. In turn, these sub-groups may serve as endophenotypes for further neurochemical and genetic exploration.

The present analyses did not include non-autism developmentally delayed controls. Without these controls it is difficult to ascertain whether the CC reduction is specific to autism. In fact, studies of other neuropsychiatric disorders have reported alterations of CC size (65). Further investigations including well-matched psychiatric controls will be useful for determining the specificity of these findings to autism. As the present analysis included only cross-sectional studies, it is difficult to ascertain whether the observed relationship between increasing age and larger reductions in total CC area is an artifact of study differences. Further, cross-sequential and longitudinal studies will be helpful for determining CC reductions across the life span. Growth mixture modeling may be useful for identifying distinct patterns of developmental changes in CC structure and for determining whether rostral brain abnormalities are the primary basis of dysfunction. This is particularly relevant since recent imaging studies in autism have shown that the most abnormal aspect of brain development in this disorder is often the time course and trajectory rather the final product (2,39).

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## References

\*indicates inclusion in the meta-analysis

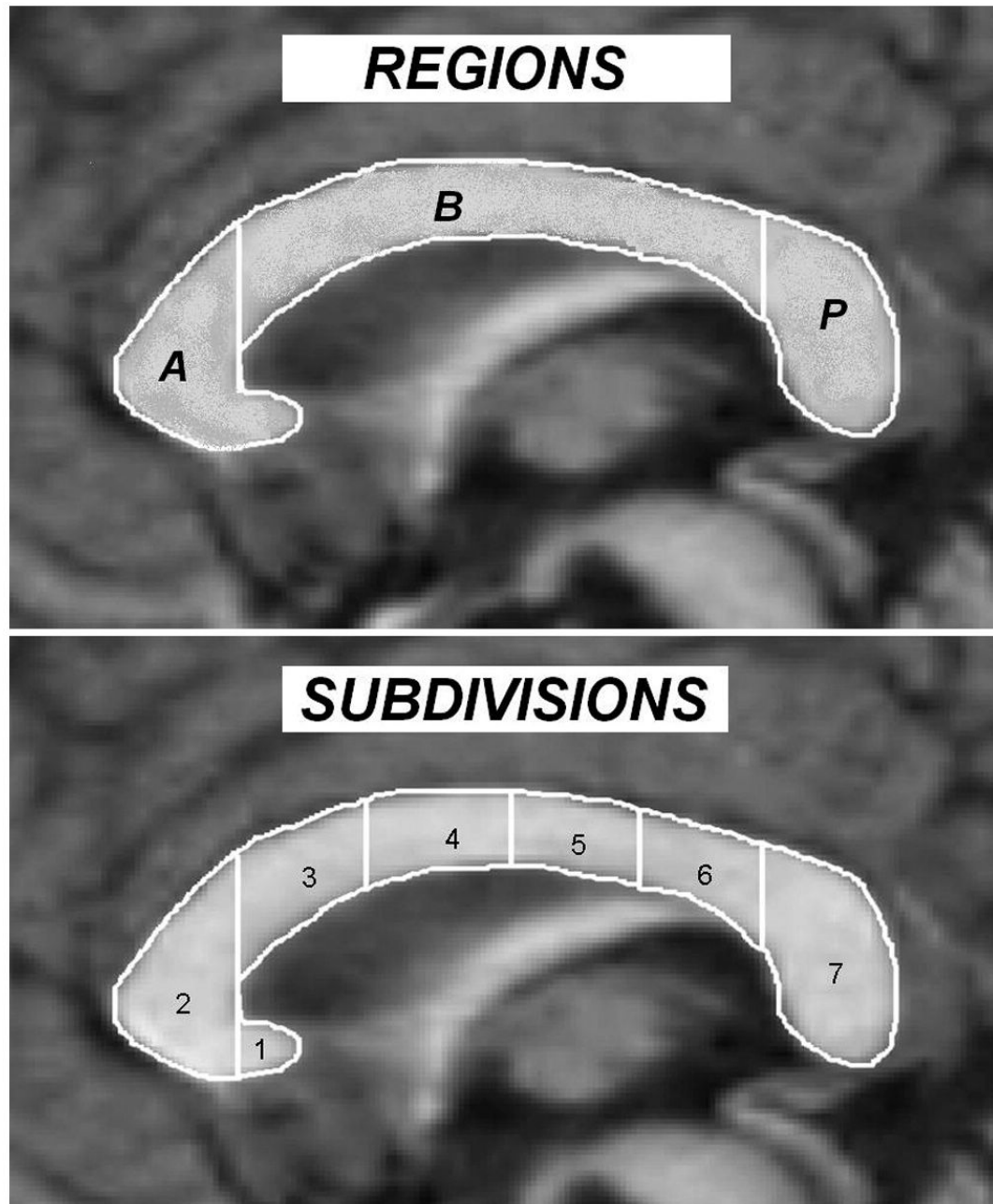
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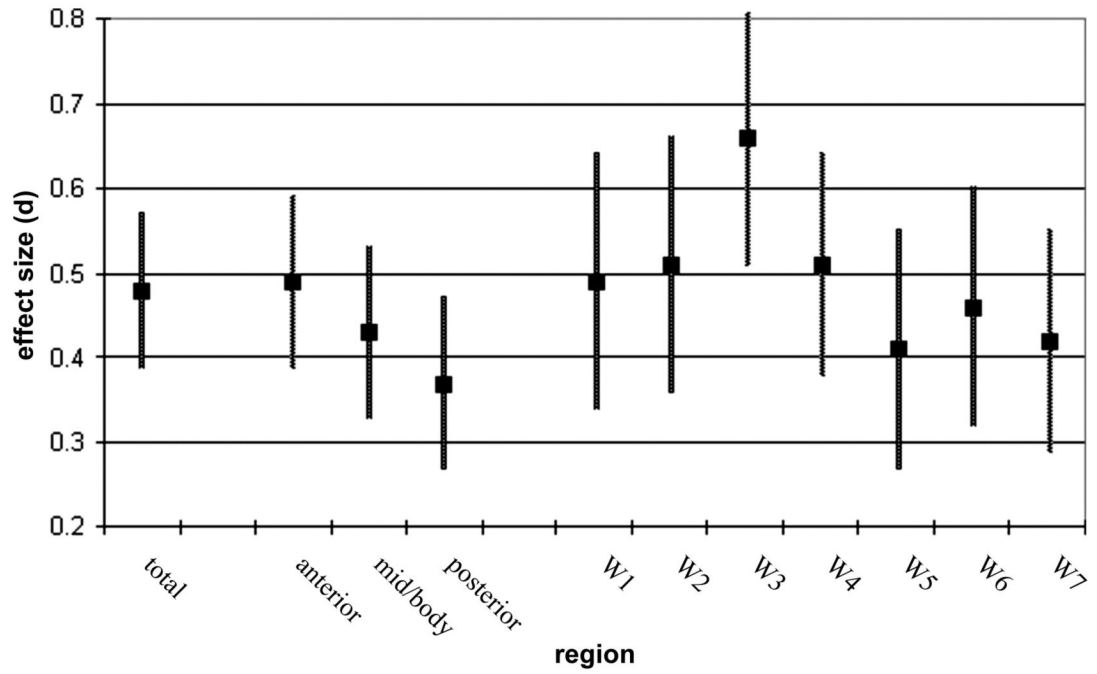
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**Figure 1.**

Corpus callosum regions and Witelson subdivisions.

Note. A=Anterior, B=Body, P=Posterior; 1=rostrum, 2=genu, 3=rostral body, 4=anterior midbody, 5=posterior midbody, 6=isthmus, 7=splenium.



**Figure 2.** Weighted mean effect sizes ( $\pm$  SE) by total, region, and Witelson subdivision.

Table 1

## Demographics and Selected Study Characteristics

Study	Year	Autism n	Control n	Autism % Male	Control % Male	Autism Age M (SD)	Control Age M (SD)	Functional Level <sup>a</sup>	Magnetic Field	Region Method	ES Corrected for Brain Size <sup>b</sup>	Method Index <sup>c</sup>	Study ES (95% CI)
Gaffney (34)	1987	13	35	77	60	11.30 (4.70)	12.00 (5.20)	Mixed	0.5T	no regions	no	6.5	.27 (-.37-.90)
Egaas (27)	1995	51	51	88.2	88.2	15.50 (10.00)	15.50 (9.90)	Mixed	1.5 T	broad regions	no	9.5	.33 (-.07-.72)
Piven (24)	1997	35	36	74.3	55.6	18.00 (4.50)	20.20 (3.80)	Mixed	1.5T	broad regions	yes	14	.31 (-.16-.77)
Manes (26)	1999	27	17	81	65	14.30 (6.80)	11.80 (5.00)	Low	1.5T	Witelson	yes	9	.87 (.22-1.49)
Elia (33)	2000	22	11	100	100	10.92 (4.02)	10.86 (2.85)	Low	0.5T	no regions	no	7.5	.16 (-.57-.88)
Hardan (25)	2000	22	22	100	100	22.40 (10.10)	22.40 (10.00)	High	1.5T	Witelson	yes	14	.64 (.02-1.23)
Rice (32)	2005	12	8	100	100	12.42 (4.32)	12.50 (3.46)	High	1.5T	modified Witelson	yes	13	.44 (-.48-1.33)
Boger- Meddido (28)	2006	29	26	89.7	69	3.90 (.32)	3.90 (.53)	Mixed	1.5T	Witelson	no	12.5	.53 (-.02-1.06)
Vidal (23)	2006	24	26	100	100	10.00 (3.30)	11.00 (2.50)	High	3.0T	modified Witelson	yes	14	.75 (.15-1.29)
Just (17)	2007	18	18	94.4	83.3	27.10 (11.90)	24.50 (9.90)	High	1.5T	Witelson	yes	14	.69 (.01-1.35)

Note.

<sup>a</sup> refers to the functional level of participants (low=study text indicated low functioning participants or majority of IQs <70, high=study text indicated all participants were high functioning, IQ>70, mixed=a combination of low and high functioning participants included in the study).

<sup>b</sup> refers to whether the effect size (ES) value was corrected for total brain/intracranial volume or uncorrected. In some cases, total brain volume or intracranial volume corrections were reported but the effect size could only be computed from the uncorrected M's and sd's.

<sup>c</sup> Method index ranges from 0-15 with higher numbers indicating better study reporting. 95% CI=95% confidence interval of the Cohen's d effect size. unadjusted for covariates or matched pairs.



Meta-analytic statistics for each classification and corpus callosum region or sub-division.

**Table 2**

Classification	Region	k effect sizes	Md	M	Weighted M	95% CI	z	Q	Fail Safe N
Total CC Area		10	.48	.50	.48	.30-.66	5.17 <sup>a</sup>	5.12 <sup>b</sup>	86
Major Regions									
	Anterior	8	.45	.52	.49	.30-.69	4.93 <sup>a</sup>	4.52 <sup>b</sup>	70
	Mid/Body	8	.41	.46	.43	.24-.63	4.35 <sup>a</sup>	5.33 <sup>b</sup>	61
	Posterior	8	.40	.37	.37	.18-.57	3.78 <sup>a</sup>	1.97 <sup>b</sup>	51
Witelson									
	W1: Rostrum	5	.41	.41	.49	.20-.77	3.32 <sup>a</sup>	5.17 <sup>b</sup>	44
	W2: Genu	5	.55	.55	.51	.22-.80	3.47 <sup>a</sup>	6.87 <sup>b</sup>	46
	W3: Rostral Body	5	.52	.60	.66	.37-.95	4.47 <sup>a</sup>	4.70 <sup>b</sup>	61
	W4: Anterior Midbody	6	.46	.49	.51	.25-.76	3.88 <sup>a</sup>	6.87 <sup>b</sup>	55
	W5: Posterior Midbody	5	.52	.41	.41	.15-.68	3.07 <sup>a</sup>	5.22 <sup>b</sup>	36
	W6: Isthmus	5	.26	.50	.46	.19-.73	3.39 <sup>a</sup>	7.73 <sup>b</sup>	41
	W7: Splenium	6	.46	.39	.42	.16-.67	3.41 <sup>a</sup>	1.46 <sup>b</sup>	44

Note. Md=median, M=mean, Q=homogeneity of effect sizes statistic with chi-square distribution. Positive effect sizes indicate a lower value in autism. All values are derived from fixed effects analysis. Fail safe N refers to the number of additional studies with null effects (d=0.00) needed to bring the observed weighted mean effect size down to a negligible effect size d=.05.

<sup>a</sup> p<.001

<sup>b</sup> p>.10.