Brain anatomy of autism spectrum disorders I. Focus on corpus callosum

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This brief review aims to examine the structural magnetic resonance imaging (sMRI) studies on corpus callosum in autism spectrum disorders (ASD) and discuss the clinical and demographic factors involved in the interpretation of results.

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Key words: autism spectrum disorders (ASD), corpus callosum, magnetic resonance imaging (MRI), volumes.

Autism spectrum disorders (ASD) are a heterogeneous group of neurodevelopmental pathologies whose diagnosis is based on the behavioural symptoms (Muratori et al. 2011) and whose intervention strategies aimed at improving socio-communicative skills as well as daily life abilities (Bellani et al. 2011). The neuroanatomical correlates of ASD are not fully elucidated. However, consistent findings based on structural magnetic resonance imaging (sMRI) data reported widespread cerebral abnormalities that include differences between ASD patients and controls in total brain volume, fronto-parieto-temporal and cerebellar regions. Moreover, a replicated altered corpus callosum (CC) size has been reported in the first sMRI analyses (for a review, see Brambilla et al. 2003). In particular, the altered CC has been considered as an anatomical substrate of processing and integration deficits peculiar to ASD, supporting the hypothesis of abnormal cortical connectivity in autism (Just et al. 2007). The CC is the largest commissural white matter (WM) tract in the human brain, and is conventionally divided into anterior CC, which comprises the rostrum, genu, rostral body, anterior mid-body and posterior CC, which includes the posterior mid-body, isthmus and splenium (Witelson, 1989). This primary WM structure connects homologous and heterotopic cortical areas of the two cerebral hemispheres and it is thought to be involved in motor and sensory integration as well as in higher cognitive function, including abstract reasoning, problem solving, ability to generalize, planning, social skills, attention, arousal, language comprehension and expression of syntax and pragmatics, emotion, memory (Paul et al. 2007). Recent investigations have employed a three-dimensional volumetric measurement of CC in ASD and frequently reported a reduction in the overall structure (Hardan et al. 2009; McAlonan et al. 2009; Duan et al. 2010; Anderson et al. 2011; Frazier et al.
Table 1. Studies investigating CC volumetry in patients with ASD compared with typically developing control subjects

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Age years (SD)</th>
<th>Full-scale IQ</th>
<th>MRI methods</th>
<th>Significant findings in ASD relative to controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbert et al. (2004)</td>
<td>13 AD</td>
<td>9.0 (0.9)</td>
<td>PIQ &gt; 80</td>
<td>Quantitative volumetric</td>
<td>No differences in CC volume</td>
</tr>
<tr>
<td></td>
<td>21 DLD</td>
<td>8.2 (1.6)</td>
<td>PIQ &gt; 80</td>
<td>analysis, 1.5 T</td>
<td></td>
</tr>
<tr>
<td></td>
<td>29 TD</td>
<td>9.1 (1.2)</td>
<td>n.r.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waiter et al. (2004)</td>
<td>16 ASD</td>
<td>15.4 (2.24)</td>
<td>100.4 (21.7)</td>
<td>VBM, 1.5 T</td>
<td>No differences in CC volume</td>
</tr>
<tr>
<td></td>
<td>16 TD</td>
<td>15.5 (1.6)</td>
<td>99.7 (18.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waiter et al. (2005)</td>
<td>15 ASD</td>
<td>15.2 (2.2)</td>
<td>100.5 (22.4)</td>
<td>VBM, 1.5 T</td>
<td>Reduction in CC volume</td>
</tr>
<tr>
<td></td>
<td>16 TD</td>
<td>15.5 (1.6)</td>
<td>99.7 (18.3)</td>
<td></td>
<td>particularly in the posterior regions</td>
</tr>
<tr>
<td>Vidal et al. (2006)</td>
<td>24 HFA</td>
<td>10.0 (3.3)</td>
<td>95.9 (11.5)</td>
<td>Three-dimensional surface</td>
<td>Reduction in the splenium and genu of CC</td>
</tr>
<tr>
<td></td>
<td>26 TD</td>
<td>11.0 (2.5)</td>
<td>104.8 (11.7)</td>
<td>models, 3 T</td>
<td></td>
</tr>
<tr>
<td>Alexander et al. (2007)</td>
<td>43 ASD</td>
<td>16.2 (6.7)</td>
<td>PIQ 107.5 (13.0)</td>
<td>DTI, 3.0 T</td>
<td>Reduction in CC volume, particularly in the</td>
</tr>
<tr>
<td></td>
<td>34 TD</td>
<td>16.4 (6.0)</td>
<td>PIQ 112.8 (12.1)</td>
<td></td>
<td>anterior regions</td>
</tr>
<tr>
<td>Bonilha et al. (2008)</td>
<td>12 AD</td>
<td>12.4 (4)</td>
<td>n.r.</td>
<td>VBM, 2.0 T</td>
<td>No differences in CC volume</td>
</tr>
<tr>
<td></td>
<td>16 TD</td>
<td>13.2 (5)</td>
<td>n.r.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ke et al. (2008)</td>
<td>17 HFA</td>
<td>8.9 (2.0)</td>
<td>108.8 (19.1)</td>
<td>VBM, 1.5 T</td>
<td>No differences in CC volume</td>
</tr>
<tr>
<td></td>
<td>15 TD</td>
<td>9.7 (1.7)</td>
<td>109.8 (19.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hardan et al. (2007)</td>
<td>22 ASD</td>
<td>10.7 (1.4)</td>
<td>95.1 (20.4)</td>
<td>ROI manual</td>
<td>Reduction in CC volume</td>
</tr>
<tr>
<td></td>
<td>23 TD</td>
<td>10.5 (1.4)</td>
<td>116.2 (13.2)</td>
<td>tracing, 1.5 T</td>
<td></td>
</tr>
<tr>
<td>Keary et al. (2009)</td>
<td>32 ASD</td>
<td>19.8 (10.2)</td>
<td>102.9 (13.6)</td>
<td>ROI manual</td>
<td>Reduction in CC volume</td>
</tr>
<tr>
<td></td>
<td>34 TD</td>
<td>18.6 (9.1)</td>
<td>104.0 (10.5)</td>
<td>tracing, 1.5 T</td>
<td></td>
</tr>
<tr>
<td>McAlonan et al. (2009)</td>
<td>18 HFA</td>
<td>11.6 (2.9)</td>
<td>VIQ 114.8 (19.1)</td>
<td>VBM, 1.5 T</td>
<td>Reduction in the genu of CC in HFA and ASP</td>
</tr>
<tr>
<td></td>
<td>18 ASP</td>
<td>11.2 (2.5)</td>
<td>VIQ 109.8 (16.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>54 TD</td>
<td>10.7 (2.7)</td>
<td>VIQ 117.1 (18.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duan et al. (2010)</td>
<td>30 ASD</td>
<td>Age range: 3–30</td>
<td>≥ 40</td>
<td>ROI manual</td>
<td>Reduction in CC volume and in all its sub-regions</td>
</tr>
<tr>
<td></td>
<td>28 TD</td>
<td>Age range: 3–30</td>
<td>n.r.</td>
<td>tracing, 1.5 T</td>
<td></td>
</tr>
<tr>
<td>Ecker et al. (2010)</td>
<td>22 ASD</td>
<td>27 (7)</td>
<td>104 (15)</td>
<td>VBM, 3.0 T</td>
<td>No differences in CC volume</td>
</tr>
<tr>
<td></td>
<td>22 TD</td>
<td>28 (7)</td>
<td>111 (10.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toal et al. (2010)</td>
<td>26 AD</td>
<td>30 (8)</td>
<td>84 (23)</td>
<td>VBM, 1.5 T</td>
<td>No differences in CC volume</td>
</tr>
<tr>
<td></td>
<td>39 ASP</td>
<td>32 (12)</td>
<td>106 (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>33 TD</td>
<td>32 (9)</td>
<td>105 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson et al. (2011)</td>
<td>53 HFA</td>
<td>22.4 (7.2)</td>
<td>PIQ 101.3 (16.5)</td>
<td>Automated volumetric</td>
<td>Reduction in CC volume</td>
</tr>
<tr>
<td></td>
<td>39 TD</td>
<td>21.1 (6.5)</td>
<td>PIQ 114.2 (13.9)</td>
<td>segmentation, 3.0 T</td>
<td></td>
</tr>
<tr>
<td>Cheng et al. (2011)</td>
<td>25 ASD</td>
<td>13.7 (2.5)</td>
<td>101.6 (18.9)</td>
<td>VBM, 1.5 T</td>
<td>No differences in CC volume</td>
</tr>
<tr>
<td></td>
<td>25 TD</td>
<td>13.5 (2.1)</td>
<td>109.0 (9.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hong et al. (2011)</td>
<td>18 HFA</td>
<td>8.7 (2.2)</td>
<td>105.2 (21.1)</td>
<td>ROI manual</td>
<td>No differences in overall CC volume and its</td>
</tr>
<tr>
<td></td>
<td>16 TD</td>
<td>9.8 (1.9)</td>
<td>106.1 (20.1)</td>
<td>tracing, 1.5 T</td>
<td>sub-regions</td>
</tr>
<tr>
<td>Mengotti et al. (2011)</td>
<td>20 AD</td>
<td>7.0 (2.7)</td>
<td>Evaluated, but</td>
<td>DTI and VBM, 1.5 T</td>
<td>No differences in CC volume</td>
</tr>
<tr>
<td></td>
<td>22 TD</td>
<td>7.7 (2.0)</td>
<td>n.r.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riva et al. (2011)</td>
<td>21 LFASD</td>
<td>6.6 (2.5)</td>
<td>52.5 (9.8)</td>
<td>VBM, 1.5 T</td>
<td>No differences in CC volume</td>
</tr>
<tr>
<td></td>
<td>21 TD</td>
<td>6.10 (2.1)</td>
<td>normal IQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thomas et al. (2011)</td>
<td>12 HFA</td>
<td>28.5 (9.7)</td>
<td>106.9 (10.5)</td>
<td>DTI, 3.0 T</td>
<td>Reduction in the body of CC</td>
</tr>
<tr>
<td></td>
<td>18 TD</td>
<td>22.4 (4.1)</td>
<td>111.6 (9.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calderoni et al. (2012)</td>
<td>38 ASD</td>
<td>4.4 (1.5)</td>
<td>72 (20)</td>
<td>VBM, 1.5 T</td>
<td>No differences in CC volume</td>
</tr>
<tr>
<td></td>
<td>38 controls (19 with DD, 19 TD)</td>
<td>4.4 (1.6)</td>
<td>73 (25)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2012), or in one or more components of this axonal pathway, including the anterior (Alexander et al. 2007; Keary et al. 2009; Thomas et al. 2011), the posterior sub-regions (Waiter et al. 2005) or some of the anterior and posterior regions contemporaneously (Vidal et al. 2006). The reductions in the CC volume is present over a wide age-range, since it is reported in ASD studies involving children (Vidal et al. 2006; Hardan et al. 2009; McAlonan et al. 2009; Frazier et al. 2012), adolescents (Waiter et al. 2004, 2005; Alexander et al. 2007) and adults (Keary et al. 2009; Ecker et al. 2010; Anderson et al. 2011; Thomas et al. 2011). On the other hand, the sparse literature on CC volume in low-functioning ASD (Riva et al. 2011) prevents us from drawing inferences about the influence of IQ on CC volume and calls for further investigation. Only a relatively few studies did not reveal significant CC volume differences between ASD patients and typically developing controls; in particular, this finding has been reported more often in voxel-based morphometry (Waiter et al. 2004; Bonilha et al. 2008; Ke et al. 2008; Ecker et al. 2010; Toal et al. 2010; Cheng et al. 2011; Mengotti et al. 2011; Calderoni et al. 2012) than in region of interest-based (Hong et al. 2011) analyses. Notably, to our knowledge, there have been no published studies reporting volumetric increase of CC (Table 1). Anyway, till date, few papers have examined the relationship between demographic клинических данных и CC volume in ASD patients. Interestingly, positive correlations of age with total CC volume were observed in ASD subjects when a longitudinal design was performed (Frazier et al. 2012), whereas a cross-sectional approach failed to detect such relationship (Alexander et al. 2007). In addition, volume reduction in the CC has been found to correlate with core ASD features such as social deficits, repetitive behaviours and sensory abnormalities (Frazier et al. 2012), as well as executive function and complex motor tasks deficits (Keary et al. 2009).

In sum, although there is more evidence to support the notion that the CC volume, especially its anterior sectors, is decreased in ASD, there are some suggestions that no differences relative to controls occurs. Specifically, the CC volume reduction may be related to altered patterns of connectivity between brain areas, and in turn it might be responsible for some of the cardinal behavioural impairments of ASD. However, a number of crucial questions remain unanswered: volumetric alterations of the CC are specific to ASD or are a more general marker of abnormal brain development shared with other neuropsychiatric disorders? What is the relationship between alterations of the CC volume and demographic and clinical variables such as age, gender, handedness, intellectual functioning, severity of symptoms, psychiatric comorbidity, psychotropic medications? What is the contribution of different CC subdivisions to overall CC volume alterations? Do the CC volume alterations persist into adulthood? What are the underlying neuro-pathological changes (e.g. reduction in number and/ or size of axons, impaired myelination, excessive synaptic pruning) responsible for decreased CC volume? Future dedicated studies should aim to address these issues more specifically.

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Conflict of Interest
None.

Ethical Standards
The authors declare that no human or animal experimentation was conducted for this work.

References


