This Section of *Epidemiology and Psychiatric Sciences* regularly appears in each issue of the Journal to describe relevant studies investigating the relationship between neurobiology and psychosocial psychiatry in major psychoses. The aim of these Editorials is to provide a better understanding of the neural basis of psychopathology and clinical features of these disorders, in order to raise new perspectives in every-day clinical practice.

Paolo Brambilla, Section Editor and Michele Tansella, Editor EPS

# 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.

Received 7 February 2013; Revised 14 February 2013; Accepted 21 February 2013; First published online 26 March 2013

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 threedimensional 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.

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Study	Subjects	Age years (SD)	Full-scale IQ	MRI methods	Significant findings in ASD relative to controls
Herbert <i>et al.</i> (2004)	13 AD	9.0 (0.9)	PIQ > 80	Quantitative volumetric	No differences in CC
	21 DLD	8.2 (1.6)	PIQ > 80	analysis, 1.5 T	volume
	29 TD	9.1 (1.2)	n.r.		
Waiter et al.	16 ASD	15.4 (2.24)	100.4 (21.7)	VBM, 1.5 T	No differences in CC
(2004)	16 TD	15.5 (1.6)	99.7 (18.3)		volume
Waiter et al.	15 ASD	15.2 (2.2)	100.5 (22.4)	VBM, 1.5 T	Reduction in CC
(2005)	16 TD	15.5 (1.6)	99.7 (18.3)		volume, particularly in the posterior regions
Vidal <i>et al.</i>	24 HFA	10.0 (3.3)	95.9 (11.5)	Three-dimensional	Reduction in the
(2006)	26 TD	11.0 (2.5)	104.8 (11.7)	surface models, 3 T	splenium and genu of CC
Alexander	43 ASD	16.2 (6.7)	PIO 107.5 (13.0)	DTI, 3.0 T	Reduction in CC
et al. (2007)	34 TD	16.4 (6.0)	PIQ 112.8 (12.1)		volume, particularly in the anterior regions
Bonilha <i>et al.</i>	12 AD	12.4 (4)	n.r.	VBM, 2.0 T	No differences in CC
(2008)	16 TD	13.2 (5)	n.r.	,	volume
Ke et al.	17 HFA	8.9 (2.0)	108.8 (19.1)	VBM, 1.5 T	No differences in CC
(2008)	15 TD	9.7 (1.7)	109.8 (19.2)		volume
Hardan et al.	22 ASD	10.7 (1.4)	95.1 (20.4)	ROI manual	Reduction in CC
(2009)	23 TD	10.5 (1.4)	116.2 (13.2)	tracing, 1.5 T	volume
Keary et al.	32 ASD	19.8 (10.2)	102.9 (13.6)	ROI manual	Reduction in CC
(2009)	34 TD	18.6 (9.1)	104.0 (10.5)	tracing, 1.5 T	volume, particularly in the anterior regions
McAlonan	18 HFA	11.6 (2.9)	VIQ 114.8 (19.1)	VBM, 1.5 T	Reduction in the genu
et al. (2009)	18 ASP	11.2 (2.5)	VIQ 109.8 (16.2)		of CC in HFA and ASP
	54 TD	10.7 (2.7)	VIQ 117.1 (18.1)		
Duan et al.	30 ASD	Age range: 3–30	$\geq 40$	ROI manual	Reduction in CC
(2010)	28 TD	Age range: 3–30	n.r.	tracing, 1.5 T	volume and in all its sub-regions
Ecker et al.	22 ASD	27 (7)	104 (15)	VBM, 3.0 T	No differences in CC
(2010)	22 TD	28 (7)	111 (10.0)		volume
Toal et al.	26 AD	30 (8)	84 (23)	VBM, 1.5 T	No differences in CC
(2010)	39 ASP	32 (12)	106 (15)		volume
	33 TD	32 (9)	105 (12)		
Anderson	53 HFA	22.4 (7.2)	PIQ 101.3 (16.5)	Automated volumetric	Reduction in CC
et al. (2011)	39 TD	21.1 (6.5)	PIQ 114.2 (13.9)	segmentation, 3.0 T	volume
Cheng et al.	25 ASD	13.7 (2.5)	101.6 (18.9)	VBM, 1.5 T	No differences in CC
(2011)	25 TD	13.5 (2.1)	109.0 (9.5)		volume
Hong et al.	18 HFA	8.7 (2.2)	105.2 (21.1)	ROI manual	No differences in
(2011)	16 TD	9.8 (1.9)	106.1 (20.1)	tracing, 1.5 T	overall CC volume and its sub-regions
Mengotti	20 AD	7.0 (2.7)	Evaluated, but	DTI and VBM, 1.5 T	No differences in CC
et al. (2011)	22 TD	7.7 (2.0)	n.r.		volume
Riva et al.	21 LFASD	6.6 (2.5)	52.5 (9.8)	VBM, 1.5 T	No differences in CC
(2011)	21 TD	6.10 (2.1)	normal IQ		volume
Thomas <i>et al.</i>	12 HFA	28.5 (9.7)	106.9 (10.5)	DTI, 3.0 T	Reduction in the body
(2011)	18 TD	22.4 (4.1)	111.6 (9.9)		of CC
Calderoni	38 ASD (19 with	4.4 (1.5)	72 (20)	VBM, 1.5 T	No differences in CC
et al. (2012)	DD, 19 no DD)	4.4 (1.6)	73 (25)		volume
	38 controls				
	(19 with DD, 19 TD)				

Table 1. Studies investigating CC volumetry in patients with ASD compared with typically developing control subjects

Continued

Study	Subjects	Age years (SD)	Full-scale IQ	MRI methods	Significant findings in ASD relative to controls
Frazier <i>et al.</i> (2012)	23 ASD 23 TD	10.6; range: 8–12	94.6 (20.0) 116.2 (13.2)	ROI manual tracing, 1.5 T	Reduction in CC volume
		10.5; range: 7–13		Ū	
Frazier <i>et al.</i> (2012)*	18 ASD 19 TD	13.1; range: 9–15 12.4; range: 9–16	94.6 (20.0) 116.2 (13.2)	ROI manual tracing, 1.5 T	Reduction in CC volume, with the exception of rostral body

Table 1. Continued

AD, autistic disorder; ASD, autism spectrum disorders; ASP, Asperger's syndrome; DD, developmental delay; DLD, developmental language disorder; CC, corpus callosum; DTI, diffusion tensor imaging; HFA, high-functioning autism; LFA, low-functioning autism; no DD, without developmental delay; n.r., not reported; PIQ, performance IQ; ROI, region of interest; TD, typically developing control subjects; VBM, voxel-based morphometry. \*Follow-up study.

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/clinical data and 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 crosssectional 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 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, intellective 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 neuropathological 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.

### Acknowledgements

None.

## **Financial Support**

S. C. was partly supported by the Italian Ministry of Health and by Tuscany Region with the grant

'GR-2010-2317873'. F. M. and S. C. were partly supported by the European Union (The MICHELANGELO Project). The other authors received no specific grant from any funding agency, commercial or not-for-profit sectors.

#### **Conflict of Interest**

None.

## **Ethical Standards**

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

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