Epidemiology and Psychiatric Sciences (2013), **22**, 217–221. © Cambridge University Press 2013 NEUROBIOLOGY OF PSYCHOSIS
doi:10.1017/S2045796013000139

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

M. Bellani[1]*, S. Calderoni[2], F. Muratori[2,3] and P. Brambilla[4,5]

[1] *Department of Public Health and Community Medicine, Section of Psychiatry and Section of Clinical Psychology, Inter-University Center for Behavioural Neurosciences (ICBN), University of Verona, Verona, Italy*
[2] *IRCCS Stella Maris Foundation, Pisa, Italy*
[3] *Department of Child Neurology and Psychiatry, University of Pisa, Pisa, Italy*
[4] *Department of Experimental Clinical Medicine, Inter-University Center for Behavioural Neurosciences (ICBN), University of Udine, Udine, Italy*
[5] *Department of Psychiatry and Behavioral Sciences, University of Texas Medical School at Houston, TX, USA*

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 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.*

* Address for correspondence: Dr. M. Bellani, Department of Public Health and Community Medicine, Section of Psychiatry and Section of Clinical Psychology, University of Verona, Piazzale L.A. Scuro 10, 37134 Verona, Italy.
(Email: marcella.bellani@univr.it)

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

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

Continued

Table 1. *Continued*

Study	Subjects	Age years (SD)	Full-scale IQ	MRI methods	Significant findings in ASD relative to controls
Frazier *et al.* (2012)	23 ASD 23 TD	10.6; range: 8–12 10.5; range: 7–13	94.6 (20.0) 116.2 (13.2)	ROI manual tracing, 1.5 T	Reduction in CC volume
Frazier *et al.* (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

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 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 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.

References

Alexander AL, Lee JE, Lazar M, Boudos R, DuBray MB, Oakes TR, Miller JN, Lu J, Jeong EK, McMahon WM, Bigler ED, Lainhart JE (2007). Diffusion tensor imaging of the corpus callosum in autism. *Neuroimage* **34**, 61–73.

Anderson JS, Druzgal TJ, Froehlich A, DuBray MB, Lange N, Alexander AL, Abildskov T, Nielsen JA, Cariello AN, Cooperrider JR, Bigler ED, Lainhart JE (2011). Decreased interhemispheric functional connectivity in autism. *Cerebral Cortex* **21**, 1134–1146.

Bellani M, Fornasari L, Chittaro L, Brambilla P (2011). Virtual reality in autism: state of the art. *Epidemiology and Psychiatric Sciences* **20**, 235–238.

Bonilha L, Cendes F, Rorden C, Eckert M, Dalgalarrondo P, Li LM, Steiner CE (2008). Gray and white matter imbalance–typical structural abnormality underlying classic autism? *Brain and Development* **30**, 396–401.

Brambilla P, Hardan A, di Nemi SU, Perez J, Soares JC, Barale F (2003). Brain anatomy and development in autism: review of structural MRI studies. *Brain Research Bulletin* **61**, 557–569.

Calderoni S, Retico A, Biagi L, Tancredi R, Muratori F, Tosetti M (2012). Female children with autism spectrum disorder: an insight from mass-univariate and pattern classification analyses. *Neuroimage* **59**, 1013–1022.

Cheng Y, Chou KH, Fan YT, Lin CP (2011). ANS: aberrant neurodevelopment of the social cognition network in adolescents with autism spectrum disorders. *PLoS ONE* **6**, e18905.

Duan Y, He Q, Yin X, Gu X, Karsch K, Miles J (2010). Detecting corpus callosum abnormalities in autism subtype using planar conformal mapping. *International Journal for Numerical Methods in Biomedical Engineering* **26**, 164–175.

Ecker C, Rocha-Rego V, Johnston P, Mourao-Miranda J, Marquand A, Daly EM, Brammer MJ, Murphy C, Murphy DG; MRC AIMS Consortium (2010). Investigating the predictive value of whole-brain structural MR scans in autism: a pattern classification approach. *NeuroImage* **49**, 44–56.

Frazier TW, Keshavan MS, Minshew NJ, Hardan AY (2012). A two-year longitudinal MRI study of the corpus callosum in autism. *Journal of Autism and Developmental Disorders* **42**, 2312–2322.

Hardan AY, Pabalan M, Gupta N, Bansal R, Melhem NM, Fedorov S (2009). Corpus callosum volume in children with autism. *Psychiatry Research: Neuroimaging* **174**, 57–61.

Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin JJ, Sanders HA, Kennedy DN, Caviness Jr. VS (2004). Localization of white matter volume increase in autism and developmental language disorder. *Annals of Neurology* **55**, 530–540.

Hong S, Ke X, Tang T, Hang Y, Chu K, Huang H, Ruan Z, Lu Z, Tao G, Liu Y (2011). Detecting abnormalities of corpus callosum connectivity in autism using magnetic resonance imaging and diffusion tensor tractography. *Psychiatry Research: Neuroimaging* **194**, 333–339.

Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ (2007). Functional and anatomical cortical underconnectivity in autism: evidence from an fMRI study of an executive function task and corpus callosum morphometry. *Cerebral Cortex* **17**, 951–961.

Ke X, Hong S, Tang T, Zou B, Li H, Hang Y, Zhou Z, Ruan Z, Lu Z, Tao G, Liu Y (2008). Voxel-based morphometry study on brain structure in children with high-functioning autism. *Neuroreport* **19**, 921–925.

Keary CJ, Minshew NJ, Bansal R, Goradia D, Fedorov S, Keshavan MS, Hardan AY (2009). Corpus callosum volume and neurocognition in autism. *Journal of Autism and Developmental Disorders* **39**, 834–841.

McAlonan GM, Cheung C, Cheung V, Wong N, Suckling J, Chua SE (2009). Differential effects on white-matter systems in high-functioning autism and Asperger's syndrome. *Psychological Medicine* **39**, 1885–1893.

Mengotti P, D'Agostini S, Terlevic R, De Colle C, Biasizzo E, Londero D, Ferro A, Rambaldelli G, Balestrieri M, Zanini S, Fabbro F, Molteni M, Brambilla P (2011). Altered white matter integrity and development in children with autism: a combined voxel-based morphometry and diffusion imaging study. *Brain Research Bulletin* **84**, 189–195.

Muratori F, Narzisi A, Tancredi R, Cosenza A, Calugi S, Saviozzi I, Santocchi E, Calderoni S (2011). The CBCL 1.5-5 and the identification of preschoolers with autism in Italy. *Epidemiology and Psychiatric Sciences* **20**, 329–338.

Paul LK, Brown WS, Adolphs R, Tyszka JM, Richards LJ, Mukherjee P, Sherr EH (2007). Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. *Nature Reviews Neuroscience* **8**, 287–299.

Riva D, Bulgheroni S, Aquino D, Di Salle F, Savoiardo M, Erbetta A (2011). Basal forebrain involvement in low-functioning autistic children: a voxel-based morphometry study. *AJNR. American Journal of Neuroradiology* **32**, 1430–1435.

Thomas C, Humphreys K, Jung KJ, Minshew N, Behrmann M (2011). The anatomy of the callosal and visual-association pathways in high-functioning autism: a DTI tractography study. *Cortex* **47**, 863–873.

Toal F, Daly EM, Page L, Deeley Q, Hallahan B, Bloemen O, Cutter WJ, Brammer MJ, Curran S, Robertson D, Murphy C, Murphy KC, Murphy DG (2010). Clinical and anatomical heterogeneity in autistic spectrum disorder: a structural MRI study. *Psychological Medicine* **40**, 1171–1181.

Vidal CN, Nicolson R, DeVito TJ, Hayashi KM, Geaga JA, Drost DJ, Williamson PC, Rajakumar N, Sui Y, Dutton RA,

Toga AW, Thompson PM (2006). Mapping corpus callosum deficits in autism: an index of aberrant cortical connectivity. *Biological Psychiatry* **60**, 218–225.

Waiter GD, Williams JH, Murray AD, Gilchrist A, Perrett DI, Whiten A (2004). A voxel-based investigation of brain structure in male adolescents with autistic spectrum disorder. *NeuroImage* **22**, 619–625.

Waiter GD, Williams JH, Murray AD, Gilchrist A, Perrett DI, Whiten A (2005). Structural white matter deficits in high-functioning individuals with autistic spectrum disorder: a voxel-based investigation. *NeuroImage* **24**, 455–461.

Witelson SF (1989). Hand and sex differences in the isthmus and genu of the human corpus callosum: a postmortem morphological study. *Brain* **112**, 799–835.