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Paolo Brambilla, *Section Editor*

Brain anatomy of autism spectrum disorders II. Focus on amygdala

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, 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 encompasses the key findings of structural Magnetic Resonance Imaging (sMRI) research on amygdala volume in autism spectrum disorders (ASD). We also highlight the possible correlation between the autistic behavioural phenotype and amygdala alteration.

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The lack of reliable, specific brain biomarkers for autism spectrum disorders (ASD) results in a diagnosis based on behavioural criteria (Muratori *et al.* 2011). However, recent structural magnetic resonance imaging (sMRI) studies provide new insights into the neuroanatomical substrate of ASD, suggesting the involvement of the corpus callosum and the fronto-parieto-temporal regions (Mengotti *et al.* 2011; Bellani *et al.* 2013). Among these latter, the amygdala is a relatively small subcortical brain region located in the anteromedial temporal lobe and included in the limbic system. It contains at least 13 distinct nuclei, among which four major nuclei (the lateral, basal, accessory basal and central nuclei) with unique patterns of connectivity with other brain regions. In particular, the central nucleus, a phylogenically primitive part, communicates mostly with brainstem and olfactory centres, while the basolateral nuclei are strongly connected to the neocortex. Besides its primary role of monitoring the environment for potential danger and modulating levels of vigilance, the amygdala plays a seminal contribution to social behaviour. Specifically, it is implicated in several cognitive functions, including social cognition, recognition of emotions, attribution of emotional valence to stimuli and regulation of the personal space. These findings have led researchers to postulate the 'amygdala theory of autism' since the amygdala may be primarily involved in the socio-emotional impairment peculiar of ASD subjects (Baron-Cohen *et al.* 2000).

* 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; paolo.brambilla@uniud.it)

Table 1. Summary of studies published between 2006–2012 investigating amygdala volumetry in patients with ASD compared with control subjects*

Study	Subjects	Age in years (S.D.)	Full-scale IQ	Field strength (T)	Significant findings in ASD relative to controls
Dziobek *et al.* (2006)	17 AS	41.4 (9.9)	113 (6)	n.r.	No differences in bilateral amygdala volume
	17 TD	40.2 (13.0)	115 (5)		
Nacewicz *et al.* (2006)	12 ASD	16.8 (4.5)	n.r.	3.0	No differences in bilateral amygdala volume
	12 TD	17.0 (2.9)	n.r.		
Nacewicz *et al.* (2006)	16 ASD	14.3 (4.7)	97 (26)	3.0	Reduction in bilateral amygdala volume, particularly in the older subgroup (>12.5 years)
	14 TD	13.7 (3.9)	122 (13)		
Palmen *et al.* (2006)	42 HFA	15.6 (5.3)	110.7 (16.9)	1.5	No differences in bilateral amygdala volume
	42 TD	15.3 (5.4)	107.6 (13.4)		
Corbett *et al.* (2009)	12 HFA	9.0 (1.6)	90.7 (13.8)	1.5	No differences in bilateral amygdala volume
	15 TD	9.2 (1.4)	115.7 (15.8)		
Mosconi *et al.* (2009)	50 ASD	2.7 (0.3)	53.8 (9.0)	1.5	Enlargement in bilateral amygdala volume
	11 DD	2.8 (0.4)	56.6 (16.9)		
	22 TD	2.5 (0.5)	105.8 (16.0)		
Mosconi *et al.* (2009)‡	31 ASD	5.0 (0.4)	56.6 (16.9)	1.5	Enlargement in bilateral amygdala volume
	6 DD	5.0 (0.5)	56.0 (6.8)		
	14 TD	4.6 (0.5)	112.3 (12.3)		
Schumann *et al.* (2009)	32 (m)AD	36 (7.2) months	58 (20)	1.5	Enlargement in bilateral amygdala volume in AD, particularly evident in (f)
	9 (f)AD	36 (4.7) months	57 (23)		
	6 (m)PDD-NOS	36 (9.1) months	93 (32)		
	3 (f)PDD-NOS	56 (6.1) months	63 (19)		
	28 (m)TD	34 (7.1) months	111 (17)		
	11 (f)PDD-NOS	37 (6.4) months	115 (15)		
Groen *et al.* (2010)	23 AD	15.1 (1.9)	99.5 (20.1)	1.5	Enlargement in right amygdala volume
	29 TD	15.6 (1.7)	104.9 (9.6)		
Kim *et al.* (2010)	31 ASD	6.5 (0.3)	70.9 (23.2)	1.5	Enlargement in bilateral amygdala volume (laterobasal subregions)
	20 TD	6.5 (0.4)	115.6 (13.9)		
Murphy *et al.* (2012)	32 AS	23 (11)	108 (13)	1.5	Enlargement in bilateral amygdala volume
	32 TD	23 (11)	111 (15)		
Nordahl *et al.* (2012)	85 ASD	36.8 (5.7) months	63.4 (22.1)	3.0	Enlargement in bilateral amygdala volume
	47 TD	36.9 (5.3) months	103.8 (11.8)		

Continued

Table 1. *Continued*

Study	Subjects	Age in years (S.D.)	Full-scale IQ	Field strength (T)	Significant findings in ASD relative to controls
Nordahl *et al.* (2012)‡	45 ASD 25 TD	49.0 (5.5) months 51.2 (4.9) months	n.r. n.r.	3.0	Enlargement in bilateral amygdala volume

*Due to editorials guideline of limited number of references, only the most recent MRI studies on amygdala in ASD were considered, starting from year 2006.
‡Follow-up study; ASD, autism spectrum disorders; TD, typically developing control subjects; RD, subjects with reading disorders; HFA, high-functioning autism; LFA, low-functioning autism; AD, autistic disorder; AS, Asperger syndrome; ADM, autistic disorder with macrocephaly; TDM, typically developing control subjects with macrocephaly PAD, parents of children with autistic disorder; (m), males; (f), females; PDD-NOS, Pervasive developmental disorder not otherwise specified; PIQ, performance IQ; n.r., not reported; DD, developmental delay.

However, the presence of amygdala structural abnormalities in ASD is unclear since previous research has produced conflicting results. Indeed, increased, decreased and preserved volumes have been shown in studies using manual tracing to define the amygdala morphology (8, 1 and 4 studies, respectively; see Table 1). Nonetheless, there is some evidence for age-related effects on amygdala volumes, confirmed by a recent meta-analysis of sMRI studies in ASD (Stanfield *et al.* 2008). Specifically, ASD toddlers and children frequently show significantly increased bilateral amygdala volumes relative to age-matched controls (Mosconi *et al.* 2009; Schumann *et al.* 2009; Kim *et al.* 2010; Nordahl *et al.* 2012), whereas older adolescents and adults either reduced (Nacewicz *et al.* 2006), or preserved size (Corbett *et al.* 2009; Dziobek *et al.* 2006; Nacewicz *et al.* 2006; Palmen *et al.* 2006). Despite the age of the subject population seems to be a critical factor, some heterogeneity in the rate of amygdala growth within the ASD population of the same age-range has been detected. Accordingly, a recent longitudinal study pointed to three ASD subgroups in the amygdala developmental time course between two and four years of age, i.e. (1) rapid growth, (2) slow growth, and (3) growth trajectories consistent with those of typically developing children (Nordahl *et al.* 2012). The behavioural correlates of different amygdala growth patterns, unfortunately, are not reported in this study. In contrast, very few papers performed a separate analysis by sex, showing more pronounced amygdala enlargement in female children with ASD (Schumann *et al.* 2009) compared with age- and gender-matched typically developing controls. These preliminary findings suggest a potential different pattern of amygdala development in ASD in accordance to gender.

Interestingly, a correlation between the severity of core ASD symptoms and amygdala anatomy has been detected in several studies, with a different trajectory in accordance to age. Indeed, a direct correlation between amygdala volumes and degree of social and communicative impairment has been found in toddlers (Munson *et al.* 2006; Schumann *et al.* 2009), and younger children with ASD (Kim *et al.* 2010). In contrast, smaller amygdalae associated with deficits of social reciprocity in older ASD children (Nacewitz *et al.* 2006) and with restricted-repetitive behaviour in adult subjects with Asperger syndrome (Dziobek *et al.* 2006).

In conclusion, there is evidence that amygdala volumes are enlarged in toddlers and younger children with ASD and correlate with social ability impairment. Nonetheless, some key issues remain to be clarified, specifically: (1) whether the onset of amygdala overgrowth in ASD is already present at birth or during

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the postnatal brain growth; (2) at which age the amygdala developmental trajectory decelerates in ASD, leading to attenuated differences with typically developing controls; (3) if gender and ASD phenotype (i.e., socio-communicative deficits) play a role on the above mentioned amygdala maturation. Only future prospective studies that follow over time, through multiple MRI scans, high-risk neonates well-characterized from the clinical point of view could provide insightful information into each of these research questions.

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Conflict of Interest

None.

Ethical Standards

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

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