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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 major depression II. Focus on amygdala

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Here, we briefly summarize the most consistent structural magnetic resonance imaging (MRI) studies on amygdala in major depression and debate the effects of clinical variables on amygdalar morphology.

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Major depressive disorder (MDD) has been associated with morphological changes of medial temporal lobe's structures, particularly of the amygdala, possibly being part of an altered limbic–thalamic–cortical circuitry (Zou *et al.* 2010; Bellani *et al.* 2010). This structure is part of the ventral limbic system and is functionally connected to the prefrontal cortex, cingulate gyrus and hypothalamus. It is a key component for affective modulation (such as negative emotions and fear), memory encoding and social behaviour (Baxter & Murray, 2002). Several magnetic resonance imaging (MRI) studies have found reduced amygdala volumes in patients suffering from depression (Sheline *et al.* 1998, 1999; Campbell *et al.* 2004; Hickie *et al.* 2007), specifically in children (Rosso *et al.* 2005), unmedicated (Caetano *et al.* 2004; Tang *et al.* 2007; Kronenberg *et al.* 2009), multiple episode (Bremner *et al.* 2000; Caetano *et al.* 2004; Hastings *et al.* 2004; Monkul *et al.* 2007), psychotic and female patients (Sheline *et al.* 1999; Hastings *et al.* 2004; Tang *et al.* 2007; Keller *et al.* 2008; Lorenzetti *et al.* 2009). In this regard, chronic or recurrent MDD patients are persistently exposed to stress-induced glucocorticoids, which may have neurotoxic effects, potentially leading to amygdala shrinkage (Hamidi *et al.* 2004). Interestingly, slight volume reductions of amygdalar grey matter have been shown over time without significant gross abnormalities (Frodl *et al.* 2008*a*, *b*), suggesting the presence of subtle microstructural processes occurring during a depression episode and after recovery. However, other structural investigations have shown preserved volumes (Mervaala *et al.* 2000; Munn *et al.* 2007; MacMaster *et al.* 2008), mainly in current non-suicidal patients (Monkul *et al.* 2007), in non-psychotic depressed patients (Keller *et al.* 2008) or in recovered patients (van Eijndhoven *et al.* 2009; Lorenzetti *et al.* 2010). Moreover, enlarged amygdalar volumes have also been reported (van Elst *et al.* 2000), particularly in subjects using antidepressants (Frodl *et al.* 2003; Weniger *et al.* 2006)

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Table 1. *Cross-sectional and follow-up studies investigating amygdalar volumetry in adult patients with MDD compared with healthy control subjects*

Study	HC	MDD subjects	Type of MDD	MRI methods	Significant findings
Sheline *et al.* (1998)	20	20 (F) outpatients, mean age: 54.0	Remission	Stereological methods, 1.5 T	Core amygdala: MDD < HC
Sheline *et al.* (1999)	24	24 (F) outpatients, 16 AD, mean age: 52.8	Recurrent	Stereological methods, 1.5 T	Core amygdala: MDD < HC
Bremner *et al.* (2000)	16	16 (10 M/6 F) outpatients, 16 AD, mean age: 43.0	Remission	ROI manual tracing, 1.5 T	R amygdala: MDD < HC
Mervaala *et al.* (2000)		34 (16M/18F) inpatients, mean age: 42.2	Drug-resistant	ROI manual tracing; 1.5 T	Total amygdala: MDD = HC MDD: R amygdala < L amygdala
van Elst *et al.* (2000)	20	17 (6 M/11 F), mean age: 32.8	Dysthymia	ROI manual tracing, 1.5 T	Total amygdala: MDD > HC
Von Gunten *et al.* (2000)	14	14 (6 M/8 F), 10 AD, mean age: 57.0	Recurrent	ROI manual tracing, 1.5 T	L amygdala: MDD < HC
Frodl *et al.* (2003)	57	57 (27 M/30 F) inpatients, 57 AD, mean age. 44.5	First episode and recurrent	ROI manual tracing, 1.5 T	Total amygdala: first episode MDD > HC and recurrent MDD recurrent MDD = HC
Caetano *et al.* (2004)	31	31 (7 M/24 F), mean age: 39.2	Current and remitted MDD episode	ROI manual tracing, 1.5 T	L Amygdala GM: MDD < HC total amygdala: current MDD = remitted MDD
Hastings *et al.* (2004)	18	18 (8 M/10 F) outpatients, mean age: 39.8	Current	ROI manual tracing, 1.5 T	R amygdala: MDD < HC only for females
Lange & Irle (2004)	17	17 (F) inpatients, mean age: 34.0	Current	Three dimensional MRI,1.5 T	Total amygdala: MDD > HC
Rosso *et al.* (2005)	24	20 (3 M/17 F), mean age: 15.3	Recent onset	ROI manual tracing, 1.5 T	Total amygdala: MDD < HC
Weniger *et al.* (2006)	23	21 (F) inpatients, 21 AD, mean age: 34.0	Recent onset	ROI manual tracing, 1.5 T	Total amygdala: MDD > HC
Hickie *et al.* (2007)	16	45 (15 M/30 F), mean age: 52.8	Current	ROI manual tracing, 1.5 T	Total amygdala: MDD < HC
Monkul *et al.* (2007)	17	17 (F), mean age: 34.4	Suicidal and non-suicidal	ROI manual tracing, 1.5 T	R amygdala: suicidal MDD > non- suicidal MDD total amygdala: non suicidal MDD = HC
Munn *et al.* (2007)	18 TP	26 (F) twins+ 24 HR (F), mean age: 20.6	Current and HR subjects	ROI manual tracing, 1.5 T	Total amygdala: MDD = HC
Tang *et al.* (2007)	13	14 (F), mean age: 29.5	First episode	VBM, 1.5 T	Total amygdala: MDD < HC
Frodl *et al.* (2008*a*)*	30	30 (11 M/19 F) inpatients. Baseline (t0): 29 AD, 3 years (t1): 25 AD, mean age: 45.0	Current MDD	ROI manual tracing, 1.5 T	Total amygdala: no significant decrease
Frodl *et al.* (2008*b*)*	30	38 (13 M/25 F) inpatients, baseline (t0): 37 AD 3 years (t1): 23 AD, mean age: 46.1	Current	VBM, 1.5 T	L amygdala grey matter: MDD < HC during the 3 year follow-up
Keller *et al.* (2008)	22	42 (19 M/23 F) outpatients, 24 AD, mean age: 36.5	Psychotic and non-psychotic	ROI manual tracing, 3 T	Total amygdala: psychotic MDD < HC non-psychotic MDD = HC.
MacMaster *et al.* (2008)	35	32 (12 M/20 F), mean age: 14.8	Current with familiar MDD	ROI manual tracing, 1.5 T	Total amygdala: MDD = HC

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Table 1. *Continued*

Study	HC	MDD subjects	Type of MDD	MRI methods	Significant findings
Kronenberg *et al.* (2009)	14	24 inpatients, mean age: 54.5	Current	ROI manual tracing, 1.5 T	Total amygdala: MDD < HC
van Eijndhoven *et al.* (2009)	20	40 (13 M/27 F) outpatients, mean age: 34.9	Current and recovered first episode	ROI manual tracing, 1.5 T	Total Amygdala: current first episode MDD > recovered MDD recovered MDD = HC
Lorenzetti *et al.* (2010)	31	56 (16 M/40 F) outpatients, 33 AD, mean age: 33.7	Current and remitted	ROI manual tracing, 1.5 T	L Amygdala: remitted MDD > current MDD and HC L amygdala: current MDD = HC R amygdala: current MDD = remitted MDD = HC

*Follow-up studies: AD, patients on antidepressants at the time of the MRI scanning; HC, healthy control subjects; HR, high risk; L, left; R, right; ROI, region of interest; T, twins; VBM, voxel-based-morphometry; M, male; F, female.

and in those with severe illness or at the early stage of the disease (Frodl *et al.* 2003, 2008*a*; Lange & Irle, 2004; Lorenzetti *et al.* 2010; Weniger *et al.* 2006).

In summary, although there is some evidence that amygdalar size is reduced in MDD patients, particularly in those with recurrent episodes (Hamilton *et al.* 2008; Lorenzetti *et al.* 2009), preserved and increased volumes have also been reported. The heterogeneity of the results summarized here (see Table 1) may in part be due to socio-demographical and clinical differences of the samples (age of onset, single or multiple episodes, familiar history of MDD, medication, psychotic symptoms and phases of the illness) (Hajek *et al.* 2009). Furthermore, the proximity of the amygdala to the head of the hippocampus makes the anatomical delineation of this structure difficult. Indeed, as reported in the meta-analysis by Campbell *et al.* (2004), MRI studies considering the amygdala–hippocampus complex revealed no significant differences between depressed and control subjects. In order to better clarify the role of amygdala for the pathophysiology of MDD, future MRI studies should explore amygdalar morphology in large sample of drug-naïve patients at their first episode of depression in comparison with matched healthy individuals, longitudinally following them after recovery.

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