Neurobiology of Psychosis. Clinical and Psychosocial Implications

This is a Section of *Epidemiologia e Psichiatria Sociale*, that regularly appears in each issue of this Journal to describe relevant neuroscience topics. In particular, studies investigating the relationship between neurobiology and psychosocial psychiatry in major psychoses will be debated. The aim of these short articles is to provide a better understanding of the neural basis of psychopathology and clinical features of these disorders in order to raise new perspective in every-day clinical practice.

Paolo Brambilla, *Section Editor* and Michele Tansella, *Editor* EPS

Brain anatomy of major depression I. Focus on hippocampus

MARCELLA BELLANI,[1] MONICA BAIANO,[2] PAOLO BRAMBILLA[3, 4]

[1]*Department of Public Health and Community Medicine, Section of Psychiatry and Clinical Psychology, Inter-University Center for Behavioural Neurosciences (ICBN), University of Verona, Verona (Italy)*
[2]*Center for Weight and Eating Disorders, Portogruaro (Italy)*
[3]*DPMSC, Section of Psychiatry, Inter-University Center for Behavioural Neurosciences (ICBN) University of Udine, Udine (Italy)*
[4]*Scientific Institute 'E. Medea', Udine (Italy)*

Abstract. Here we briefly summarize the most consistent structural MRI studies on hippocampus in major depression and debate the effects of clinical variables on hippocampal morphology.

KEY WORDS: major depressive disorder, volumes, MRI.

The hippocampus is part of the dorsal limbic system and is connected with critical regions for cognitive and emotional functioning, such as cingulate gyrus, entorhinal cortex, septal nuclei and brainstem. Alterations of neural networks involving the hippocampus have been associated with impaired emotional processes, memory and executive functions in major depression (Drevets *et al*., 2008; Sala *et al*., 2004). Furthermore, the hippocampus is crucial in regulating the activity of hypothalamic-pituitary-adrenal (HPA) axis and in producing glucocorticoids. The hippocampus itself is a target region for stress hormones, which are known to influence local neurogenesis and synaptic remodeling (Paizanis *et al*., 2007). To this regard, hypercortisolemia has often been found in major depression and may have neurotoxic effects, ultimately resulting in morphological changes of the hippocampus (Ballmaier *et al*., 2008).

Abnormally small hippocampal volumes have been shown in depressed subjects by several cross sectional magnetic resonance imaging (MRI) studies (Table I; for review Campbell *et al*., 2004), particularly in chronic, stressed and severely ill patients (Colla *et al*., 2007; Kronmuller *et al*., 2008; McKinnon *et al*., 2009; Vythilingam *et al*., 2002; Bearden *et al*., 2009). Therefore, recurrent exposure to stressful events or chronicity may be involved in hippocampal shrinkage in depression (Sala *et al*., 2004; Videbech & Ravnkilde, 2004). Interestingly, reduced hippocampal volumes were also found in healthy carriers of the L-allele of 5-HTTLPR gene (Frodl *et al*., 2008a), of the 66Met allele of the BDNF gene (Montag *et al*., 2009), as well as in juvenile

Address for correspondence: Dr. M. Bellani, Department of Public Health and Community Medicine, Section of Psychiatry and Clinical Psychology, University of Verona, Piazzale L.A. Scuro 10, 37134 Verona (Italy).
Fax: +39-045-8027498
E-mail: marcella.bellani@univr.it

Table I – *Cross-sectional and follow-up studies investigating hippocampal volumetry in adults with MDD compared to healthy control subjects.*

Study	Subjects	Type of MDD	MRI methods	Significant findings
Bremner *et al*., 2000	16 patients (10M/6F) Mean age: 43	MDD episode in remission	ROI manual tracing 1.5 T	Left HP: MDD < HC
Bell-McGinty *et al*., 2002	30 patients Aged between 59-78	Current MDD episode	VBM, 1.5 T	Right HP: MDD < HC
Shah *et al*., 2002	40 (26M/14F) in and outpatients Mean age: 48.3	(20) remitted MDD episode (20) treatment-resistant current MDD episode	VBM, 1.0 T	HP: MDD < HC
Vythilingam *et al*., 2002	32 (F) inpatients (21 with CA) Mean age: 33.3	Current MDD episode	ROI manual tracing, 1.5 T	Left HP: MDD with CA < MDD without CA and HC
Sheline *et al*., 2003	38 (F) patients Mean age: 50.8	Recurrent MDD episode in remission	ROI stereological estimation methods, 1.5 T	HP: MDD < HC
MacQueen *et al*., 2003	27 patients (13M/14F) Mean age: 30.3	First and multiple MDD episode	ROI stereological estimation methods, 1.5 T	HP: Multiple MDD < first episode MDD and HC
Caetano *et al*., 2004	31 patients (7M/24F) Mean age: 39.2	Current and remitted MDD episode	ROI manual tracing, 1.5 T	HP: Current MDD < remitted MDD
Neumeister *et al*., 2005	31 patients (8M/23F) Mean age: 40.1	Recurrent MDD in remission	ROI manual tracing, 3 T	Total and posterior HP: MDD < HC
Frodl *et al*., 2006	34 (19M/15F) inpatients Mean age: 45.5	Recurrent and first-MDD episode	ROI manual tracing, 1.5 T	HP: MDD < HC
Caetano *et al*., 2007	19 patients (13M/6F) Mean age: 13.0	Early onset MDD	ROI manual tracing, 1.5 T	Left HP: MDD < HC
Ballmaier *et al*., 2008	46 patients (12M/34F) Mean age: 71.1	Early and late onset MDD	ROI manual tracing, 1.5 T	Head of HP: MDD < HC Left HP: Late onset < early onset
Frodl *et al*., 2008b*	30 (11M/19F) inpatients Mean age: 45.0 30 HC Mean age: 43.6	Current MDD episode at baseline (t0) and after 3 years (t1)	ROI manual tracing, 1.5 T	HP t0 and t1: MDD = HC Left HP: MDD t1 > MDD t0
Frodl *et al*., 2008c*	38 (13M/25F) inpatients Mean age: 46.1 30 HC Mean age: 43.6	Current MDD episode at baseline (t0) and after 3 years (t1)	VBM (SPM2), 1.5 T	HP: MDD < HC Left HP t1: remitted MDD > non remitted MDD
McMaster *et al*., 2008	32 (12M/20F) patients with familiar MDD Mean age: 14.08	Early onset MDD	ROI manual tracing, 1.5 T	Right and left HP: MDD < HC
Bearden *et al*., 2009	31 unmedicated Mean age: 39.2	(20) current MDD episode (11) euthymia	ROI manual tracing, 1.5 T	HP: MDD = HC
Zou *et al*., 2010	23 patients (10M/13F) Mean age: 31.1	First episode MDD	VBM, 3 T	HP: MDD < HC

* follow-up studies; F=females; ROI: region of interest; HP: hippocampus; HC: healthy control subjects; M=males; VBM: voxel-based-morphometry; CA: childhood abuse.

patients and at-risk individuals (Caetano *et al*., 2007; Chen *et al*., 2010; MacMaster *et al*., 2008). It has been hypothesized that the exposure to early life adversities may influence the maturation of hippocampus in subjects with genetic susceptibility to major depression, partly sustaining the onset of depressive symptoms (Rao *et al*., 2010).

Interestingly, a 3-year longitudinal study showed increased hippocampal volumes (normalization) in treated depressed patients, but not in those who discontinued (Frodl *et al*., 2008b). It has indeed been noted that long lasting antidepressant therapy may have neuroplastic effect on the hippocampus in depressed patients (i.e, Santarelli *et al*., 2003; Vythilingam *et al*., 2004), possibly through the enhancement of neurotrophins synthesis, such as BDNF as suggested in several animal studies (Paizanis *et al*., 2007). In addition good response and low relapse rate were associated with larger volumes (Frodl *et al*., 2008b), while worst outcome was associated with volume decrease (Frodl *et al*., 2008c).

Taken together, these findings suggest that the hippocampus may represent an anatomical marker of major depression, especially for stressed patients with genetic susceptibility, and it may also be useful for characterizing treatment response and outcome. However, some methodological limitations may prevent the generalization of these results such as the relatively small sample sizes of most of the studies, the different MRI techniques, the cross-sectional investigations, and the prevalence of medicated and chronic patients. Hence, large MRI studies are expected to explore the maturation of hippocampus in at-risk subjects and in first-episode patients with major depression, trying to further investigate the potential resilience after antidepressant treatment. Furthermore, genetic and neuropsychological studies, coupled with imaging investigations, will be crucial to distinguish between trait and state neurobiological markers of major depression (Danese, 2008; Tosato & Lasalvia, 2009).

REFERENCES

Ballmaier M., Narr K.L., Toga A.W., Elderkin-Thompson V., Thompson P.M., Hamilton L., Haroon E., Pham D., Heinz A. & Kumar A. (2008). Hippocampal morphology and distinguishing late-onset from early-onset elderly depression. *American Journal of Psychiatry* 165, 229-237.

Bearden C.E., Thompson P.M., Avedissian C., Klunder A.D., Nicoletti M., Dierschke N., Brambilla P. & Soares J.C. (2009). Altered hippocampal morphology in unmedicated patients with major depressive illness. *ASN Neuro10*, 265-273.

Bell-McGinty S., Butters M.A., Meltzer C.C., Greer P.J., Reynolds C.F., 3rd & Becker J.T. (2002). Brain morphometric abnormalities in geriatric depression: long-term neurobiological effects of illness duration. *American Journal of Psychiatry* 159, 1424-1427.

Bremner J.D., Narayan M., Anderson E.R., Staib L.H., Miller H.L. & Charney D.S. (2000). Hippocampal volume reduction in major depression. *American Journal of Psychiatry* 157, 115-118.

Caetano S.C., Hatch J.P., Brambilla P., Sassi R.B., Nicoletti M., Mallinger A.G., Frank E., Kupfer D.J., Keshavan M.S. & Soares J.C. (2004). Anatomical MRI study of hippocampus and amygdala in patients with current and remitted major depression. *Psychiatry Research* 132, 141-147.

Caetano S.C., Fonseca M., Hatch J.P., Olvera R.L., Mark Nicoletti M., Hunter K., Lafer B., Steven R., Pliszka S.R. & Soares J.C. (2007). Medial temporal lobe abnormalities in pediatric unipolar depression. *Neuroscience Letters* 427, 142-147.

Campbell S., Marriott M., Nahmias C. & MacQueen G.M. (2004). Lower hippocampal volume in patients suffering from depression: a meta-analysis. *American Journal of Psychiatry* 161, 598-607.

Chen M.C., Hamilton P. & Gotlib I.H. (2010). Decreased hippocampus volume in healthy girls at risk for depression. *Archives of General Psychiatry* 67, 270-276.

Colla M., Kronenberg G., Deuschle M., Meichel K., Hagen T., Bohrer M. & Heuser I. (2007). Hippocampal volume reduction and HPA-system activity in major depression. *Journal of Psychiatry Research* 41, 553-560.

Danese A. (2008). Genetic opportunities for psychiatric epidemiology: on life stress and depression. *Epidemiologia e Psichiatria Sociale* 17, 201-210.

Drevets W.C., Price J.L. & Furey M.L. (2008). Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Structure and Function* 213, 93-118.

Frodl T., Schaub A., Banac S., Charypar M., Jäger M., Kümmler P., Bottlender R., Zetzsche T., Born C., Leinsinger G., Reiser M., Möller H.J. & Meisenzahl E.M. (2006). Reduced hippocampal volume correlates with executive dysfunctioning in major depression. *Journal of Psychiatry and Neuroscience* 31, 316-325.

Frodl T., Zill P., Baghai T., Schüle C., Rupprecht R., Zetzsche T., Bondy B., Reiser M., Möller H.J. & Meisenzahl E.M. (2008a). Reduced hippocampal volumes associated with the long variant of the tri- and diallelic serotonin transporter polymorphism in major depression. *American Journal of Medical Genetics Part B: Neuropsychiatry Genetics* 147, 1003-1007.

Frodl T., Jäger M., Smajstrlova I., Born C., Bottlender R., Palladino T., Reiser M., Möller H.J. & Meisentzhal E. (2008b). Effect of hippocampal and amygdala volumes on clinical outcomes in major depression: a 3 year prospective magnetic resonance imaging study. *Journal of Psychiatry and Neuroscience* 33, 423-430.

Frodl T.S., Koutsouleris N., Bottlender R., Born C., Jäger M., Scupin I., Reiser M., Möller H.J., & Meisenzahl M.E. (2008c). Depression-related variation in brain morphology over 3 years. Effects of Stress? *Archives of General Psychiatry* 65, 1156-1165.

Kronmuller K.T., Pantel J., Götz B., Köhler S., Victor D., Mundt C., Magnotta V., Giesel F., Essig M. & Schröder J. (2008). Life events and hippocampal volume in first-episode major depression. *Journal of Affective Disorders* 110, 241-247.

MacMaster F.P., Mirza Y., Szeszko P.R., Kmiecik L.E., Easter P., Taormina S.P., Lynch M., Rose M., Moore G.J. & Rosenberg D.R. (2008). Amygdala and hippocampal volumes in familial early onset major depressive disorder. *Biological Psychiatry* 63, 385-390.

MacQueen G.M., Campbell S., McEwen B.S., MacDonald K., Amano S., Joffe R.T., Nahmias C. & Young L.T. (2003). Course of illness, hippocampal function, and hippocampal volume in major depression. *Proceedings of National Academy of Science* U.S. A. 3, 1387-1392.

McKinnon M.C., Yucel K., Nazarov A. & MacQueen G.M. (2009). A meta-analysis examining clinical predictors of hippocampal volume in patients. *Journal of Psychiatry and Neuroscience* 34, 41-54.

Montag C., Weber B., Fliessbach K., Elger C. & Reuter M. (2009). The BDNF Val66Met polymorphism impacts parahippocampal and amygdala volume in healthy humans: incremental support for a genetic risk factor for depression. *Psychological Medicine* 39, 1831-1839.

Neumeister A., Wood S., Bonne O., Nugent A.C., Luckenbaugh D.A., Young T., Bain E.E., Charney D.S. & Drevets W. (2005). Reduced hippocampal volume in unmedicated, remitted patients with major depression versus control subjects. *Biological Psychiatry* 57, 935-937.

Paizanis E., Hamon M. & Lanfumey L. (2007). Hippocampal neurogenesis, depressive disorders and antidepressant therapy. *Neural Plasticity* 2007, 1-7.

Rao U., Chen L.A., Bidesi A.S., Shad M.U., Thomas M.A. & Hammen C.L. (2010). Hippocampal changes associated with early-life adversity and vulnerability to depression. *Biological Psychiatry* 67, 357-364.

Sala M., Perez J., Soloff P., Ucelli di Nemi S., Caverzasi E., Soares J.C. & Brambilla P. (2004). Stress and hippocampal abnormalities in psychiatric disorders. *European Neuropsychopharmacology* 14, 393-405.

Santarelli L., Saxe M., Gross C., Surget A., Battaglia F., Dulawa S., Weisstaub N., Lee J., Duman R., Arancio O., Belzung C. & Hen R. (2003). Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 301, 805-809.

Shah P.J., Glabus M.F., Goodwin G.M. & Ebmeier K.P. (2002). Chronic, treatment resistant depression and right fronto-striatal atrophy. *British Journal of Psychiatry* 180, 434-440.

Sheline Y.I., Gado M.H. & Kraemer H.C. (2003). Untreated depression and hippocampal volume loss. *American Journal of Psychiatry* 160, 1516-1518.

Tosato S. & Lasalvia A. (2009). The contribution of epidemiology to defining the most appropriate approach to genetic research on schizophrenia. *Epidemiologia e Psichiatria Sociale* 18, 81-90.

Videbech P. & Ravnkilde B. (2004). Hippocampal volume and depression: a meta-analysis of MRI studies. *American Journal of Psychiatry* 161, 1957-1966.

Vythilingam M.H., Newport J., Miller A.H., Anderson E., Bronen R., Brumner M., Staib L., Vermetten E., Charney D.S., Nemeroff C.B. & Bremner J.D. (2002). Childhhod trauma associated with smaller hippocampal volume in women with major depression. *American Journal of Psychiatry* 159, 2072-2080.

Vythilingam M., Vermetten E., Anderson G.M., Luckenbaugh D., Anderson E.R., Snow J., Staib L.H., Charney D.S. & Bremner J.D. (2004). Hippocampal volume, memory, and cortisol status in major depressive disorder: effects of treatment. *Biological Psychiatry* 56, 101-12.

Zou K., Deng W., Li T., Zhang B., Jiang L., Huang C., Sun X. & Sun X. (2010). Changes of brain morphometry in first-episode, drug-naïve, non-late-life adult patients with major depression: optimized voxel-based morphometry study. *Biological Psychiatry* 67, 186-188.