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Brain Structural Effects of Antidepressant Treatment in Major Depression

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Abstract: Depressive disorder is a very frequent and heterogeneous syndrome. Structural imaging techniques offer a useful tool in the comprehension of neurobiological alterations that concern depressive disorder. Altered brain structures in depressive disorder have been particularly located in the prefrontal cortex (medial prefrontal cortex and orbitofrontal cortex, OFC) and medial temporal cortex areas (hippocampus). These brain areas belong to a structural and functional network related to cognitive and emotional processes putatively implicated in depressive symptoms. These volumetric alterations may also represent biological predictors of response to pharmacological treatment. In this context, major findings of magnetic resonance (MR) imaging, in relation to treatment response in depressive disorder, will here be presented and discussed.

Keywords: amitriptyline, amygdala, cingulate, citalopram, doxepine, fluoxetine, fluxovamine, hippocampus, mirtazapine, paroxetine, prefrontal cortex, reboxetine, sertraline, trimipramine, venlafaxine.

INTRODUCTION

Depression is a very common disease, being an important cause of burden worldwide [1]. Patients with depressive disease have different clinical outcome with some of them facing a benign course of illness and others presenting severe, recurrent and remitting episodes [2]. To date, the neuropathological alterations that sustain this wide syndromic entity and the mechanisms behind drug response are still not completely understood [3, 4]. Many hypothesis have been proposed regarding the alterations involved in the neurobiology of depressive disorder: most of them have been focused on brain areas that are implicated in the circuits of serotonin and norepinephrine [5], which are also the main target neurotransmitters of antidepressants [6-9]. Impaired neural circuits that involve these neurotransmitters and encode cognitive and emotional functions have been observed in depressive disorder [10]. Brain areas that are implicated in these networks have been studied with neuroimaging techniques that have revealed specific structural [11-13] and functional alterations [14] features.

Magnetic resonance imaging (MRI) studies on depressive disorder have shown volume reductions in frontal regions, hippocampus, putamen and caudate nucleus [15-18], anterior cingulate [19], amygdala [20], as well as white matter hyperintense lesions [21]. Alterations in limbic and prefrontal areas are suggested to be involved in affective symptoms, such as exaggerated response to negative emotions, guilt, hopelessness and despair, whereas alterations in hypothalamus, locus coeruleus and periacqueductal grey matter may be involved in neurovegetative and neuroendocrine alterations, such as sleep and appetite disturbances, loss of weight, psychomotor retardation or agitation [22].

Imaging methods are required to overcome classical nosological definitions based on syndromic clinical descriptions, by offering reliable models of neuro-morphological alterations that can explain those phenotypes commonly considered as part of the disease [23]. In addition, imaging methods have also been applied to evaluate treatment response to antidepressants among responder and non-responder patients, in order to establish trait markers of depression biological features of refractory illness and predictors of clinical outcome [24, 25]. While pharmacotherapy is often prescribed as an effective intervention for depressive disorder, not all patients who undergo antidepressant treatment get significant amelioration, with almost one third of them failing to achieve remission even after several pharmacological trials [26]. Despite prescriptions of pharmacological therapy for depressive disorder are incresing world wide, treatment response is still uncertain and there is a lack of indicators of those group of patients who can actually benefit from antidepressant therapy or not. In general, neurobiological features are relevant key factors in understanding the course of illness in psychiatric disorders, therefore their identification would help both clinical and research progress. Characterizing homogeneous diagnostic groups based on neural features will facilitate genetic investigations on the etiology of depression and will ameliorate the effectiveness of interventions [27, 28]. In this perspective, evidence from imaging research has shed light on the importance of early diagnosis and intervention on

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major depression [29-31]. In particular, MRI offers, *in vivo*, the possibility to explore the structural basis of the response mechanisms to antidepressants, allowing to improve the understanding of how these compounds work on the brain, and ultimately lead to clinical improvement.

We here first review the most robust findings on brain areas involved in depressive disorder and then debate them in relationship to antidepressant treatment response.

MAJOR STRUCTURAL BRAIN ALTERATIONS IN DEPRESSIVE DISORDER

Whole Brain

Total brain volume and whole gray matter volume have not consistently been reported to be altered in adult and geriatric patients with depressive disorder [32-37], as recently confirmed by a meta-analysis [38]. White matter hyperintensities have also been reported, particularly in older patients [38-41].

FRONTAL LOBES AND CINGULATE

Patients with depressive disorder have been shown lower volume in prefrontal/orbitofrontal cortex (OFC) [32, 42-44] and anterior cingulate [33, 37, 38, 42, 45, 46]. These findings were not always replicated in other research studies [38, 47]. Interestingly, shrinkage of medial prefrontal cortex in drug naïve patients [48], along with anterior cingulate volume reduction, seem to progress over time at a faster rate than healthy controls [49]. In regards of cortical folding, lower gyrification index has been reported in orbitofrontal and cingulate cortices as well as in the insula and temporal operculum [12].

TEMPORAL LOBES

Evidence of reduced temporal gray matter has been found by some studies [42, 50], though not confirmed by others [33, 51, 52]. Furthermore, an inverse relationship between superior temporal gyrus volume and length of illness has been shown in unmedicated patients [53]. On the other hand, greater cortical thickness was reported on some paralimbic areas located in the temporal lobes, such as temporal poles in first episode [54] and child-adolescence depression [55].

BASAL GANGLIA AND THALAMUS

Volume reduction in putamen and caudate nucleus have been reported in depression [36-38, 42, 56, 57]. Hyperintensities in putamen and globus pallidus have also been shown, mostly in elderly patients [58, 59], being possible predictors of lack of response in geriatric population [60-63].

Reduced thalamus have been observed in patients with depression by some reports [34, 42, 48], whereas others found no difference [64, 65].

HIPPOCAMPUS AND AMYGDALA

Smaller hippocampal volumes have consistently been observed in chronic, acute and non remitting patients with depression [18, 49, 66-69], as confirmed by a comprehensive meta-analysis [15], with progressive reduction over time [70]. Amygdala has also been reported as reduced by some studies [71-75], particularly in unmedicated [53, 76, 77] and recurrent patients [51, 53, 78]. However, preserved [74, 79-84] or even enlarged amygdala volumes [49, 84-88] have been observed. Inconsistency across findings has been attributed to differences in illness stage, age and gender composition of samples and effect of treatment [15, 89, 90].

CEREBELLUM AND BRAINSTEM

Depressed patients have been reported to have smaller cerebellar [42, 91, 92] and brain stem [92] volumes compared to healthy controls. However, the literature is limited by the paucity of the studies.

VENTRICLES AND CEREBROSPINAL FLUID (CSF)

A vast majority of studies has shown larger volume of third [93-96], lateral ventricles [95, 97-101] and CSF in patients with depressive disorder, whereas some others found preserved size [33, 92, 102-106]. A recent meta-analysis reported a trend of enlargement of CSF among patients with depression, but remarked the heterogeneity across studies [38].

CORPUS CALLOSUM

Enlarged corpus callosum has been observed by one study [107], though not confirmed by others [36, 57, 108].

PITUITARY

A reduced volume in pituitary gland has been reported by one study [109], whereas others did not find any difference [110], even longitudinally after remission [111]. Morover, in a recent meta-analysis that included psychotic depression [112], pituitary gland was larger in depressed patients, relative to healthy controls [38].

EFFECTS OF ANTIDEPRESSANT TREATMENT ON BRAIN MORPHOLOGY IN DEPRESSION

Several imaging studies have assessed the effects of antidepressant treatment - in terms of duration, efficacy and compounds - on brain volumes in patients with depressive disorder. The purpose of this kind of investigation is twofold: on one hand to investigate how treatment affects brain anatomy; on the other hand, to understand the mechanism of action of antidepressants. Furthermore, clinical outcome of patients with depressive disorder can be fairly variable and prediction of treatment response is a challenge for development of reliable therapies [113].

As previously mentioned, there is a convergent research line focusing on hippocampus as a possible biomarker of depressive disorder, even in relation to clinical outcome and treatment effect. Indeed, a smaller hippocampal volume has been associated with severity of depression [114, 115], early onset [116-118], refractory illness [70, 114, 119, 120], longer duration of untreated depression [121], comorbidity with childhood abuse [122] and high levels of disease burden [72, 123-125] or anxiety [126, 127].

In this context, increased right hippocampal volumes have been found in female responders compared to non-responders after eight weeks of fluoxetine treatment [114]; female responders also had larger caudate nucleus compared to male responders and to female non responders [128, 129]. This may indicate a modulatory response effect influenced by gender [67, 130]. In another (one-year) longitudinal study non remitting patients to various antidepressants (including fluxovamine, paroxetine, sertraline, citalopram, venlafaxine, mirtazapine, amitriptyline, doxepine, trimipramine and reboxetine) had lower bilateral hippocampal volumes both at baseline and at follow-up, compared to remitted patients [70], whereas patients who remitted at 3 years follow-up had lower shrinkage of hippocampus [49]. In agreement with these observations, larger hippocampal volumes at baseline predicted remission after antidepressant treatment [131, 132], whereas lower volumes predicted relapse or lack of remission [119, 131]. However, it has to be noted that no effects on hippocampal size after remission mostly with SSRIs have been found in patients with major depression by one study [68].

Morover, imaging studies have produced interesting findings on the structural effects of antidepressant treatment in prefrontal areas. Larger frontal cortical thickness [131] and medial frontal gyrus, dorsolateral prefrontal cortex (DLPFC) and cingulate cortex volumes [24, 133, 134] predicted remission after antidepressant treatment [84, 128]. Furthermore, effective treatment with fluoxetine and sertraline determined enlargement in middle frontal gyrus, DLPFC and OFC [48, 135]. Accordingly, it has been shown that remission correlates to more preserved volumes of anterior cingulate, dorsomedial prefrontal cortex and DLPFC over time [49, 136]. Finally, geriatric patients previously exposed to antidepressant treatment had larger OFC volumes compared to drug-naïve patients [32].

However, even though there is convergent evidence from MRI studies of antidepressant effect on an altered prefrontal-limbic network, some controversial results deserve consideration. Drug-naïve, first-episode patients with depression and comorbid panic disorder treated with duloxetine for 6 weeks had only subtle enlargement of infero-frontal areas, although they underwent clinical amelioration [137]. Furthermore, in two other longitudinal studies, no volumetric changes were observed to SSRIs or nortriptiline, though in presence of clinical response [68, 138], and no predictive property of hippocampal volume was observed [66].

DISCUSSION

Based on the above reviewed literature, it looks that depressive disorder is characterized by an altered structural network that encompasses reduced volumes of OFC, anterior cingulate, hippocampus, and striatum with enlarged ventricles. Also, in regards to the structural effects of antidepressants, taken together the literature's results underlie the implication of hippocampus, DLPFC and cingulate cortex in their neurobiological mechanisms. In this regards, other imaging techniques that specifically assess white matter, such as diffusion tensor imaging (DTI), corroborated these data showing an impaired fiber integrity connecting cingulate, DLPFC, and hippocampus in non remitter patients [136, 139]. Therefore, such brain areas may represent the biological markers of treatment response and outcome in depressive disorder.

Effective antidepressant treatment might have a neurobiological impact on depressive disorder by reducing structural shrinkage processes in hippocampus and prefrontal cortex, based on a putative neuroprotective or neuro-modulatory effect [140, 141]. In this perspective, antidepressants SSRIs have caused an increase of volume in cingulate subdivisions and precuneus in healthy controls under short administration, confirming a structural remodeling, independent of depressive illness, by serotonergic neurotransmission [142]. Serotonin and norepinephrine have indeed been observed in some reports to enhance neuro-trophic factors, such as BDNF, that increases neurogenesis on grey matter [143]. Furthermore, according to *f*MRI studies, antidepressants affect this network by reversing hyperactivation of limbic areas to emotional stimuli and by enhancing frontal cortex and cingulate top-down modulatory influence on subcortical structures [144-146].

However, larger studies, focused on specific compounds administered longitudinally to drug-naive patients are needed to finally clarify the impact of antidepressants on brain morphology in major depression. Indeed, a major limitation of the studies presented here is the low sample size, with most studies below 50 subjects and only one over 100 [62, 131]. Moreover, it is impossible to draw conclusions on the effect of single specific compounds because many studies include multiple antidepressants [49, 67, 68, 84, 119, 132, 133, 147] and very few studies focused on the effect of "non SSRIs" antidepressants [138, 148, 149]. Although these designs are closer to real world interventions which apply multiple drugs [150] they limit the possibility to investigate the contribute of different compounds to the brain altered circuits, in order to plan more effective and targeted interventions.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

[1] Aakhus, E.; Flottorp, S. A.; Oxman, A. D. Implementing evidence-based guidelines for managing depression in elderly patients: a Norwegian perspective. *Epidemiol. Psychiatric Sci.,* **2012**, *21* (3), 237-40. http://dx.doi.org/10.1017/S204579601200025X

[2] Li, C. T.; Bai, Y. M.; Huang, Y. L.; Chen, Y. S.; Chen, T. J.; Cheng, J. Y.; Su, T. P. Association between antidepressant resistance in unipolar depression and subsequent bipolar disorder: cohort study. *Br. J. Psychiatry: J. Mental Sci.,* **2012**, *200* (1), 45-51. http://dx.doi.org/10.1192/bjp.bp.110.086983

[3] Brambilla, P.; Perez, J.; Barale, F.; Schettini, G.; Soares, J. C. GABAergic dysfunction in mood disorders. *Mol. Psychiatry,* **2003**, *8* (8), 721-37, 715.

[4] Brambilla, P.; Cipriani, A.; Hotopf, M.; Barbui, C. Side-effect profile of fluoxetine in comparison with other SSRIs, tricyclic and newer antidepressants: a meta-analysis of clinical trial data. *Pharmacopsychiatry,* **2005**, *38* (2), 69-77. http://dx.doi.org/10.1055/s-2005-837806

[5] Mann, J. J.; Malone, K. M.; Diehl, D. J.; Perel, J.; Cooper, T. B.; Mintun, M. A. Demonstration *in vivo* of reduced serotonin responsivity in the brain of untreated depressed patients. *Am. J. Psychiatry,* **1996**, *153* (2), 174-82.

[6] Manji, H. K.; Quiroz, J. A.; Sporn, J.; Payne, J. L.; Denicoff, K.; N, A. G.; Zarate, C. A., Jr.; Charney, D. S. Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. *Biol. Psychiatry,* **2003**, *53* (8), 707-42. http://dx.doi.org/10.1016/S0006-3223(03)00117-3

[7] Sala, M.; Coppa, F.; Cappucciati, C.; Brambilla, P.; d'Allio, G.; Caverzasi, E.; Barale, F.; De Ferrari, G. M. Antidepressants: their effects on cardiac channels, QT prolongation and Torsade de Pointes. *Curr. Opin. Investig. Drugs,* **2006**, *7* (3), 256-63.

[8] Sala, M.; Caverzasi, E.; Marraffini, E.; De Vidovich, G.; Lazzaretti, M.; d'Allio, G.; Isola, M.; Balestrieri, M.; D'Angelo, E.; Thyrion, F. Z.; Scagnelli, P.; Barale, F.; Brambilla, P. Cognitive memory control in borderline personality disorder patients. *Psychol. Med.,* **2009**, *39* (5), 845-53. http://dx.doi.org/10.1017/S0033291708004145

[9] Verdoux, H.; Tournier, M.; Begaud, B. Pharmacoepidemiology of psychotropic drugs: examples of current research challenges on major public health issues. *Epidemiologia e psichiatria sociale* **2009**, *18* (2), 107-13.

[10] Murrough, J. W.; Iacoviello, B.; Neumeister, A.; Charney, D. S.; Iosifescu, D. V. Cognitive dysfunction in depression: neurocircuitry and new therapeutic strategies. *Neurobiol. Learning Memory,* **2011**, *96* (4), 553-63. http://dx.doi.org/10.1016/j.nlm.2011.06.006

[11] Malykhin, N. V.; Carter, R.; Hegadoren, K. M.; Seres, P.; Coupland, N. J. Fronto-limbic volumetric changes in major depressive disorder. *J. Affect. Disord.,* **2012**, *136* (3), 1104-13. http://dx.doi.org/10.1016/j.jad.2011.10.038

[12] Zhang, Y.; Yu, C.; Zhou, Y.; Li, K.; Li, C.; Jiang, T. Decreased gyrification in major depressive disorder. *Neuroreport,* **2009**, *20* (4), 378-80. http://dx.doi.org/10.1097/WNR.0b013e3283249b34

[13] Tu, P. C.; Chen, L. F.; Hsieh, J. C.; Bai, Y. M.; Li, C. T.; Su, T. P. Regional cortical thinning in patients with major depressive disorder: a surface-based morphometry study. *Psychiatry Res.,* **2012**, *202* (3), 206-13. http://dx.doi.org/10.1016/j.pscychresns.2011.07.011

[14] Graham, J.; Salimi-Khorshidi, G.; Hagan, C.; Walsh, N.; Goodyer, I.; Lennox, B.; Suckling, J. Meta-analytic evidence for neuroimaging models of depression: State or trait? *J. Affect. Disord.,* **2013**, *151* (2), 423-431. http://dx.doi.org/10.1016/j.jad.2013.07.002

[15] Campbell, S.; Marriott, M.; Nahmias, C.; MacQueen, G. M. Lower hippocampal volume in patients suffering from depression: a meta-analysis. *Am. J. Psychiatry,* **2004**, *161* (4), 598-607. http://dx.doi.org/10.1176/appi.ajp.161.4.598

[16] Koolschijn, P. C.; van Haren, N. E.; Lensvelt-Mulders, G. J.; Hulshoff Pol, H. E.; Kahn, R. S. Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Hum. Brain Mapping,* **2009**, *30* (11), 3719-35. http://dx.doi.org/10.1002/hbm.20801

[17] Videbech, P.; Ravnkilde, B. Hippocampal volume and depression: a meta-analysis of MRI studies. *Am. J. Psychiatry,* **2004**, *161* (11), 1957-66. http://dx.doi.org/10.1176/appi.ajp.161.11.1957

[18] McKinnon, M. C.; Yucel, K.; Nazarov, A.; MacQueen, G. M. A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. *J. Psychiatry Neurosci.,* **2009**, *34* (1), 41-54.

[19] Hajek, T.; Kozeny, J.; Kopecek, M.; Alda, M.; Hoschl, C. Reduced subgenual cingulate volumes in mood disorders: a meta-analysis. *J. Psychiatry Neurosci.,* **2008**, *33* (2), 91-9.

[20] Hamilton, J. P.; Siemer, M.; Gotlib, I. H. Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Mol. Psychiatry,* **2008**, *13* (11), 993-1000. http://dx.doi.org/10.1038/mp.2008.57

[21] Videbech, P. MRI findings in patients with affective disorder: a meta-analysis. *Acta Psychiatrica Scandinavica,* **1997**, *96* (3), 157-68. http://dx.doi.org/10.1111/j.1600-0447.1997.tb10146.x

[22] Agarwal, N.; Port, J. D.; Bazzocchi, M.; Renshaw, P. F. Update on the use of MR for assessment and diagnosis of psychiatric diseases. *Radiology,* **2010**, *255* (1), 23-41. http://dx.doi.org/10.1148/radiol.09090339

[23] Andreone, N.; Tansella, M.; Cerini, R.; Rambaldelli, G.; Versace, A.; Marrella, G.; Perlini, C.; Dusi, N.; Pelizza, L.; Balestrieri, M.; Barbui, C.; Nose, M.; Gasparini, A.; Brambilla, P. Cerebral atrophy and white matter disruption in chronic schizophrenia. *Eur. Arch. Psychiatry Clin. Neurosci.,* **2007**, *257* (1), 3-11. http://dx.doi.org/10.1007/s00406-006-0675-1

[24] Chen, C. H.; Ridler, K.; Suckling, J.; Williams, S.; Fu, C. H.; Merlo-Pich, E.; Bullmore, E. Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. *Biol. Psychiatry,* **2007**, *62* (5), 407-14. http://dx.doi.org/10.1016/j.biopsych.2006.09.018

[25] Phillips, J. L.; Batten, L. A.; Aldosary, F.; Tremblay, P.; Blier, P. Brain-volume increase with sustained remission in patients with treatment-resistant unipolar depression. *J. Clin. Psychiatry,* **2012**, *73* (5), 625-31. http://dx.doi.org/10.4088/JCP.11m06865

[26] Gaynes, B. N.; Warden, D.; Trivedi, M. H.; Wisniewski, S. R.; Fava, M.; Rush, A. J. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. *Psychiatric Services,* **2009**, *60 (11),* 1439-45. http://dx.doi.org/10.1176/ps.2009.60.11.1439

[27] Bellani, M.; Dusi, N.; Brambilla, P. Can brain imaging address psychosocial functioning and outcome in schizophrenia? In *Improving Mental Health Care: The Global Challenge*, Thornicroft, G.; Ruggeri, M.; Goldberg, D., Eds. Wiley-Blackwell: **2013**, pp. 281-290. http://dx.doi.org/10.1002/9781118337981.ch18

[28] Buchsbaum, M. S.; Haznedar, M.; Newmark, R. E*., et al.* FDG-PET and MRI imaging of the effects of sertindole and haloperidol in the prefrontal lobe in schizophrenia. *Schizophr. Res.,* **2009**, *114* (1-3), 161-71. http://dx.doi.org/10.1016/j.schres.2009.07.015

[29] Horga, G.; Bernacer, J.; Dusi, N.; Entis, J.; Chu, K.; Hazlett, E. A.; Haznedar, M. M.; Kemether, E.; Byne, W.; Buchsbaum, M. S. Correlations between ventricular enlargement and gray and white matter volumes of cortex, thalamus, striatum, and internal capsule in schizophrenia. *Eur. Arch. Psychiatry Clin. Neurosci.,* **2011**, *261* (7), 467-76. http://dx.doi.org/10.1007/s00406-011-0202-x

[30] Bellani, M.; Dusi, N.; Brambilla, P. Longitudinal imaging studies in schizophrenia: the relationship between brain morphology and outcome measures. *Epidemiologia e Psichiatria Sociale* **2010**, *19* (3), 207-10.

[31] Bellani, M.; Dusi, N.; Yeh, P. H.; Soares, J. C.; Brambilla, P. The effects of antidepressants on human brain as detected by imaging studies. Focus on major depression. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry,* **2011**, *35* (7), 1544-52. http://dx.doi.org/10.1016/j.pnpbp.2010.11.040

[32] Lavretsky, H.; Roybal, D. J.; Ballmaier, M.; Toga, A. W.; Kumar, A. Antidepressant exposure may protect against decrement in frontal gray matter volumes in geriatric depression. *J. Clin. Psychiatry,* **2005**, *66* (8), 964-7. http://dx.doi.org/10.4088/JCP.v66n0801

[33] Coffey, C. E.; Wilkinson, W. E.; Weiner, R. D.; Parashos, I. A.; Djang, W. T.; Webb, M. C.; Figiel, G. S.; Spritzer, C. E. Quantitative cerebral anatomy in depression. A controlled magnetic resonance imaging study. *Arch. General. Psychiatry,* **1993**, *50* (1), 7-16. http://dx.doi.org/10.1001/archpsyc.1993.01820130009002

[34] Dupont, R. M.; Jernigan, T. L.; Heindel, W*., et al.* Magnetic resonance imaging and mood disorders. Localization of white matter and other subcortical abnormalities. *Arch. General Psychiatry,* **1995**, *52* (9), 747-55. http://dx.doi.org/10.1001/archpsyc.1995.03950210041009

[35] Axelson, D. A.; Doraiswamy, P. M.; McDonald, W. M.; Boyko, O. B.; Tupler, L. A.; Patterson, L. J.; Nemeroff, C. B.; Ellinwood, E. H., Jr.; Krishnan, K. R. Hypercortisolemia and hippocampal changes in depression. *Psychiatry Res.,* **1993**, *47* (2), 163-73. http://dx.doi.org/10.1016/0165-1781(93)90046-J

[36] Husain, M. M.; McDonald, W. M.; Doraiswamy, P. M.; Figiel, G. S.; Na, C.; Escalona, P. R.; Boyko, O. B.; Nemeroff, C. B.; Krishnan, K. R. A magnetic resonance imaging study of putamen nuclei in major depression. *Psychiatry Res.,* **1991**, *40* (2), 95-9. http://dx.doi.org/10.1016/0925-4927(91)90001-7

[37] Krishnan, K. R.; McDonald, W. M.; Escalona, P. R.; Doraiswamy, P. M.; Na, C.; Husain, M. M.; Figiel, G. S.; Boyko, O. B.; Ellinwood, E. H.; Nemeroff, C. B. Magnetic resonance imaging of

the caudate nuclei in depression. Preliminary observations. *Arch. General Psychiatry,* **1992**, *49* (7), 553-7. http://dx.doi.org/10.1001/archpsyc.1992.01820070047007

[38] Arnone, D.; McIntosh, A. M.; Ebmeier, K. P.; Munafo, M. R.; Anderson, I. M. Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses. *Eur. Neuropsychopharmacol.,* **2012**, *22* (1), 1-16.

[39] Guze, B. H.; Szuba, M. P. Leukoencephalopathy and major depression: a preliminary report. *Psychiatry Res.,* **1992**, *45* (3), 169-75. http://dx.doi.org/10.1016/0925-4927(92)90024-X

[40] Sassi, R. B.; Brambilla, P.; Nicoletti, M.; Mallinger, A. G.; Frank, E.; Kupfer, D. J.; Keshavan, M. S.; Soares, J. C White matter hyperintensities in bipolar and unipolar patients with relatively mild-to-moderate illness severity. *J. Affect. Disord.,* **2003**, *77* (3), 237-45.

[41] Salloway, S.; Correia, S.; Boyle, P.; Malloy, P.; Schneider, L.; Lavretsky, H.; Sackheim, H.; Roose, S.; Krishnan, K. R. R. MRI subcortical hyperintensities in old and very old depressed outpatients: The important role of age in late-life depression. *J. Neurol. Sci.,* **2002**, *203–204*, 227-233. http://dx.doi.org/10.1016/S0022-510X(02)00296-4

[42] Grieve, S. M.; Korgaonkar, M. S.; Koslow, S. H.; Gordon, E.; Williams, L. M. Widespread reductions in gray matter volume in depression. *NeuroImage Clin.,* **2013**, *3*, 332-339. http://dx.doi.org/10.1016/j.nicl.2013.08.016

[43] Salvadore, G.; Nugent, A. C.; Lemaitre, H.; Luckenbaugh, D. A.; Tinsley, R.; Cannon, D. M.; Neumeister, A.; Zarate Jr, C. A.; Drevets, W. C. Prefrontal cortical abnormalities in currently depressed versus currently remitted patients with major depressive disorder. *NeuroImage,* **2011**, *54* (4), 2643-2651. http://dx.doi.org/10.1016/j.neuroimage.2010.11.011

[44] Lai, T.; Payne, M. E.; Byrum, C. E.; Steffens, D. C.; Krishnan, K. R. Reduction of orbital frontal cortex volume in geriatric depression. *Biol. Psychiatry,* **2000**, *48* (10), 971-5. http://dx.doi.org/10.1016/S0006-3223(00)01042-8

[45] Drevets, W. C.; Frank, E.; Price, J. C.; Kupfer, D. J.; Holt, D.; Greer, P. J.; Huang, Y.; Gautier, C.; Mathis, C. PET imaging of serotonin 1A receptor binding in depression. *Biol. Psychiatry,* **1999**, *46* (10), 1375-87. http://dx.doi.org/10.1016/S0006-3223(99)00189-4

[46] Hirayasu, Y.; Shenton, M. E.; Salisbury, D. F.; Kwon, J. S.; Wible, C. G.; Fischer, I. A.; Yurgelun-Todd, D.; Zarate, C.; Kikinis, R.; Jolesz, F. A.; McCarley, R. W. Subgenual cingulate cortex volume in first-episode psychosis. *Am. J. Psychiatry,* **1999**, *156* (7), 1091-3.

[47] Brambilla, P.; Nicoletti, M. A.; Harenski, K.; Sassi, R. B.; Mallinger, A. G.; Frank, E.; Kupfer, D. J.; Keshavan, M. S.; Soares, J. C. Anatomical MRI study of subgenual prefrontal cortex in bipolar and unipolar subjects. *Neuropsychopharmacology,* **2002**, *27* (5), 792-9.

[48] Kong, L.; Wu, F.; Tang, Y.; Ren, L.; Kong, D.; Liu, Y.; Xu, K.; Wang, F. Frontal-subcortical volumetric deficits in single episode, medication-naive depressed patients and the effects of 8 weeks fluoxetine treatment: a VBM-DARTEL study. *PloS One,* **2014**, *9* (1), e79055. http://dx.doi.org/10.1371/journal.pone.0079055

[49] Frodl, T. S.; Koutsouleris, N.; Bottlender, R.; Born, C.; Jager, M.; Scupin, I.; Reiser, M.; Moller, H. J.; Meisenzahl, E. M. Depression-related variation in brain morphology over 3 years: effects of stress? *Arch. General Psychiatry,* **2008**, *65* (10), 1156-65. http://dx.doi.org/10.1001/archpsyc.65.10.1156

[50] Shah, P. J.; Ebmeier, K. P.; Glabus, M. F.; Goodwin, G. M. Cortical grey matter reductions associated with treatment-resistant chronic unipolar depression. Controlled magnetic resonance imaging study. *Br. J. Psychiatry,* **1998**, *172*, 527-32. http://dx.doi.org/10.1192/bjp.172.6.527

[51] Bremner, J. D.; Narayan, M.; Anderson, E. R.; Staib, L. H.; Miller, H. L.; Charney, D. S. Hippocampal volume reduction in major depression. *Am. J. Psychiatry,* **2000**, *157* (1), 115-8. http://dx.doi.org/10.1176/ajp.157.1.115

[52] Pantel, J.; Schröder, J.; Essig, M.; Popp, D.; Dech, H.; Knopp, M. V.; Schad, L. R.; Eysenbach, K.; Backenstraβ, M.; Friedlinger, M. Quantitative magnetic resonance imaging in geriatric depression and primary degenerative dementia. *J. Affect. Disord.,* **1997**, *42* (1), 69-83. http://dx.doi.org/10.1016/S0165-0327(96)00105-X

[53] 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. Anatomical MRI study of hippocampus and amygdala in patients with current and remitted major depression. *Psychiatry Res. Neuroimaging,* **2004**, *132* (2), 141-147. http://dx.doi.org/10.1016/j.pscychresns.2004.08.002

[54] van Eijndhoven, P.; van Wingen, G.; Katzenbauer, M.; Groen, W.; Tepest, R.; Fernandez, G.; Buitelaar, J.; Tendolkar, I. Paralimbic cortical thickness in first-episode depression: evidence for trait-related differences in mood regulation. *Am. J. Psychiatry,* **2013**, *170* (12), 1477-86. http://dx.doi.org/10.1176/appi.ajp.2013.12121504

[55] Fallucca, E.; MacMaster, F. P.; Haddad, J.; Easter, P.; Dick, R.; May, G.; Stanley, J. A.; Rix, C.; Rosenberg, D. R. Distinguishing between major depressive disorder and obsessive-compulsive disorder in children by measuring regional cortical thickness. *Arch. General Psychiatry,* **2011**, *68* (5), 527-33. http://dx.doi.org/10.1001/archgenpsychiatry.2011.36

[56] Krishnan, K. R.; McDonald, W. M.; Tupler, L. A. Neuropathology in affective illness. *Am. J. Psychiatry,* **1993**, *150* (10), 1568-9. http://dx.doi.org/10.1176/ajp.150.10.1568b

[57] Parashos, I. A.; Tupler, L. A.; Blitchington, T.; Krishnan, K. R. Magnetic-resonance morphometry in patients with major depression. *Psychiatry Res.,* **1998,** *84* (1), 7-15. http://dx.doi.org/10.1016/S0925-4927(98)00042-0

[58] Greenwald, B. S.; Kramer-Ginsberg, E.; Krishnan, R. R.; Ashtari, M.; Aupperle, P. M.; Patel, M. MRI signal hyperintensities in geriatric depression. *Am. J. Psychiatry,* **1996**, *153* (9), 1212-5. http://dx.doi.org/10.1176/ajp.153.9.1212

[59] Iidaka, T.; Nakajima, T.; Kawamoto, K.; Fukuda, H.; Suzuki, Y.; Maehara, T.; Shiraishi, H. Signal hyperintensities on brain magnetic resonance imaging in elderly depressed patients. *Eur. Neurol.,* **1996**, *36* (5), 293-9. http://dx.doi.org/10.1159/000117275

[60] Papakostas, G. I.; Iosifescu, D. V.; Renshaw, P. F.; Lyoo, I. K.; Lee, H. K.; Alpert, J. E.; Nierenberg, A. A.; Fava, M. Brain MRI white matter hyper intensities and one-carbon cycle metabolism in non-geriatric outpatients with major depressive disorder (Part II). *Psychiatry Res.,* **2005**, *140* (3), 301-307. http://dx.doi.org/10.1016/j.pscychresns.2005.09.001

[61] Sneed, J. R.; Culang-Reinlieb, M. E.; Brickman, A. M.; Gunning-Dixon, F. M.; Johnert, L.; Garcon, E.; Roose, S. P. MRI signal hyperintensities and failure to remit following antidepressant treatment. *J. Affect. Disord.,* **2011**, *135* (1–3), 315-320. http://dx.doi.org/10.1016/j.jad.2011.06.052

[62] Sheline, Y. I.; Pieper, C. F.; Barch, D. M.; Welsh-Bohmer, K.; McKinstry, R. C.; MacFall, J. R.; D'Angelo, G.; Garcia, K. S.; Gersing, K.; Wilkins, C.; Taylor, W.; Steffens, D. C.; Krishnan, R. R.; Doraiswamy, P. M. Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. *Arch. General Psychiatry,* **2010**, *67* (3), 277-85. http://dx.doi.org/10.1001/archgenpsychiatry.2009.204

[63] Gunning-Dixon, F. M.; Walton, M.; Cheng, J.; Acuna, J.; Klimstra, S.; Zimmerman, M. E.; Brickman, A. M.; Hoptman, M. J.; Young, R. C.; Alexopoulos, G. S. MRI signal hyperintensities and treatment remission of geriatric depression. *J. Affect. Disord.,* **2010**, *126* (3), 395-401. http://dx.doi.org/10.1016/j.jad.2010.04.004

[64] Krishnan, K. R.; McDonald, W. M.; Doraiswamy, P. M.; Tupler, L. A.; Husain, M.; Boyko, O. B.; Figiel, G. S.; Ellinwood, E. H., Jr. Neuroanatomical substrates of depression in the elderly. *Eur. Arch. Psychiatry Clin. Neurosci.,* **1993**, *243* (1), 41-6. http://dx.doi.org/10.1007/BF02191522

[65] Caetano, S. C.; Sassi, R.; Brambilla, P.; Harenski, K.; Nicoletti, M.; Mallinger, A. G.; Frank, E.; Kupfer, D. J.; Keshavan, M. S.; Soares, J. C. MRI study of thalamic volumes in bipolar and unipolar patients and healthy individuals. *Psychiatry Res.,* **2001,** *108* (3), 161-8. http://dx.doi.org/10.1016/S0925-4927(01)00123-8

[66] Colla, M.; Kronenberg, G.; Deuschle, M.; Meichel, K.; Hagen, T.; Bohrer, M.; Heuser, I. Hippocampal volume reduction and HPA-system activity in major depression. *J. Psychiatric Res.,* **2007**, *41* (7), 553-60. http://dx.doi.org/10.1016/j.jpsychires.2006.06.011

[67] Kronmuller, K. T.; Pantel, J.; Gotz, B.; Kohler, S.; Victor, D.; Mundt, C.; Magnotta, V. A.; Giesel, F.; Essig, M.; Schroder, J. Life events and hippocampal volume in first-episode major depression. *J. Affect. Disord.,* **2008**, *110* (3), 241-7. http://dx.doi.org/10.1016/j.jad.2008.01.022

[68] Vythilingam, M.; Vermetten, E.; Anderson, G. M.; Luckenbaugh, D.; Anderson, E. R.; Snow, J.; Staib, L. H.; Charney, D. S.; Bremner, J. D. Hippocampal volume, memory, and cortisol status in major depressive disorder: effects of treatment. *Biol. Psychiatry,* **2004**, *56* (2), 101-12. http://dx.doi.org/10.1016/j.biopsych.2004.04.002

[69] Bearden, C. E.; Thompson, P. M.; Avedissian, C.; Klunder, A. D.; Nicoletti, M.; Dierschke, N.; Brambilla, P.; Soares, J. C. Altered hippocampal morphology in unmedicated patients with major depressive illness. *ASN Neuro,* **2009**, *1* (4). http://dx.doi.org/10.1042/AN20090026

[70] Frodl, T.; Meisenzahl, E. M.; Zetzsche, T.; Hohne, T.; Banac, S.; Schorr, C.; Jager, M.; Leinsinger, G.; Bottlender, R.; Reiser, M.; Moller, H. J. Hippocampal and amygdala changes in patients with major depressive disorder and healthy controls during a 1-year follow-up. *J. Clin. Psychiatry,* **2004**, *65* (4), 492-9. http://dx.doi.org/10.4088/JCP.v65n0407

[71] Sheline, Y. I.; Gado, M. H.; Price, J. L. Amygdala core nuclei volumes are decreased in recurrent major depression. *Neuroreport,* **1998**, *9* (9), 2023-8. http://dx.doi.org/10.1097/00001756-199806220-00021

[72] Sheline, Y. I.; Sanghavi, M.; Mintun, M. A.; Gado, M. H. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J. Neurosci.,* **1999**, *19* (12), 5034-43.

[73] Hickie, I. B.; Naismith, S. L.; Ward, P. B.; Scott, E. M.; Mitchell, P. B.; Schofield, P. R.; Scimone, A.; Wilhelm, K.; Parker, G. Serotonin transporter gene status predicts caudate nucleus but not amygdala or hippocampal volumes in older persons with major depression. *J. Affect. Disord.,* **2007**, *98* (1-2), 137-42. http://dx.doi.org/10.1016/j.jad.2006.07.010

[74] Keller, J.; Shen, L.; Gomez, R. G.; Garrett, A.; Solvason, H. B.; Reiss, A.; Schatzberg, A. F. Hippocampal and amygdalar volumes in psychotic and nonpsychotic unipolar depression. *Am. J. Psychiatry,* **2008**, *165* (7), 872-80. http://dx.doi.org/10.1176/appi.ajp.2008.07081257

[75] Lorenzetti, V.; Allen, N. B.; Fornito, A.; Yücel, M. Structural brain abnormalities in major depressive disorder: A selective review of recent MRI studies. *J. Affect. Disord.,* **2009**, *117* (1–2), 1-17. http://dx.doi.org/10.1016/j.jad.2008.11.021

[76] Tang, Y.; Wang, F.; Xie, G.; Liu, J.; Li, L.; Su, L.; Liu, Y.; Hu, X.; He, Z.; Blumberg, H. P. Reduced ventral anterior cingulate and amygdala volumes in medication-naïve females with major depressive disorder: A voxel-based morphometric magnetic resonance imaging study. *Psychiatry Res., 2007*, *156* (1), 83-86. http://dx.doi.org/10.1016/j.pscychresns.2007.03.005

[77] Kronenberg, G.; Tebartz van Elst, L.; Regen, F.; Deuschle, M.; Heuser, I.; Colla, M. Reduced amygdala volume in newly admitted psychiatric in-patients with unipolar major depression. *J. Psychiatric Res.,* **2009**, *43* (13), 1112-1117. http://dx.doi.org/10.1016/j.jpsychires.2009.03.007

[78] Hastings, R. S.; Parsey, R. V.; Oquendo, M. A.; Arango, V.; Mann, J. J. Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. *Neuropsychopharmacology,* **2004**, *29* (5), 952-9.

[79] Mervaala, E.; Fohr, J.; Kononen, M.; Valkonen-Korhonen, M.; Vainio, P.; Partanen, K.; Partanen, J.; Tiihonen, J.; Viinamaki, H.; Karjalainen, A. K.; Lehtonen, J. Quantitative MRI of the hippocampus and amygdala in severe depression. *Psychol. Med.,* **2000**, *30* (1), 117-25. http://dx.doi.org/10.1017/S0033291799001567

[80] Munn, M. A.; Alexopoulos, J.; Nishino, T.; Babb, C. M.; Flake, L. A.; Singer, T.; Ratnanather, J. T.; Huang, H.; Todd, R. D.; Miller, M. I.; Botteron, K. N. Amygdala volume analysis in female twins with major depression. *Biol. Psychiatry,* **2007**, *62* (5), 415-22. http://dx.doi.org/10.1016/j.biopsych.2006.11.031

[81] MacMaster, F. P.; Leslie, R.; Rosenberg, D. R.; Kusumakar, V. Pituitary gland volume in adolescent and young adult bipolar and unipolar depression. *Bipolar Disord.,* **2008**, *10* (1), 101-4. http://dx.doi.org/10.1111/j.1399-5618.2008.00476.x

[82] Monkul, E. S.; Hatch, J. P.; Nicoletti, M. A.; Spence, S.; Brambilla, P.; Lacerda, A. L.; Sassi, R. B.; Mallinger, A. G.; Keshavan, M. S.; Soares, J. C. Frontolimbic brain structures in suicidal and non-suicidal female patients with major depressive disorder. *Mol. Psychiatry,* **2007**, *12* (4), 360-6. http://dx.doi.org/10.1038/sj.mp.4001919

[83] van Eijndhoven, P.; van Wingen, G.; van Oijen, K.; Rijpkema, M.; Goraj, B.; Jan Verkes, R.; Oude Voshaar, R.; Fernández, G.; Buitelaar, J.; Tendolkar, I. Amygdala Volume Marks the Acute State in the Early Course of Depression. *Biol. Psychiatry,* **2009**, *65* (9), 812-818. http://dx.doi.org/10.1016/j.biopsych.2008.10.027

[84] Lorenzetti, V.; Allen, N. B.; Whittle, S.; Yücel, M. Amygdala volumes in a sample of current depressed and remitted depressed patients and healthy controls. *J. Affect. Disord.,* **2010**, *120* (1–3), 112-119. http://dx.doi.org/10.1016/j.jad.2009.04.021

[85] Tebartz van Elst, L.; Woermann, F.; Lemieux, L.; Trimble, M. R. Increased amygdala volumes in female and depressed humans. A quantitative magnetic resonance imaging study. *Neurosci. Lett.,* **2000**, *281* (2-3), 103-6. http://dx.doi.org/10.1016/S0304-3940(00)00815-6

[86] Frodl, T.; Meisenzahl, E. M.; Zetzsche, T.; Born, C.; Jager, M.; Groll, C.; Bottlender, R.; Leinsinger, G.; Moller, H. J. Larger amygdala volumes in first depressive episode as compared to recurrent major depression and healthy control subjects. *Biol. Psychiatry,* **2003**, *53* (4), 338-44. http://dx.doi.org/10.1016/S0006-3223(02)01474-9

[87] Weniger, G.; Lange, C.; Irle, E. Abnormal size of the amygdala predicts impaired emotional memory in major depressive disorder. *J. Affect. Disord.,* **2006**, *94* (1-3), 219-29. http://dx.doi.org/10.1016/j.jad.2006.04.017

[88] Lange, C.; Irle, E. Enlarged amygdala volume and reduced hippocampal volume in young women with major depression. *Psychol., Med.,* **2004**, *34* (6), 1059-64. http://dx.doi.org/10.1017/S0033291703001806

[89] Bellani, M.; Baiano, M.; Brambilla, P. Brain anatomy of major depression II. Focus on amygdala. *Epidemiol. Psychiatric Sci.,* **2011**, *20* (1), 33-6. http://dx.doi.org/10.1017/S2045796011000096

[90] Arnone, D.; McIntosh, A. M.; Tan, G. M.; Ebmeier, K. P. Meta-analysis of magnetic resonance imaging studies of the corpus callosum in schizophrenia. *Schizophr. Res.,* **2008**, *101* (1-3), 124-32. http://dx.doi.org/10.1016/j.schres.2008.01.005

[91] Machino, A.; Kunisato, Y.; Matsumoto, T.; Yoshimura, S.; Ueda, K.; Yamawaki, Y.; Okada, G.; Okamoto, Y.; Yamawaki, S. Possible involvement of rumination in gray matter abnormalities in persistent symptoms of major depression: An exploratory magnetic resonance imaging voxel-based morphometry study. *J. Affect. Disord.,* **2014**, *168C*, 229-235. http://dx.doi.org/10.1016/j.jad.2014.06.030

[92] Shah, S. A.; Doraiswamy, P. M.; Husain, M. M.; Escalona, P. R.; Na, C.; Figiel, G. S.; Patterson, L. J.; Ellinwood, E. H., Jr.; McDonald, W. M.; Boyko, O. B.; *et al*. Posterior fossa abnormalities in major depression: a controlled magnetic resonance imaging study. *Acta Psychiatrica Scandinavica,* **1992**, *85* (6), 474-9. http://dx.doi.org/10.1111/j.1600-0447.1992.tb03214.x

[93] Schlegel, S.; Kretzschmar, K. Computed tomography in affective disorders. Part I. Ventricular and sulcal measurements. *Biol. Psychiatry* **1987**, *22* (1), 4-14. http://dx.doi.org/10.1016/0006-3223(87)90124-7

[94] Beats, B.; Levy, R.; Forstl, H. Ventricular enlargement and caudate hyperdensity in elderly depressives. *Biol. Psychiatry,* **1991**, *30* (5), 452-8. http://dx.doi.org/10.1016/0006-3223(91)90306-7

[95] Rabins, P. V.; Pearlson, G. D.; Aylward, E.; Kumar, A. J.; Dowell, K. Cortical magnetic resonance imaging changes in elderly inpatients with major depression. *Am. J. Psychiatry,* **1991**, *148* (5), 617-20. http://dx.doi.org/10.1176/ajp.148.5.617

[96] Baumann, B.; Bornschlegl, C.; Krell, D.; Bogerts, B. Changes in CSF spaces differ in endogenous and neurotic depression. A planimetric CT scan study. *J. Affect. Disord.,* **1997**, *45* (3), 179-88. http://dx.doi.org/10.1016/S0165-0327(97)00073-6

[97] Scott, M. L.; Golden, C. J.; Ruedrich, S. L.; Bishop, R. J. Ventricular enlargement in major depression. *Psychiatry Res.,* **1983**, *8* (2), 91-3. http://dx.doi.org/10.1016/0165-1781(83)90095-1

[98] Shima, S.; Shikano, T.; Kitamura, T.; Masuda, Y.; Tsukumo, T.; Kanba, S.; Asai, M. Depression and ventricular enlargement. *Acta Psychiatrica Scandinavica,* **1984**, *70* (3), 275-7. http://dx.doi.org/10.1111/j.1600-0447.1984.tb01208.x

[99] Dolan, R. J.; Calloway, S. P.; Mann, A. H. Cerebral ventricular size in depressed subjects. *Psychol. Med.,* **1985**, *15* (4), 873-8. http://dx.doi.org/10.1017/S0033291700005110

[100] Andreasen, N. C.; Swayze, V., 2nd; Flaum, M.; Alliger, R.; Cohen, G. Ventricular abnormalities in affective disorder: clinical and

demographic correlates. *Am. J. Psychiatry,* **1990**, *147* (7), 893-900. http://dx.doi.org/10.1176/ajp.147.7.893

[101] Wurthmann, C.; Bogerts, B.; Falkai, P. Brain morphology assessed by computed tomography in patients with geriatric depression, patients with degenerative dementia, and normal control subjects. *Psychiatry Res.,* **1995**, *61* (2), 103-11. http://dx.doi.org/10.1016/0925-4927(95)02592-L

[102] Weinberger, D. R.; DeLisi, L. E.; Perman, G. P.; Targum, S.; Wyatt, R. J. Computed tomography in schizophreniform disorder and other acute psychiatric disorders. *Arch. General Psychiatry,* **1982**, *39* (7), 778-83. http://dx.doi.org/10.1001/archpsyc.1982.04290070014004

[103] Rossi, A.; Stratta, P.; di Michele, V.; Bolino, F.; Nistico, R.; de Leonardis, R.; Sabatini, M. D.; Casacchia, M. A computerized tomographic study in patients with depressive disorder: a comparison with schizophrenic patients and controls. *Acta Psychiatrica Belgica,* **1989**, *89* (1-2), 56-61.

[104] Abas, M. A.; Sahakian, B. J.; Levy, R. Neuropsychological deficits and CT scan changes in elderly depressives. *Psychol. Med.,* **1990**, *20* (3), 507-20. http://dx.doi.org/10.1017/S0033291700017025

[105] Lesser, I. M.; Miller, B. L.; Boone, K. B.; Hill-Gutierrez, E.; Mehringer, C. M.; Wong, K.; Mena, I. Brain injury and cognitive function in late-onset psychotic depression. *J. Neuropsychiatry Clin. Neurosci.,***1991**, *3* (1), 33-40. http://dx.doi.org/10.1176/jnp.3.1.33

[106] Van den Bossche, B.; Maes, M.; Brussaard, C.; Schotte, C.; Cosyns, P.; De Moor, J.; De Schepper, A. Computed tomography of the brain in unipolar depression. *J. Affect. Disord.,* **1991**, *21* (1), 67-74. http://dx.doi.org/10.1016/0165-0327(91)90020-S

[107] Wu, J. C.; Buchsbaum, M. S.; Johnson, J. C.; Hershey, T. G.; Wagner, E. A.; Teng, C.; Lottenberg, S. Magnetic resonance and positron emission tomography imaging of the corpus callosum: size, shape and metabolic rate in unipolar depression. *J. Affect. Disord.,* **1993**, *28* (1), 15-25. http://dx.doi.org/10.1016/0165-0327(93)90073-S

[108] Lacerda, A. L.; Nicoletti, M. A.; Brambilla, P.; Sassi, R. B.; Mallinger, A. G.; Frank, E.; Kupfer, D. J.; Keshavan, M. S.; Soares, J. C. Anatomical MRI study of basal ganglia in major depressive disorder. *Psychiatry Res.,* **2003**, *124* (3), 129-40. http://dx.doi.org/10.1016/S0925-4927(03)00123-9

[109] Krishnan, K. R.; Doraiswamy, P. M.; Lurie, S. N.; Figiel, G. S.; Husain, M. M.; Boyko, O. B.; Ellinwood, E. H., Jr.; Nemeroff, C. B. Pituitary size in depression. *J. Clin. Endocrinol. Metabol.,* **1991**, *72* (2), 256-9. http://dx.doi.org/10.1210/jcem-72-2-256

[110] Sassi, R. B.; Nicoletti, M.; Brambilla, P.; Harenski, K.; Mallinger, A. G.; Frank, E.; Kupfer, D. J.; Keshavan, M. S.; Soares, J. C. Decreased pituitary volume in patients with bipolar disorder. *Biol. Psychiatry,* **2001**, *50* (4), 271-80. http://dx.doi.org/10.1016/S0006-3223(01)01086-1

[111] Schwartz, P. J.; Loe, J. A.; Bash, C. N.; Bove, K.; Turner, E. H.; Frank, J. A.; Wehr, T. A.; Rosenthal, N. E. Seasonality and pituitary volume. *Psychiatry Res.,* **1997**, *74* (3), 151-7. http://dx.doi.org/10.1016/S0925-4927(97)00015-2

[112] Pariante, C. M.; Dazzan, P.; Danese, A.; Morgan, K. D.; Brudaglio, F.; Morgan, C.; Fearon, P.; Orr, K.; Hutchinson, G.; Pantelis, C.; Velakoulis, D.; Jones, P. B.; Leff, J.; Murray, R. M. Increased pituitary volume in antipsychotic-free and antipsychotic-treated patients of the AEsop first-onset psychosis study. *Neuropsychopharmacology,* **2005**, *30* (10), 1923-31.

[113] Berton, O.; Nestler, E. J. New approaches to antidepressant drug discovery: beyond monoamines. *Nat. Rev. Neurosci.,* **2006**, *7* (2), 137-51. http://dx.doi.org/10.1038/nrn1846

[114] Vakili, K.; Pillay, S. S.; Lafer, B.; Fava, M.; Renshaw, P. F.; Bonello-Cintron, C. M.; Yurgelun-Todd, D. A. Hippocampal volume in primary unipolar major depression: a magnetic resonance imaging study. *Biol. Psychiatry,* **2000**, *47* (12), 1087-1090. http://dx.doi.org/10.1016/S0006-3223(99)00296-6

[115] Saylam, C.; Ucerler, H.; Kitis, O.; Ozand, E.; Gonul, A. S. Reduced hippocampal volume in drug-free depressed patients. *Surg. Radiol. Anat.,* **2006**, *28* (1), 82-7.

[116] Hickie, I.; Naismith, S.; Ward, P. B.; Turner, K.; Scott, E.; Mitchell, P.; Wilhelm, K.; Parker, G. Reduced hippocampal volumes and memory loss in patients with early- and late-onset depression. *Br. J. Psychiatry,* **2005**, *186*, 197-202. http://dx.doi.org/10.1192/bjp.186.3.197

[117] Lloyd, A. J.; Ferrier, I. N.; Barber, R.; Gholkar, A.; Young, A. H.; O'Brien, J. T. Hippocampal volume change in depression: late- and early-onset illness compared. *Br. J. Psychiatry,* **2004**, *184*, 488-95. http://dx.doi.org/10.1192/bjp.184.6.488

[118] Taylor, J. L.; Blanton, R. E.; Levitt, J. G.; Caplan, R.; Nobel, D.; Toga, A. Superior temporal gyrus differences in childhood-onset schizophrenia. *Schizophr. Res.,* **2005**, *73* (2-3), 235-41. http://dx.doi.org/10.1016/j.schres.2004.07.023

[119] Hsieh, M. H.; McQuoid, D. R.; Levy, R. M.; Payne, M. E.; MacFall, J. R.; Steffens, D. C. Hippocampal volume and antidepressant response in geriatric depression. *Intl. J. Geriatric Psychiatry,* **2002**, *17* (6), 519-25. http://dx.doi.org/10.1002/gps.611

[120] Neumeister, A.; Wood, S.; Bonne, O.; Nugent, A. C.; Luckenbaugh, D. A.; Young, T.; Bain, E. E.; Charney, D. S.; Drevets, W. C. Reduced hippocampal volume in unmedicated, remitted patients with major depression versus control subjects. *Biol. Psychiatry,* **2005**, *57* (8), 935-7. http://dx.doi.org/10.1016/j.biopsych.2005.01.016

[121] Sheline, Y. I. Neuroimaging studies of mood disorder effects on the brain. *Biol. Psychiatry,* **2003**, *54* (3), 338-52. http://dx.doi.org/10.1016/S0006-3223(03)00347-0

[122] Vythilingam, M.; Heim, C.; Newport, J.; Miller, A. H.; Anderson, E.; Bronen, R.; Brummer, M.; Staib, L.; Vermetten, E.; Charney, D. S.; Nemeroff, C. B.; Bremner, J. D. Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am. J. Psychiatry,* **2002**, *159* (12), 2072-80. http://dx.doi.org/10.1176/appi.ajp.159.12.2072

[123] Sheline, Y. I. Hippocampal atrophy in major depression: a result of depression-induced neurotoxicity? *Mol. Psychiatry,* **1996**, *1* (4), 298-9.

[124] MacMaster, F. P.; Kusumakar, V. Hippocampal volume in early onset depression. *BMC Med.,* **2004**, *2*, 2. http://dx.doi.org/10.1186/1741-7015-2-2

[125] MacQueen, G. M.; Campbell, S.; McEwen, B. S.; Macdonald, K.; Amano, S.; Joffe, R. T.; Nahmias, C.; Young, L. T. Course of illness, hippocampal function, and hippocampal volume in major depression. *Proc. Natl. Acad. Sci. U.S.A.,* **2003**, *100* (3), 1387-92. http://dx.doi.org/10.1073/pnas.0337481100

[126] Frodl, T.; Schaub, A.; Banac, S.; Charypar, M.; Jager, M.; Kummler, P.; Bottlender, R.; Zetzsche, T.; Born, C.; Leinsinger, G.; Reiser, M.; Moller, H. J.; Meisenzahl, E. M. Reduced hippocampal volume correlates with executive dysfunctioning in major depression. *J. Psychiatry Neurosci.,* **2006**, *31* (5), 316-23.

[127] MacMillan, S.; Szeszko, P. R.; Moore, G. J.; Madden, R.; Lorch, E.; Ivey, J.; Banerjee, S. P.; Rosenberg, D. R. Increased amygdala: hippocampal volume ratios associated with severity of anxiety in pediatric major depression. *J. Child Adolescent Psychopharmacol.,* **2003**, *13* (1), 65-73. http://dx.doi.org/10.1089/104454603321666207

[128] Pillay, S. S.; Yurgelun-Todd, D. A.; Bonello, C. M.; Lafer, B.; Fava, M.; Renshaw, P. F. A quantitative magnetic resonance imaging study of cerebral and cerebellar gray matter volume in primary unipolar major depression: Relationship to treatment response and clinical severity. *Biol. Psychiatry,* **1997**, *42* (2), 79-84. http://dx.doi.org/10.1016/S0006-3223(96)00335-6

[129] Pillay, S. S.; Renshaw, P. F.; Bonello, C. M.; Lafer, B. C.; Fava, M.; Yurgelun-Todd, D. A quantitative magnetic resonance imaging study of caudate and lenticular nucleus gray matter volume in primary unipolar major depression: relationship to treatment response and clinical severity. *Psychiatry Res.,* **1998**, *84* (2-3), 61-74. http://dx.doi.org/10.1016/S0925-4927(98)00048-1

[130] Hankin, B. L.; Abramson, L. Y.; Moffitt, T. E.; Silva, P. A.; McGee, R.; Angell, K. E. Development of depression from preadolescence to young adulthood: emerging gender differences in a 10-year longitudinal study. *J. Abnormal Psychol.,* **1998**, *107* (1), 128-40. http://dx.doi.org/10.1037/0021-843X.107.1.128

[131] Sheline, Y. I.; Disabato, B. M.; Hranilovich, J.; Morris, C.; D'Angelo, G.; Pieper, C.; Toffanin, T.; Taylor, W. D.; MacFall, J. R.; Wilkins, C.; Barch, D. M.; Welsh-Bohmer, K. A.; Steffens, D. C.; Krishnan, R. R.; Doraiswamy, P. M. Treatment course with antidepressant therapy in late-life depression. *Am. J. Psychiatry,* **2012**, *169* (11), 1185-93. http://dx.doi.org/10.1176/appi.ajp.2012.12010122

[132] MacQueen, G. M.; Yucel, K.; Taylor, V. H.; Macdonald, K.; Joffe, R. Posterior Hippocampal Volumes Are Associated with Remission Rates in Patients with Major Depressive Disorder. *Biol. Psychiatry,*

2008, *64* (10), 880-883. http://dx.doi.org/10.1016/j.biopsych.2008.06.027

[133] Yucel, K.; McKinnon, M.; Chahal, R.; Taylor, V.; Macdonald, K.; Joffe, R.; MacQueen, G. Increased subgenual prefrontal cortex size in remitted patients with major depressive disorder. *Psychiatry Res.,* **2009**, *173* (1), 71-76. http://dx.doi.org/10.1016/j.pscychresns.2008.07.013

[134] Costafreda, S. G.; Chu, C.; Ashburner, J.; Fu, C. H. Prognostic and diagnostic potential of the structural neuroanatomy of depression. *PloS One,* **2009**, *4* (7), e6353. http://dx.doi.org/10.1371/journal.pone.0006353

[135] Smith, R.; Chen, K.; Baxter, L.; Fort, C.; Lane, R. D. Antidepressant effects of sertraline associated with volume increases in dorsolateral prefrontal cortex. *J. Affect. Disord.,* **2013**, *146* (3), 414-419. http://dx.doi.org/10.1016/j.jad.2012.07.029

[136] Gunning, F. M.; Cheng, J.; Murphy, C. F.; Kanellopoulos, D.; Acuna, J.; Hoptman, M. J.; Klimstra, S.; Morimoto, S.; Weinberg, J.; Alexopoulos, G. S. Anterior cingulate cortical volumes and treatment remission of geriatric depression. *Intl. J. Geriatric Psychiatry,* **2009**, *24* (8), 829-36. http://dx.doi.org/10.1002/gps.2290

[137] Lai, C. H. Duloxetine-related growth of putamen and brainstem in first-onset drug-naive major depressive disorder with panic disorder: a case series. *J. Neuropsychiatry Clin. Neurosci.,* **2011**, *23* (2), E40-1. http://dx.doi.org/10.1176/jnp.23.2.jnpe40

[138] Pizzagalli, D. A.; Oakes, T. R.; Fox, A. S.; Chung, M. K.; Larson, C. L.; Abercrombie, H. C.; Schaefer, S. M.; Benca, R. M.; Davidson, R. J. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. *Mol. Psychiatry,* **2004**, *9* (4), 325, 393-405. http://dx.doi.org/10.1038/sj.mp.4001501

[139] Alexopoulos, G. S.; Murphy, C. F.; Gunning-Dixon, F. M.; Latoussakis, V.; Kanellopoulos, D.; Klimstra, S.; Lim, K. O.; Hoptman, M. J. Microstructural white matter abnormalities and remission of geriatric depression. *Am. J. Psychiatry,* **2008**, *165* (2), 238-44. http://dx.doi.org/10.1176/appi.ajp.2007.07050744

[140] Fossati, P.; Radtchenko, A.; Boyer, P. Neuroplasticity: from MRI to depressive symptoms. *Eur. Neuropsychopharmacol.,* **2004**, *14 Suppl 5*, S503-10.

[141] Ohira, K.; Takeuchi, R.; Shoji, H.; Miyakawa, T. Fluoxetine-induced cortical adult neurogenesis. *Neuropsychopharmacology,* **2013**, *38* (6), 909-20.

[142] Kraus, C.; Ganger, S.; Losak, J.; Hahn, A.; Savli, M.; Kranz, G. S.; Baldinger, P.; Windischberger, C.; Kasper, S.; Lanzenberger, R. Gray matter and intrinsic network changes in the posterior cingulate cortex after selective serotonin reuptake inhibitor intake. *NeuroImage,* **2014**, *84*, 236-244. http://dx.doi.org/10.1016/j.neuroimage.2013.08.036

[143] Brody, A. L.; Saxena, S.; Mandelkern, M. A.; Fairbanks, L. A.; Ho, M. L.; Baxter, L. R. Brain metabolic changes associated with symptom factor improvement in major depressive disorder. *Biol. Psychiatry,* **2001**, *50* (3), 171-8. http://dx.doi.org/10.1016/S0006-3223(01)01117-9

[144] Brody, A. L.; Saxena, S.; Silverman, D. H.; Alborzian, S.; Fairbanks, L. A.; Phelps, M. E.; Huang, S. C.; Wu, H. M.; Maidment, K.; Baxter, L. R., Jr. Brain metabolic changes in major depressive disorder from pre- to post-treatment with paroxetine. *Psychiatry Res.,* **1999**, *91* (3), 127-39. http://dx.doi.org/10.1016/S0925-4927(99)00034-7

[145] Little, J. T.; Ketter, T. A.; Kimbrell, T. A.; Dunn, R. T.; Benson, B. E.; Willis, M. W.; Luckenbaugh, D. A.; Post, R. M. Bupropion and venlafaxine responders differ in pretreatment regional cerebral metabolism in unipolar depression. *Biol. Psychiatry,* **2005**, *57* (3), 220-8. http://dx.doi.org/10.1016/j.biopsych.2004.10.033

[146] Konarski, J. Z.; Kennedy, S. H.; Segal, Z. V.; Lau, M. A.; Bieling, P. J.; McIntyre, R. S.; Mayberg, H. S. Predictors of nonresponse to cognitive behavioural therapy or venlafaxine using glucose metabolism in major depressive disorder. *J. Psychiatry Neurosci.,* **2009**, *34* (3), 175-80.

[147] Frodl, T.; Jager, M.; Smajstrlova, I.; Born, C.; Bottlender, R.; Palladino, T.; Reiser, M.; Moller, H. J.; Meisenzahl, E. M. Effect of hippocampal and amygdala volumes on clinical outcomes in major depression: a 3-year prospective magnetic resonance imaging study. *J. Psychiatry Neurosci.,* **2008**, *33* (5), 423-30.

[148] Janssen, J.; Hulshoff Pol, H. E.; Schnack, H. G.; Kok, R. M.; Lampe, I. K.; de Leeuw, F. E.; Kahn, R. S.; Heeren, T. J. Cerebral volume measurements and subcortical white matter lesions and short-term treatment response in late life depression. *Intl. J. Geriatric Psychiatry,* **2007**, *22* (5), 468-74. http://dx.doi.org/10.1002/gps.1790

[149] Lai, C. H.; Wu, Y. T. Duloxetine's modest short-term influences in subcortical structures of first episode drug-naive patients with major depressive disorder and panic disorder. *Psychiatry Res.,* **2011**, *194* (2), 157-62. http://dx.doi.org/10.1016/j.pscychresns.2011.03.011

[150] Ostuzzi, G.; Bighelli, I.; Carrara, B. V.; Dusi, N.; Imperadore, G.; Lintas, C.; Nifosi, F.; Nose, M.; Piazza, C.; Purgato, M.; Rizzo, R.; Barbui, C. Making the use of psychotropic drugs more rational through the development of GRADE recommendations in specialist mental healthcare. *Intl. J. Mental Health Systems,* **2013**, *7* (1), 14. http://dx.doi.org/10.1186/1752-4458-7-14

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