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REVIEW

HIPPOCAMPAL NEUROPLASTICITY IN MAJOR DEPRESSIVE DISORDER

N. V. MALYKHIN [a,b,c*] **AND N. J. COUPLAND** [b]

[a] *The Neuroscience and Mental Health Institute, University of Alberta, Edmonton, Alberta, Canada*

[b] *Department of Psychiatry, University of Alberta, Edmonton, Alberta, Canada*

[c] *Department of Biomedical Engineering, University of Alberta, Edmonton, Alberta, Canada*

Abstract—One of the most replicated findings has been that hippocampus volume is decreased in patients with major depressive disorder (MDD). Recent volumetric magnetic resonance imaging (MRI) studies suggest that localized differences in hippocampal volume may be more prominent than global differences. Preclinical and post-mortem studies in MDD indicated that different subfields of the hippocampus may respond differently to stress and may also have differential levels of plasticity in response to antidepressant treatment. Advances in high-field MRI allowed researchers to visualize and measure hippocampal subfield volumes in MDD patients *in vivo*. The results of these studies provide the first *in vivo* evidence that hippocampal volume reductions in MDD are specific to the cornu ammonis and dentate gyrus hippocampal subfields, findings that appear, on the surface, consistent with preclinical evidence for localized mechanisms of hippocampal neuroplasticity. In this review we discuss how recent advances in neuroimaging allow researchers to further understand hippocampal neuroplasticity in MDD and how it is related to antidepressant treatment, memory function, and disease progression.

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Key words: hippocampus, memory, major depressive disorder, antidepressant treatment, dentate gyrus, cornu ammonis.

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INTRODUCTION

Major depressive disorder (MDD) is a major challenge for society affecting 2–5% of the population and is a major cause of disability worldwide (Murray and Lopez, 2013). At least 30% of patients do not remit after a year of multiple antidepressant trials (Warden et al., 2007) and this overestimates positive outcomes (Frank et al., 1991).

The causes of MDD remain uncertain, although a number of factors are known to increase risk including abuse during childhood and chronic stress as an adult (Paolucci et al., 2001; Widom et al., 2007; Bradley et al., 2008; Danese et al., 2009; Risch et al., 2009). The well-described effects of stress on risk of developing MDD have been supported by findings that there are abnormalities in the hypothalamic–pituitary–adrenal (HPA) axis in patients with MDD, and this may impact the release of glucocorticoids. That the HPA axis is dysregulated is evidenced by studies examining cortisol hypersecretion, dexamethasone non-suppression, and exaggerated responses to dex amethasone–corticotropin-releasing hormone challenges (Barden, 2004). In particular several components of the HPA axis have been implicated in the development of MDD, specifically the hippocampus (HC), amygdala and prefrontal cortex (PFC) (Pittenger and Duman, 2008; Ulrich-Lai and Herman, 2009).

One of the most replicated findings has been that HC volume is decreased in patients with MDD, with the degree of change having been confirmed by several meta-analyses of magnetic resonance imaging (MRI) studies (Videbech and Ravnkilde, 2004; McKinnon et al., 2009). Based on preclinical studies, several mechanisms, including neuronal and glial remodeling or loss,

*Correspondence to: N. V. Malykhin, Research Transition Facility 1069, University of Alberta, Edmonton, Alberta T6G 2V2, Canada. Tel: +1-(780)-248-1120; fax: +1-(780)-492-8259.
E-mail address: nikolai@ualberta.ca (N. V. Malykhin).

Abbreviations: BDNF, brain-derived neurotrophic factor; CA, childhood adversity; CA1-3, cornu ammonis; Cho, choline; DG, dentate gyrus; DTI, diffusion tensor imaging; FA, fractional anisotropy; Glx, glutamate–glutamine; GR, glucocorticoid receptor; HC, hippocampus; HPA, hypothalamic–pituitary–adrenal axis; MDD, major depressive disorder; MI, myo-inositol; MRI, magnetic resonance imaging; NAA, N-acetyl-aspartate; PFC, prefrontal cortex; SSRI, selective serotonin reuptake inhibitors; UF, uncinate fascicles.

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neuronal death and suppressed adult neurogenesis, apparently involving elevated levels of glucocorticoids, have been suggested as potential causative factors in low HC volume (Sapolsky, 2000; Czéh and Lucassen, 2007). MRI studies have consistently shown that the reductions in HC volumes in MDD have been associated with episode recurrence (MacQueen et al., 2003; McKinnon et al., 2009), history of childhood maltreatment (Vythilingam et al., 2002; Frodl et al., 2010) deficits in memory performance (Lee et al., 2012). Only a few MRI studies have analyzed the HC in medication-free MDD (MacQueen et al., 2003; Posener et al., 2003; Vythilingam et al., 2004; Frodl et al., 2010) while the majority of studies included participants on antidepressant treatment (Videbech and Ravnkilde, 2004; McKinnon et al., 2009). Several genetic associations have been suggested to play an important role with associations between mood, memory and HC volume (Eker et al., 2011; Kohli et al., 2011; Price et al., 2013; Dunn et al., 2015).

There is preclinical evidence that stress and glucocorticoids negatively impact HC neuroplasticity, neuronal survival, and glial survival (Czéh and Lucassen, 2007; Pittenger and Duman, 2008). Other preclinical studies have suggested that antidepressants have stress-protective effects on HC neuroplasticity (Pittenger and Duman, 2008), and such a positive effect also appears to occur in humans (Boldrini et al., 2009). Therefore, these findings might suggest that stress, possibly acting via glucocorticoids, may negatively affect HC neuronal plasticity, which in turn is reflected in decreased HC volumes (Dranovsky and Hen, 2006). This information may also suggest that one effect of antidepressant treatment would be to reverse some of these changes. Clearly, if this were known to be the case it could open up significant new possibilities for both the etiology and treatment of MDD. However, the information from most previous MRI studies has been inadequate to allow measurement of any such effects (McKinnon et al., 2009). In this review we discuss how recent advances in neuroimaging allow researchers to further understand HC neuroplasticity in MDD and how it is related to antidepressant treatment, memory function, and disease progression.

HC VOLUME CHANGES IN MDD: FOCUS ON HC SUBREGIONS

Most MRI studies in MDD reported differences in global HC volume (Videbech and Ravnkilde, 2004; McKinnon et al., 2009). However, the HC can be further subdivided along its longitudinal axis into ventral–dorsal (rodent) and head–body–tail (human) subregions (Fig. 1). A new development in volumetric MRI analysis has been to segment the HC head, body and tail, and/or to include the tail in volume calculations (Maller et al., 2006; Malykhin et al., 2007). These anatomically and functionally different subregions (Duvernoy, 2005) are not uniformly affected by disease (Maller et al., 2007; Bouchard et al., 2008; Malykhin et al., 2008a,b). Until recently it was unclear whether HC subregions are differentially affected in MDD, or in association with specific risk factors or treatment. Neumeister and colleagues (2005) first reported that posterior HC (posterior to the head; i.e. body + tail), rather than the HC head was smaller bilaterally in remitted, recurrent MDD (Table 1). Maller and colleagues (2007) found that low HC volume was limited primarily to the tail in treatment resistant MDD, particularly in females, with more anterior (i.e. body + head) changes also present in males. Next MacQueen and colleagues (2008) reported that MDD participants who met criteria for clinical remission at 8 weeks of treatment had larger pre-treatment HC body/tail volumes bilaterally than those who did not achieve remission. de Geus and colleagues (2007), using voxel-based morphometry and a twin design, reported a volume reduction in the left posterior HC region in monozygotic co-twins discordant for having high environmental risk factors for depression. Posener and colleagues (2003), using high-dimensional brain mapping, did not find differences in total HC volume between MDD and controls, but did report localized differences in HC surface deformation. The most prominent inward deformation of the HC was located in the head (asymmetrically more prominent on the right) and tail, whereas the most prominent outward deformation was in the HC body. Vythilingam and colleagues (2004) did not find significant differences in HC subregion volumes between untreated MDD and healthy subjects. In our own cross-sectional study (Malykhin et al., 2010b) we reported that MDD patients had a smaller HC tail bilaterally and unilaterally smaller right HC and right head volumes, compared with controls. A history of multiple types of child abuse was associated with more extensive and bilateral reductions in HC head and tail volume, but also with more recurrent depression.

Despite the increasing number of MRI studies in MDD, only a few have included medication-free participants and with sometimes brief washout periods, such that data on medication effects were not considered adequate for meta-analysis (McKinnon et al., 2009). Several studies have suggested that lower total HC volume in MDD predicts worse treatment outcomes (Vakili et al., 2000; Frodl et al., 2008; MacQueen et al., 2008), but only one study has demonstrated that global HC volume increases after treatment (Frodl et al., 2008). A significant increase in the left HC volume was shown in participants who continued antidepressants for 3 years, but was not dependent on clinical response (Frodl et al., 2008) and changes after not been shown after shorter treatment duration (Vythilingam et al., 2004). In our study (Malykhin et al., 2010b) we did not confirm that unmedicated participants were more vulnerable to low HC head or tail volumes; although differences from controls were marginally more significant, unmedicated and medicated MDD did not differ. However, we demonstrated that long-term antidepressant treatment may affect total HC volume in MDD with the most notable difference in HC body, which was increased above that in controls, as well as unmedicated MDD. Although interpretation of this finding was limited by the cross-sectional design, the medicated patients were symptomatic and the data appear more consistent with evidence that increased HC volume