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Invited review

Hippocampal neurogenesis as a target for the treatment of mental illness: A critical evaluation

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ABSTRACT

Over one-quarter of adult Americans are diagnosed with a mental illness like Major Depressive Disorder (MDD), Post-Traumatic Stress Disorder (PTSD), schizophrenia, and Alzheimer's Disease. In addition to the exceptional personal burden these disorders exert on patients and their families, they also have enormous cost to society. Although existing pharmacological and psychosocial treatments alleviate symptoms in many patients, the comorbidity, severity, and intractable nature of mental disorders strongly underscore the need for novel strategies. As the hippocampus is a site of structural and functional pathology in most mental illnesses, a hippocampal-based treatment approach has been proposed to counteract the cognitive deficits and mood dysregulation that are hallmarks of psychiatric disorders. In particular, preclinical and clinical research suggests that hippocampal neurogenesis, the generation of new neurons in the adult dentate gyrus, may be harnessed to treat mental illness. There are obvious applications and allures of this approach; for example, perhaps stimulating hippocampal neurogenesis would reverse the overt and noncontroversial hippocampal atrophy and functional deficits observed in Alzheimer's Disease and schizophrenia, or the more controversial hippocampal deficits seen in MDD and PTSD. However, critical examination suggests that neurogenesis may only correlate with mental illness and treatment, suggesting targeting neurogenesis alone is not a sufficient treatment strategy. Here we review the classic and causative links between adult hippocampal neurogenesis and mental disorders, and provide a critical evaluation of how (and if) our basic knowledge of new neurons in the adult hippocampus might eventually help combat or even prevent mental illness.

1. Introduction

Each year over 25% of adult Americans carry the diagnosis of at least one mental disorder (Kessler et al., 2005a,b). By far, the greatest percentage of the adult US population – 18.7% – is diagnosed with an anxiety disorder like Post-Traumatic Stress Disorder (PTSD, 3.5%), but notable percentages of the population are also diagnosed with mood disorders (9.5%) like Major Depressive Disorder (MDD, 6.7%), or with Alzheimer's Disease (~2%) and schizophrenia (1.1%) (Kessler et al., 2005a,b). Combined with psychosocial support, pharmacological interventions like anxiolytic, antidepressive, and antipsychotic drugs alleviate many symptoms associated anxiety disorders, MDD, and schizophrenia, respectively. However, the persistence and severity of symptoms of these individual disorders, the high proportion of individuals with comorbid psychiatric disorders, like addiction, or other severe health challenges, like obesity or cardiovascular disease, results in enormous personal and societal cost. Therefore, there is extraordinary interest in identifying and pursuing novel strategies for the treatment and even prevention of mental illness.

While mental disorders are exceptionally diverse and likely have discrete and complex neurobiological underpinnings, one particular brain region has long been studied for its potential involvement in mental illness in general: the hippocampus (Fig. 1) (Bloom, 1975, 1984; Frith and Done, 1988; Holsboer, 1988; Kling et al., 1987; McEwen et al., 1992; Meaney et al., 1988). Primarily known for its role in learning and memory, the hippocampus also has an important role in general cognition, mood regulation, response to stress, and even in encoding predictions for future events (Bast, 2007; Eichenbaum and Fortin, 2009; Fuchs and Flugge, 1998; Price and Drevets, 2009; Squire, 2004). A large body of literature shows that, in general, mental illness is marked by diminished hippocampal structure and function. For example, MDD, PTSD, schizophrenia, Alzheimer's disease and even stress – a precipitating factor in many mental disorders – are marked by decreased hippocampal volume, learning and memory deficits, and

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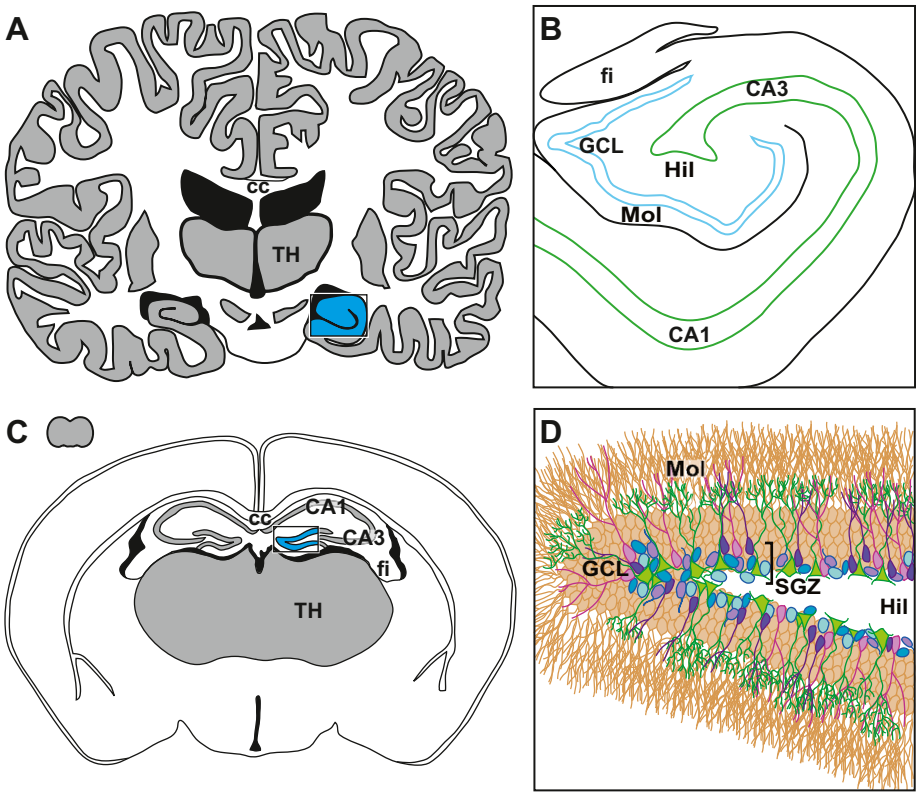

Fig. 1. Schematic of hippocamapal dentate gyrus in (A, B) human and (C, D) mouse brains. (A) Schematic of human brain, cut through the frontal/coronal plane at the level of the thalamus (TH) and corpus callosum (cc). The hippocampus is a bilateral structure nestled within the temporal lobe; the right hippocampus is shaded in blue. (B) Human hippocampus, enlarged from blue region in (A). Adult-generated neurons in the human dentate gyrus reside in the granule cell layer (GCL; blue) and the nearby hilus (Hil). For context, other human hippocampal regions are also depicted, such as the molecular layer of the dentate gyrus (Mol), regions of Ammon's Horn (CA1, CA3), and the nearby white matter structure the fimbria (fi). (C) Small grey form in upper-left represents the mouse brain in size relation to the human brain in (A). Larger image is schematic of the adult mouse brain in the coronal plane, with the majority of the right hippocampal dentate gyrus highlighted in blue. For context, regions of Ammon's horn (CA1, CA3) and nearby grey matter (TH) and white matter structures (cc, fi) are provided. (D) Mouse dentate gyrus, enlarged from blue region in (C). Detail is shown in (D) to highlight the current view on the "stages" or phases of neurogenesis and the cellular diversity that thus exists in the neurogenic region of the subgranular zone (SGZ). Note many aspects of the neurogenic niche are not depicted, including vasculature, inhibitory interneurons, and astrocytes. Based on current understanding, the putative stem cell (green) gives rise to progenitor cells (blue), some of which become immature neurons (purple), which eventually mature into granule cell neurons (brown) and incorporate into hippocampal circuitry by projecting axons to CA3 via the mossy fiber pathway. In the rodent, projections may enter the mossy fiber pathway in less than 7 days and adult-generated neurons can present indices of morphological and phenotypic maturity from 2 weeks to 2 months later. In the human, the timing of adult hippocampal neurogenesis is unknown. In addition, the anatomic and morphologic features of the human hippocampal stem cell remains unknown. CA1, CA3, Cornu Ammon subregions 1, 3; cc, corpus callosum; fi, fimbria; GCL, granule cell layer; Hil, hilus; Mol, molecular layer; SGZ, subgranular zone; TH, thalamus.

mood dysregulation (e.g. Bremner, 1999; Campbell and Macqueen, 2004; Geuze et al., 2005; Goldman and Mitchell, 2004; Liberzon and Sripada, 2008; Lupien et al., 2007b; Pfefferbaum and Marsh, 1995; Sala et al., 2004; Sapolsky, 2000b; Savitz and Drevets, 2009; Villarreal and King, 2001). Intriguingly, successful improvement of the behavioral and cognitive symptoms of these disorders is often linked to attenuation or reversal of these changes in hippocampal structure and function. Such work has encouraged consideration of whether hippocampal atrophy is a useful target for the treatment of mental illness (Dhikav and Anand, 2007; Sala et al., 2004; Sapolsky, 2000a).

The hippocampus is one of most "responsive" brain structures in that it demonstrates rapid plasticity at the molecular, cellular, structural, and functional levels after specific stimuli. Thus, it has been challenging for scientists to narrow which aspect of hippocampal plasticity might be best targeted to counteract the symptoms of such diverse disorders. One particular aspect of hippocampal plasticity that has received significant attention is adult hippocampal neurogenesis, or the ability of the hippocampus to generate new neurons throughout life. First discovered by Joseph Altman more than forty-five years ago (Altman, 1963), it is now accepted that stem-like and progenitor cells residing in the aptly-named subgranular zone (SGZ; Fig. 1) give rise to dentate gyrus granule neurons that integrate into circuitry and contribute to discrete aspects of hippocampal functions (Balu and Lucki, 2009; Pathania et al., this issue). As reviewed in detail elsewhere (Abrous et al., 2005; Kempermann et al., 2008) and briefly here (Table 1), there is an enormous amount of correlative evidence linking hippocampal neurogenesis with mental disorders. More recent work has provided striking causative connections as well (e.g. Li et al., 2008b; Revest et al., 2009; Santarelli et al., 2003). The surge of primary and review papers on this topic urge revisiting the question, "Is manipulation of hippocampal neurogenesis a promising target for the treatment of mental disorders?"

A number of excellent reviews have recently tackled questions including "What is neurogenesis good for?" and "Is targeting hippocampal atrophy useful for mental illness?" (e.g. Aimone et al., 2006; Becker and Wojtowicz, 2007; Bruel-Jungerman et al., 2007; Drew and Hen, 2007; Eisch et al., 2008; Elder et al., 2006; Gould et al., 1999; Kempermann et al., 2008; Kempermann and Kronenberg, 2003; Ming and Song, 2005; Morgan, 2007; Perera et al., 2008; Sahay and Hen, 2007; Thomas and Peterson, 2008; Thompson et al., 2008; Vaidya et al., 2007). Therefore, the goal for this brief review is to critically evaluate hippocampal neurogenesis as