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REVIEW ARTICLE

Purposeful Activity in Psychiatric Rehabilitation: Is Neurogenesis a Key Player?

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Summary Adult neurogenesis, defined as the generation of new neurons in adulthood, has been a fascinating discovery in neuroscience, as the continuously replenishing neuronal population provides a new perspective to understand neuroplasticity. Besides maintaining normal physiological function, neurogenesis also plays a key role in pathophysiology and symptomatology for psychiatric conditions. In the past decades, extensive effort has been spent on the understanding of the functional significance of neurogenesis in psychiatric conditions, mechanisms of pharmacological treatment, and discovery of novel drug candidates for different conditions. In a clinical situation, however, long-term rehabilitation treatment, in which occupational therapy is the key discipline, is a valuable, economical, and commonly used treatment alternative to psychotropic medications. Surprisingly, comparatively few studies have investigated the biological and neurogenic effects of different psychiatric rehabilitative treatments. To address the possible linkage between psychiatric rehabilitation and neurogenesis, this review discusses the role of neurogenesis in schizophrenia, major depression, and anxiety disorders. The review also discusses the potential neurogenic effect of currently used psychiatric rehabilitation treatments. With a better understanding of the biological effect of psychiatric rehabilitation methods and future translational studies, it is hoped that the therapeutic effect of psychiatric rehabilitation methods could be explained with a novel perspective. Furthermore, this knowledge will benefit future formulation of treatment methods, especially purposeful activities in occupational therapy, for the treatment of psychiatric disorders.

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Introduction

Generation of new neurons in adulthood, a process termed "adult neurogenesis," is a specific form of neuroplasticity that occurs in mammals (Ruan et al., 2014). This biological process has challenged a dogma in neuroscience that all neurons are born at the prenatal and early postnatal periods. The discovery of adult neurogenesis has shed light on the treatment of neurological conditions, including neurodegeneration, with the hope that the newly generated neurons could replace the lost ones. Interestingly, the process of neurogenesis is related to the efficacy of psychiatric medications and psychiatric illnesses, and the discovery of the neurogenic effect of antidepressant was one of the pioneer studies that lead to the intensive investigation of the role of neurogenesis in psychiatric illnesses (Malberg, Eisch, Nestler, & Duman, 2000).

Dentate gyrus of the hippocampus and subventricular zone are the brain regions demonstrating neurogenesis. Because the hippocampus is recognized by its importance in learning, memory, and emotional regulation, the downregulation of neurogenesis in the dentate gyrus may cause dysfunction in these aspects (Ruan et al.). Recent studies have suggested that hippocampal neurogenesis is essential for regulating the hypothalamic—pituitary—adrenal gland axis, which in turn modulates physiological response to stress (Snyder, Soumier, Brewer, Pickel, & Cameron, 2011). Because stress is a common risk factor for various psychiatric illnesses, altered (usually suppressed) neurogenesis would increase the vulnerability to psychiatric illnesses and may contribute to the cognitive and emotional signs and symptoms of the diseases.

Basic research studies have demonstrated that neurogenesis could be regulated by environmental stimulation or individual activity (Fabel & Kempermann, 2008). Physical activity, environmental enrichment, learning, and reduction in social stress are proven to be proneurogenic and could reverse the related behavioural disturbances. When comparing the abovementioned stimulation or activity with psychiatric rehabilitation, a number of commonalities could be observed. For example, providing sensory stimulation for patients in a rehabilitation program is similar to the multisensory stimulation delivered by enriched environment (Yang, Zhou, Chung, Li-Tsang, & Fong, 2013); physical exercise is known to promote both cognition and emotion; stress, regardless of the origins, is a well-known risk factor of psychiatric illnesses. These suggest that neurogenic modalities are common among psychiatric rehabilitation treatments, and the patients may be benefited through the regulation of neurogenesis. This review will discuss research findings on regulation of neurogenesis by nonpharmacological methods, which may provide a novel perspective to explain the effectiveness of psychiatric rehabilitation.

Neurogenesis and psychiatric disorders

Depressive disorders

Depressive disorder is one of the leading causes of disability. The exact pathophysiology, however, still remains obscure. From the current understanding, risk factors of depressive disorder would alternate the availability of different monoamines and neurotrophic factors (Krishnan & Nestler, 2008), and subsequently induce pathological changes on both macroscopic (volume of grey/white matter) and microscopic (cellular and subcellular) structures. Such changes lead to the signs and symptoms of depression. In contrast to the hypothetical pathology, antidepressant treatment would reverse the shortage of monoamine/neurotrophic factors thereby reversing the impairment. About a decade ago, the proneurogenic properties of antidepressants were discovered (Malberg et al., 2000) and this led to the proposal of *neurogenesis hypothesis*, which suggests that the impairment in patients with depression is caused by the disruption in neurogenesis. This hypothesis fuelled the studies that examined whether disrupted neurogenesis is the key mechanism underlying depression.

Clinical and laboratory findings suggested that neurogenesis is involved in depressive disorder. While antidepressant treatments are usually found to be proneurogenic, stress, which is widely accepted as a risk factor of depression (Lau et al., 2011), is usually found to suppress neurogenesis. The opposite effects of antidepressants and stress on neurogenesis have been tested in various animal depression models and the occurrence of depression-like behaviour was found to be associated with neurogenesis (DeCarolis & Eisch, 2010). Because the hippocampus is a key component of the limbic system, it is not surprising that the new-born neurons are commonly assumed to take part in mood regulation (Ruan et al., 2014). To understand the causal role of neurogenesis in depression, several experimental techniques that suppress neurogenesis were developed, including X-irradiation, antimitotic drugs, and transgenic animals, which are used in ablation of neurogenesis and to study the effect of neurogenesis-suppressing drugs (Ruan et al.). In the study by Santarelli et al. (2003), after blocking neurogenesis with X-irradiation, the anxiety level of mice did not decrease even after treatment with antidepressants. In another study, blocking hippocampal neurogenesis was found to prevent the therapeutic effect of antidepressants or psychotropic medication treatment (Jiang et al., 2005). Furthermore, after blocking neurogenesis, animals showed a slower recovery after exposure to moderate stress, and demonstrated changes in behavioural phenotypes including increased depression-like behaviour and anhedonia (Snyder et al., 2011).

Similar to other psychiatric disorders, depressive disorder has a complex and elusive pathophysiology. Neurogenesis is unlikely to be the sole mechanism underlying the disease, whereas other cofactors such as stress and neuroinflammation are potential players in the pathology. For example, when animals were subjected to neurogenesis suppression without exposure to stress, no behavioural despair was found (David et al., 2009). Nevertheless, the neurogenesis hypothesis provides a novel point of view on the biology of depression, and an increasing number of preclinical research suggests the linkage between neurogenesis and depression, but clinical evidence is needed to further confirm the association.

Schizophrenia

The first study that investigated neurogenesis in schizophrenia examined postmortem brain sample from