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REVIEW ARTICLE

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

Joyce Siu-Chong Cheung [1], Jackie Ngai-Man Chan [1], Benson Wui-Man Lau*, Shirley Pui-Ching Ngai

Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong Special Administrative Region, China

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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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* Corresponding author. Room Number ST507, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, 11 Yuk Choi Road, Hung Hom, Kowloon, Hong Kong Special Administrative Region, China.
E-mail address: benson.lau@polyu.edu.hk (B.W.-M. Lau).
[1] These two authors contributed equally to this work.

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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

schizophrenia patients. During immunostaining, hippocampal cell proliferation was found to be suppressed in the diseased samples (Reif et al., 2006), which was 60% lower when compared with a control group. Although Reif et al. only studied cell proliferation and not the other processes of neurogenesis, their results demonstrated that deficits of neurogenesis may be a pathological feature of schizophrenia. To simulate one of the hypothetical causes of schizophrenia (prenatal infection), different studies used animal model with maternal viral infection (e.g., models using polyriboinosinic—polyribocytidilic acid; Meyer & Feldon, 2010). Interestingly, behavioural and cognitive deficits related to the suppressed neurogenesis were found in the infected offspring (Meyer & Feldon), including prepulse inhibition disruption, decreased attention, and reduced working memory. The antipsychotic drug, risperidone, however, could reverse the behavioural deficit and increase neurogenesis (Piontkewitz et al., 2012). The importance of neurogenesis is further supported by other pharmacological studies. Phencyclidine, a hallucination-inducing drug that causes schizophrenia-like symptoms in animal models, was shown to suppress neurogenesis (Liu et al., 2006). By contrast, antipsychotics, such as clozapine, increased the proliferation of new cells in different structures of the brain, such as prefrontal cortex, dorsal striatum, and hippocampus (Halim, Weickert, McClintock, Weinberger, & Lipska, 2004). Neurogenesis might be altered in the hippocampi of schizophrenic patients and is subjected to the regulation of antipsychotics.

The association between schizophrenia and neurogenesis was also shown by genetic analysis. A strong linkage between schizophrenia and gene was initially suggested by the disruption in the expression of the schizophrenia 1 gene (*DISC1*) in a Scottish family (Enomoto et al., 2009). *DISC1* regulates cognitive performance, working memory, formation of the hippocampus, and has significant neurodevelopmental functions that are important for neurogenesis. *Neuronal PAS domain-containing 3 (NPAS3)* is another gene that is related to schizophrenia (Erbel-Sieler et al., 2004). Transgenic animals with *NPAS3* disruption demonstrated a schizophrenia-like phenotype, including impaired memory, deformed sensorimotor gating, and social recognition (Erbel-Sieler et al.). Simultaneously, suppressed neurogenesis in the hippocampus was shown in these animals (Pieper et al., 2010). *Neuregulin 1* (*NRG1*) is also reported to be associated with schizophrenia (Law, Shannon Weickert, Hyde, Kleinman, & Harrison, 2004). *NGR1* participates in synaptogenesis, activity-dependent plasticity of synapse, expression of excitatory neurotransmitters, and processes of neurogenesis (Law et al., 2004), and is thus essential for the normal functioning of the central nervous system (CNS). Disruption of the signalling pathway of *NRG1* results in hypofunction of the *N*-methyl-D-aspartate receptor (Hahn et al., 2006), which resembles the *N*-methyl-D-aspartate receptor hypofunction hypothesis of schizophrenia.

Anxiety disorders

Anxiety disorder is one of the most common psychiatric conditions with a lifetime prevalence over 25% (Ruan et al., 2014). Patients with anxiety disorder show exaggerated reactions to certain stimuli, but these normally would not impose immediate threats. Because the response may root at conditioning, blocking of hippocampal neurogenesis was suggested to be one of the mechanisms responsible for this category of disorder.

When it was proven that selective serotonin reuptake inhibitors could promote neurogenesis (Malberg et al., 2000), anxiety disorders were suggested to be associated with neurogenesis because antidepressants are used clinically to treat anxiety disorders, and the aforementioned speculation was confirmed later (Santarelli et al., 2003). After blocking neurogenesis, the anxiolytic effect of fluoxetine was abolished in a novelty suppressed feeding test. A similar result was found for HU-210, a synthetic cannabinoid (Jiang et al., 2005): the anxiolytic effect could only be found in animals with intact neurogenesis. Pregabalin, another class of anticonvulsant drug for generalized anxiety disorder, could increase neurogenesis and prevent depression-like behaviour in animals (Valente et al., 2012).

Available evidence suggests that among different anxiety disorders, post-traumatic stress disorder (PTSD) is related to neurogenesis. Previous studies have shown that patients with PTSD had a reduction in hippocampal volume, which had an impact on their declarative verbal memory (Bremner, Elzinga, Schmahl, & Vermetten, 2008). Interestingly, increase in hippocampal volume was reported in patients with PTSD who received phenytoin (antiepileptic drug) treatment (Bremner et al.). In addition, the brain-derived neurotrophic factor signalling pathway, which regulates neurogenesis, was disrupted in patients with PTSD (Kaplan, Vasterling, & Vedak, 2010). A preclinical study showed that animal models of PTSD, induced by inescapable electric shock, exhibited a physiological arousal response associated with suppressed hippocampal neurogenesis (Kikuchi et al., 2008). Recently, neurogenesis in an animal model of generalized anxiety disorder was studied and it was found to be suppressed as expected (Dias et al., 2014).

Regarding the mechanisms, it is possible that the new neurons may be required in pattern separation, which is the ability to differentiate highly similar stimulus or experiences. Patients with anxiety disorders may have dysfunctions in pattern separation, and thus could not differentiate between dangerous and safe cues. Because animal studies showed that an increase in neurogenesis would benefit pattern separation (Aimone, Deng, & Gage, 2011; Winocur, Wojtowicz, & Tannock, 2015), further studies are needed to test whether the failure in pattern separation is the key issue in anxiety disorders.

Psychiatric rehabilitation and potential association with neurogenesis

Psychiatric rehabilitation plays an essential role in disease management for improving functioning and reducing rehospitalization rate of the affected individuals. As discussed earlier, neurogenesis could be regulated by various activity-based modalities, including enriched environment, physical exercise, and learning (Brown et al., 2003). Interestingly,

psychiatric rehabilitation (especially occupational therapy) usually incorporates activities that are related to the aforementioned modalities. In this section, we will discuss the potential neurogenic effect of psychiatric rehabilitative methods, which could alleviate the psychiatric signs and symptoms.

Enriched physical and social environment

The robust neurogenic effect of enriched environment was identified two decades ago (Kempermann, Kuhn, & Gage, 1997). It was later shown that the neurogenic effect is due to the positive influence of the enriched environment on promoting survival of new-born neurons by suppressing apoptosis (cell suicide). A typical enriched environmental setup consists of a living environment with various stimulations including a larger cage; tunnel system, which is frequently changed; toys; and housing with larger groups of animals. The environment was suggested to provide multisensory stimulations, social interaction, and equipment for physical activity. Although the effect of the whole environment is strong, specific studies on the separate components (i.e., social, different sensory, and physical activities) are still missing.

Similar to enriched environment, rehabilitation of psychiatric patients was thought to be benefited by situating patients in the community, which is full of different types of physical stimulations, social interaction, and novelty. Assertive community treatment, a rehabilitation treatment that places patients in the community, is given to schizophrenic patients who are at risk of repeated hospitalization or are homeless. When the patient is discharged from the institution, mental health professionals provide continuous and intensive support to schizophrenia patients and their support network, such as families, employers, and friends, so as to help them to adapt to their community life. With professionals' assistance, the patients are needed to face different tasks such as maintaining medication regime, housing, finance, or issues that are valued by the patients (Kreyenbuhl, Buchanan, Dickerson, & Dixon, 2010). Community rehabilitation through assertive community treatment can effectively reduce hospitalization and homeless rates (Bustillo, Lauriello, Horan, & Keith, 2001), which echoes with the findings in animal studies that enriched environment reduces functioning deficit in schizophrenia models (McOmish et al., 2008).

Physical exercise and activity

Voluntary physical activity is a well-known inducer of hippocampal neurogenesis (Brown et al., 2003). The activity is usually delivered by placing a running wheel inside the cage of animals, as voluntary running was found to be endogenously rewarding for the laboratory rodent. Physical activity has recently been proven to improve cognitive function and benefit mental health (Bowes, Dawson, Jepson, & McCabe, 2013), while the promotion of neurogenesis may be the key factor underlying the benefits. Apart from cognition, exercising may act as a diversion from negative thoughts, so as to master new skills, improve social contacts, or may have physiological effects on patients' CNS (National Collaborating Centre for Mental Health [UK], 2010).

While involving both physical and mental activities, supported employment (SE; Kreyenbuhl et al., 2010) or productive activities (Nakamae, Yotsumoto, Tatsumi, & Hashimoto, 2014) could include activities that are meaningful to the patient. SE is given to patients with schizophrenia who wish to be employed and the *individual placement and support* model is the most widely researched model. Individually tailored job development, job search, ongoing job supports, and integration of vocational and mental health services are provided and patients receiving SE can gain further competitive employment and extended work hours (Kreyenbuhl et al., 2010). In addition, patients receiving SE did not show increased stress, exacerbation of symptoms, or other negative symptoms due to taking up a worker role.

Learning and cognitive challenges

Because learning is regarded as a primary function of hippocampus, the findings on adult neurogenesis suggested that learning may be regulated via hippocampal neurogenesis (Deng, Aimone, & Gage, 2010). Some evidence support the roles of new neurons in learning and memory, but the effect of learning on neurogenesis remains unclear. When compared with enriched environment and physical activity, there is less concrete evidence to support the neurogenic role of learning. Some studies showed that isolated learning stimuli was neurogenic by promoting the survival of neurons (Gould, Beylin, Tanapat, Reeves, & Shors, 1999). However, because learning is usually introduced in a complex environment with different contexts, its presentation may be embedded in the context with other stimulus. Thus, studies on causal relationship between learning and neurogenesis are usually interfered by confounders (Ehninger & Kempermann, 2006).

Although the direct causal effect needs to be further confirmed, learning is a commonly adopted treatment strategy for psychiatric patients. The lasting beneficial effect implies the structural modification of the CNS and probably neurogenesis. Usual treatment methods utilizing learning include cognitive remediation therapy, cognitive behavioural therapy, problem-solving therapy, and behavioural activation. These methods enable patients to learn new skills to reduce the impact exerted by the diseases (De Silva, Cooper, Li, Lund, & Patel, 2013), and even induce improvement in cognitive functions.

Management of psychosocial stress

Stress is well accepted as a negative regulator of neurogenesis (Alonso et al., 2004), and in cases of severe stress, the effect could even be seen in acute situations (e.g., within a few hours). In animal experiments, psychosocial stress is usually used to study the neurogenic effect of stress, including predator odour, social isolation, uncontrollable foot shocks, and social defeat (Blanchard, McKittrick, & Blanchard, 2001). Interestingly, the use of psychosocial stress in animal studies is comparable with the living environment of human beings, in which the social

environment is a major source of stress. It is possible that therapies that tackle social stress would influence the patient's neurogenesis.

To reduce social stress, emphasis is usually put on the family relationship because it is a key social environment for psychiatric patients. For example, family members and patients are educated in aspects including illness education, crisis intervention, emotional support, and training for ways to cope with illness symptoms. Some studies reported that these measures could increase medical adherence, reduce psychiatric symptoms, reduce level of stress perceived by the individuals, and reduce rehospitalization rate (Kreyenbuhl et al., 2010; Wong, Li-Tsang, & Siu, 2014). The key objectives of modifying the social environment are to solve interpersonal problems and provide social support. Animal models demonstrated alteration of neurogenesis when the experimental animals were subjected to chronic stress, but social support from conspecies (delivered by housing in the same cage) was found to normalize neurogenesis (Westenbroek, Den Boer, Veenhuis, & Ter Horst, 2004).

Conclusion

Psychiatric rehabilitation, especially those with activity components, is an important intervention for people suffering from chronic psychiatric diseases, although the neurobiological effect may be underestimated. The discovery of neurogenesis provides a novel perspective to support the effectiveness and efficacy of psychiatric rehabilitation and occupational therapy. Future translations between the basic science studies and clinical situation will benefit the development of more effective treatment methods (e.g., purposeful activities in occupational therapy) for psychiatric disorders.

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