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Psychosis is an extension of mood swings from the perspective of neuronal plasticity impairments

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A B S T R A C T

We previously hypothesized that depressive and manic states may be consecutive presentations of the same underlying neuronal plasticity, and that moderate impairments in neuronal plasticity cause depressive states while further impairment to neuronal plasticity causes manic states. Psychopathological or biological relationships between bipolar disorder and schizophrenia have also been revealed. Therefore, in addition to depressive and manic states, psychosis may also be considered a manifestation resulting from additional impairments to neuronal plasticity. In the present manuscript, we hypothesize that moderate and more severe impairments to neuronal plasticity cause depressive and manic states, respectively, and that more serious impairments to neuronal plasticity cause psychosis.

Many studies have suggested that impairments in neuronal plasticity contribute to schizophrenia and other mental disorders with psychotic features, and that the impairment of neuronal plasticity in schizophrenia is more severe than that in bipolar disorder. Therefore, we hypothesize more specifically that impairments in neuronal plasticity may be more severe in the order of the cases featuring psychosis, mania, and depression. This progression notably overlaps with the arrangement of schizophrenia, bipolar disorder, and depressive disorder in the DSM-5. Psychotic symptoms are thought to appear further towards the base of the psychopathological hierarchy than are manic or depressive symptoms. If impairments to neuronal plasticity contribute to this psychopathological hierarchy, as we contest that they do, our hypothesis may serve as a bridge between clinical psychopathology, diagnosis, and biological psychiatry.

Introduction

We previously hypothesized that depressive and manic states might be subserved by the same progressive neuronal plasticity [1]. Given this hypothesis, we argued that moderate impairments to neuronal plasticity cause depressive states and that further impairments to neuronal plasticity cause manic states.

Despite this background work, this hypothesis does not explain bipolar disorder, which presents with mood swings, and schizophrenia, which is the most psychosis-representative mental disorder. Other have pointed out that, from the view of psychopathology, bipolar disorder and schizophrenia might shift into each other during their course and lack a strictly alternative diagnosis [2]. Furthermore, recent studies have revealed a biological relationship between bipolar disorder and schizophrenia. Additionally, the genetic and environmental factors which underlie the etiology of bipolar disorder and schizophrenia also interact with one another [3] and the two share familial risk factors [4]. Many brain function abnormalities overlap in bipolar disorder and schizophrenia [5,6]. Some atypical antipsychotics used for the treatment of schizophrenia have also been used for the treatment of bipolar disorder as mood stabilizers [7,8]. Interestingly, the animal literature also provides some evidence for this overlap. For instance, social isolation in animals is often used to induce depressive-like behavior [9], but also often induces schizophrenia-like behavior [10].

It has been reported that impairments to neuronal plasticity contribute to both bipolar disorder and also schizophrenia [11]. Therefore, psychosis may also be thought of as a further progression of the neuronal plasticity impairments that underlie depressive and manic states.

Hypothesis

Our hypothesis is that the moderate and more severe impairments in neuronal plasticity cause depressive and manic states, respectively, and that more serious impairments to neuronal plasticity also cause psychosis. Fig. 1 illustrates this proposed relationship between normal, depressive, manic, and psychotic states from the perspective of neuronal plasticity.

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Fig. 1. Relationship among normal, depressive, manic, and psychotic states from the perspective of the impairment of neuronal plasticity. The moderate impairment and further impairment of neuronal plasticity causes depressive state and manic state, respectively, and more serious impairment of neuronal plasticity causes psychosis.

Evaluation of the hypothesis

Contribution of neurotrophins to psychosis

Brain-derived neurotrophic factor (BDNF) is one of the most critical proteins related to neuronal plasticity [12]; impairments to BDNF have further been linked to psychosis. In first episode schizophrenia patients, blood concentrations of BDNF have been found to be significantly lower than in healthy controls [13]. Serum BDNF has also been reported to be inversely related to the severity of psychotic symptoms [14].

Psychosis is not only a feature of schizophrenia, but also of various other mental disorders including stimulant-induced psychosis, Alzheimer's disease, and neuropsychiatric systemic lupus erythematosus. In these diseases, decreases in blood concentrations of BDNF or its gene polymorphism can serve as biomarkers of psychosis [15–18]. In addition, the neuroinflammation and dysregulated oxidative stress levels present in many psychopathologies, including those enumerated above, can further impair neuronal plasticity [19,20]. For instance, Doorduin et al. suggested that neuroinflammation in the hippocampus is seen in psychosis in schizophrenia [21]. At the onset of the first episode of psychosis, total antioxidant status is also positively related to the severity of patients' clinical status [22].

Nerve growth factor and neurotrophin 3 are also neuronal plasticity-related proteins [23]. The immunoreactivity of these proteins was lower in mesial temporal lobe epilepsy (MTLE) patients with psychosis than in MTLE patients without psychosis [24]. Collectively, these data indicate that BDNF and other growth factors may be implicated in the aberrant synaptic physiology that underlies psychosis.

Comparison of neuronal plasticity impairment severity in psychosis and manic and depressive states

As discussed above, impairments in neuronal plasticity contribute to bipolar disorder and schizophrenia [11]. Given this, a clear follow-up question is how the severity of these neuronal plasticity impairments differs between psychosis, manic states, and depressive states. Schizophrenia patients often have lower grey matter volumes than do bipolar disorder patients in the fronto-temporal cortex, thalamus, and amygdala [25]. In the postmortem frontal cortex of patients with schizophrenia, expression of neuronal plasticity-related proteins was generally lower than that of patients with bipolar disorder [26]. Similarly, patients with schizophrenia have lower blood concentrations of BDNF when compared to those with bipolar/depression [27].

In adults, the hippocampal dentate gyrus has a high rate of neurogenesis [28]. In addition to the several brain regions mentioned above, patients with schizophrenia show a lower volume of the hippocampus than bipolar patients [25]. In the adult brain, the Wnt signaling pathway plays a crucial role in neurogenesis [29]. In general, Wnt pathway-related gene expression in the blood of patients compared to healthy controls was quite similar for schizophrenia and bipolar disorder, with more obvious changes in noticed in schizophrenia [30]. N-acetylcysteine (NAC), which is a glutathione precursor and neurogenesis enhancer, is one of the useful agents in the treatment of schizophrenia and bipolar disorder [31], and the efficacy of adjunctive NAC was greater for schizophrenia than bipolar disorder [32]. From these findings, it is thought that the impairment of neurogenesis contributes more to schizophrenia than to bipolar disorder.

In addition to discrete differences in biomarkers, neuronal plasticity, which has been shown to regulate cognitive function [33], is correlated with more severe and pervasive cognitive deficits in patients with schizophrenia. Additionally, those with bipolar disorder present with milder and more confined cognitive impairments than healthy controls [34]. Based on these points, we hypothesize that impairments to neuronal plasticity are more severe in psychosis than in manic or depressive states (Fig. 1).

Interpretation of our hypothesis considering DSM criteria and affective spectrum

Changes between the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV and DSM-5 included separation of "Mood Disorders" into "Bipolar and Related Disorders" and "Depressive Disorders." Further, the "Bipolar and Related Disorders" category was placed between "Schizophrenia Spectrum and Other Psychotic Disorders" and "Depressive Disorders," bridging the symptomatology, family history dynamics, and genetics of these two disorders [35]. Schizophrenia is the most representative mental disorder to involve psychosis. Bipolar disorder is characterized by both depressive and manic states. Depressive disorder is characterized by depressive states, but not manic states. Thus, ordering these psychopathologies as they are in the DSM-5 (schizophrenia, bipolar disorder, and depressive disorder) overlaps with the order we hypothesize here (psychosis, manic states, and depressive states), which is predicated on their relative degrees of neuronal plasticity impairments.

In addition to the DSM-5, other organizational constructs have been proposed for these psychopathologies. For instance, Ghaemi et al. proposed an affective spectrum, in which bipolar disorder and depressive disorder are considered to be consecutive. In this model, bipolar spectrum disorder is located between bipolar disorder and depressive disorder [36,37]. Furthermore, the fact that schizoaffective disorder is located beyond bipolar disorder in this affective spectrum supports the conclusions drawn by the proposed hypothesis.

Consequences of the hypothesis and discussion

The hypothesis proposed here provides for the explanation of some clinical dynamics previously difficult to understand. The lifetime prevalence of these disorders follows the following order: depressive disorders, bipolar disorder, and then schizophrenia [38,39]. This may mean that impairments to neuronal plasticity typically remain at less severe levels, resulting in the common occurrence of depressive disorder. However, when these plasticity pathologies extend to more severe levels, bipolar disorder or schizophrenia can develop. Schizoaffective disorder may further lie between schizophrenia and bipolar disorder from the perspective of neuronal plasticity impairments. Based on this hypothesis, outcomes associated with schizoaffective disorder may further be poorer than those associated with bipolar disorder and improved relative to those associated with schizophrenia [40]. However, our hypothesis has several limitations. For instance, the influence of impairment of neuronal plasticity in clinical settings needs to be clarified, and further examination is warranted in this respect.

In unitary psychosis, endogenous mental disorders, including schizophrenia and bipolar disorder, are essentially considered a single disease, with superficial clinical differences [41]. Our hypothesis supports this theory of unitary psychosis from the perspective of neuronal plasticity impairments. From the view of the psychopathological

hierarchy, psychotic symptoms are thought to be more foundational than manic or depressive symptoms [2]. If these impairments to neuronal plasticity contribute to the psychopathological hierarchy, our hypothesis may also serve as a bridge between psychopathology and biological psychiatry.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.02.001.

References

[1] Mizuno T, Omata N, Murata T, et al. Mania: not the opposite of depression, but an extension? Neuronal plasticity and polarity. Med Hypotheses 2013;81:175–9.
[2] Huber G. PSYCHIATRIE Systematischer Letrrext für Studenten und Ärzte. Stuttgart: Schattaur GmbH; 1981.
[3] Misiak B, Stramecki F, Gawęda Ł, et al. Interactions between variation in candidate genes and environmental factors in the etiology of schizophrenia and bipolar disorder: a systematic review. Mol Neurobiol 2018;55:5075–100.
[4] Berrettini W. Evidence for shared susceptibility in bipolar disorder and schizophrenia. Am J Med Genet C Semin Med Genet 2003;123C:59–64.
[5] Wang Y, Jia Y, Feng Y, et al. Overlapping auditory M100 and M200 abnormalities in schizophrenia and bipolar disorder: a MEG study. Schizophr Res 2014;160:201–7.
[6] Wei Y, Chang M, Womer FY, et al. Local functional connectivity alterations in schizophrenia, bipolar disorder, and major depressive disorder. J Affect Disord 2018;236:266–73.
[7] Karanti A, Kardell M, Lundberg U, Landén M. Changes in mood stabilizer prescription patterns in bipolar disorder. J Affect Disord 2016;195:50–6.
[8] Wang M, Tong JH, Huang DS, Zhu G, Liang GM, Du H. Efficacy of olanzapine monotherapy for treatment of bipolar I depression: a randomized, double-blind, placebo controlled study. Psychopharmacology 2014;231:2811–8.
[9] Mitsuya H, Omata N, Kiyono Y, et al. The co-occurrence of zinc deficiency and social isolation has the opposite effects on mood compared with either condition alone due to changes in the central norepinephrine system. Behav Brain Res 2015;284:125–30.
[10] Sun L, Min L, Zhou H, Li M, Shao F, Wang W. Adolescent social isolation affects schizophrenia-like behavior and astrocyte biomarkers in the PFC of adult rats. Behav Brain Res 2017;333:258–66.
[11] Reinhart V, Bove SE, Volfson D, Lewis DA, Kleiman RJ, Lanz TA. Evaluation of TrkB and BDNF transcripts in prefrontal cortex, hippocampus, and striatum from subjects with schizophrenia, bipolar disorder, and major depressive disorder. Neurobiol Dis 2015;77:220–7.
[12] Karpova NN. Role of BDNF epigenetics in activity-dependent neuronal plasticity. Neuropharmacology 2014;76(Pt C):709–18.
[13] Li C, Tao H, Yang X, et al. Assessment of a combination of Serum Proteins as potential biomarkers to clinically predict Schizophrenia. Int J Med Sci 2018;15:900–6.
[14] Buckley PF, Pillai A, Evans D, Stirewalt E, Mahadik S. Brain derived neurotropic factor in first-episode psychosis. Schizophr Res 2007;91:1–5.
[15] Di Filippo M, Sarchielli P, Picconi B, Calabresi P. Neuroinflammation and synaptic plasticity: theoretical basis for a novel, immune-centred, therapeutic approach to neurological disorders. Trends Pharmacol Sci 2008;29:402–12.
[16] Watts ME, Pocock R, Claudianos C. Brain energy and oxygen metabolism: emerging role in normal function and disease. Front Mol Neurosci 2018;11:216.
[17] Doorduin J, de Vries EF, Willemsen AT, de Groot JC, Dierckx RA, Klein HC. Neuroinflammation in schizophrenia-related psychosis: a PET study. J Nucl Med 2009;50:1801–7.
[18] García S, Alberich S, Martínez-Cengotitabengoa M, et al. The complex association between the antioxidant defense system and clinical status in early psychosis. PLoS ONE 2018;13:e0194685.
[19] Angelucci F, Ricci V, Martinotti G, et al. Ecstasy (MDMA)-addicted subjects show increased serum levels of brain-derived neurotrophic factor, independently from a rise of drug-induced psychotic symptoms. Addict Biol 2010;15:365–7.
[20] Ikenouchi A, Yoshimura R, Ikemura N, Utsunomiya K, Mitoma M, Nakamura J. Plasma levels of brain derived-neurotrophic factor and catecholamine metabolites are increased during active phase of psychotic symptoms in CNS lupus: a case report. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:1359–63.
[21] Pivac N, Nikolac M, Nedic G, et al. Brain derived neurotrophic factor Val66Met polymorphism and psychotic symptoms in Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:356–62.
[22] Roncero C, Palma-Álvarez RF, Ros-Cucurull E, et al. Cocaine-induced psychosis and brain-derived neurotrophic factor in patients with cocaine dependence: report of two cases. Clin Psychopharmacol Neurosci 2016;14:109–13.
[23] Keefe KM, Sheikh IS, Smith GM. Targeting neurotrophins to specific populations of neurons: NGF, BDNF, and NT-3 and their relevance for treatment of spinal cord injury. Int J Mol Sci 2017;18.
[24] Kandratavicius L, Monteiro MR, Assirati Jr JA, Carlotti Jr. CG, Hallak JE, Leite JP. Neurotrophins in mesial temporal lobe epilepsy with and without psychiatric comorbidities. J Neuropathol Exp Neurol 2013;72:1029–42.
[25] Maggioni E, Bellani M, Altamura AC, Brambilla P. Neuroanatomical voxel-based profile of schizophrenia and bipolar disorder. Epidemiol Psychiatr Sci 2016;25:312–6.
[26] Yuan P, Zhou R, Wang Y, et al. Altered levels of extracellular signal-regulated kinase signaling proteins in postmortem frontal cortex of individuals with mood disorders and schizophrenia. J Affect Disord 2010;124:164–9.
[27] Xiong P, Zeng Y, Wu Q, et al. Combining serum protein concentrations to diagnose schizophrenia: a preliminary exploration. J Clin Psychiatry 2014;75:e794–801.
[28] Christian KM, Song H, Ming GL. Functions and dysfunctions of adult hippocampal neurogenesis. Annu Rev Neurosci 2014;37:243–62.
[29] Valvezan AJ, Klein PS. GSK-3 and Wnt signaling in neurogenesis and bipolar disorder. Front Mol Neurosci 2012;5:1.
[30] Hoseth EZ, Krull F, Dieset I, et al. Exploring the Wnt signaling pathway in schizophrenia and bipolar disorder. Transl Psychiatry 2018;8:55.
[31] Dean O, Giorlando F, Berk M. N-acetylcysteine in psychiatry: current therapeutic evidence and potential mechanisms of action. J Psychiatry Neurosci 2011;36:78–86.
[32] Zheng W, Zhang QE, Cai DB, et al. N-acetylcysteine for major mental disorders: a systematic review and meta-analysis of randomized controlled trials. Acta Psychiatr Scand 2018;137:391–400.
[33] Lu B, Nagappan G, Lu Y. BDNF and synaptic plasticity, cognitive function, and dysfunction. Handb Exp Pharmacol 2014;220:223–50.
[34] Vöhringer PA, Barroilhet SA, Amerio A, et al. Cognitive impairment in bipolar disorder and schizophrenia: a systematic review. Front Psychiatry 2013;4:87.
[35] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Washington, DC. 2013.
[36] Ghaemi SN. Bipolar spectrum: a review of the concept and a vision for the future. Psychiatry Investig 2013;10:218–24.
[37] Goodwin FK, Ghaemi SN, editors. An introduction to and history of affective disorders. New York: Oxford University Press; 2000.
[38] Hirschfeld RM. Differential diagnosis of bipolar disorder and major depressive disorder. J Affect Disord 2014;169(Suppl. 1):S12–6.
[39] Perälä J, Suvisaari J, Saarni SI, et al. Lifetime prevalence of psychotic and bipolar I disorders in a general population. Arch Gen Psychiatry 2007;64:19–28.
[40] Harrow M, Grossman LS. Outcome in schizoaffective disorders: a critical review and reevaluation of the literature. Schizophr Bull 1984;10:87–108.
[41] Kumbier E, Herpertz SC. Helmut Rennert's universal genesis of endogenous psychoses: the historical concept and its significance for today's discussion on unitary psychosis. Psychopathology 2010;43:335–44.