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REVIEW ARTICLE

Specificity and Continuity of Schizophrenia and Bipolar Disorder: Relation to Biomarkers

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Abstract: Schizophrenia and bipolar disorder overlap considerably in terms of symptoms, familial patterns, risk genes, outcome, and treatment response. This article provides an overview of the specificity and continuity of schizophrenia and mood disorders on the basis of biomarkers, such as genes, molecules, cells, circuits, physiology and clinical phenomenology. Overall, the discussions herein provided support for the view that schizophrenia, schizoaffective disorder and bipolar disorder are in the continuum of severity of impairment, with bipolar disorder closer to normality and schizophrenia at the most severe end. This approach is based on the concept that examining biomarkers in several modalities across these diseases from the dimensional perspective would be meaningful. These considerations are expected to help develop new treatments for unmet needs, such as cognitive dysfunction, in psychiatric conditions.

Keywords: Schizophrenia, bipolar disorder, psychosis, differential diagnosis, RDoC, spectrum, cognitive dysfunction.

1. INTRODUCTION

Schizophrenia and bipolar disorder, operationally defined by clinical features, overlap considerably in terms of symptoms, familial patterns, risk genes, outcome and treatment response [1]. Although Kraepelin differentiated between schizophrenia and bipolar disorder as two forms of psychoses on the basis of the clinical course, he also pointed out that both disorders shared certain symptoms, such as hallucinations, delusions, and mood symptoms [2]. To interpret the overlap of schizophrenia and bipolar disorder, Kasanin [3] introduced a concept of schizoaffective disorder that elicits clinical features of both diseases. Nevertheless, it was sometimes difficult to clearly distinguish between schizophrenia, schizoaffective disorder and bipolar disorder solely by phenomenological features (Fig. **1**) [4]. Accordingly, there has been a growing need for a valid diagnostic system based on biological indicators.

Operational diagnostic criteria, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Statistical Classification of Diseases and Related Health Problems (ICD), have been developed to improve the reliability of symptom-based diagnosis. However, these diagnostic criteria may not be valid enough because they do not incorporate neuroscience and genetics information, or resolve the issues of coexistence and heterogeneity. Thus, the National Institute of Mental Health (NIMH) has proposed the Research Domain Criteria (RDoC) system, as a new evaluation system to study mental illnesses [5, 6]. RDoC provides a framework that excludes categorical diagnoses, and adopts dimensional evaluation based on genetic, neural and behavioral indicators. The system consists of six research domains and eight analysis units (https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml, 21/2/2019). The research domains include Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Systems for Social Processes, Arousal and Regulatory Systems, and Sensorimotor Systems. For each research domain, genes, molecules, cells, circuits, physiology, behavior, self-reports, and paradigm are provided as analysis units (Fig. **2**) [7].

This review article is intended to provide an up-to-date insight into the specificity and continuity of schizophrenia and bipolar disorder based on the concept of RDoC.

2. SPECIFICITY AND CONTINUITY IN GENES

Genetic research of schizophrenia and bipolar disorder includes quantitative genetics, such as family, twin and adoption studies, while molecular genetics concerns common risk variants and variants of rare chromosomal structures. Results of quantitative genetics show notable similarities across these disorders [8]. Conventional studies show a substantial familial aggregation with sibling relative risks of around 8-10 for schizophrenia [9-11], bipolar disorder [12, 13], and schizoaffective disorder [14]. Twin studies show concordances of around 40-45% in monozygotic and 0-10% in dizygotic twin pairs for schizophrenia [15], bipolar disorder, and schizoaffective disorder [16]. In a meta-analysis [17], first-degree relatives of schizophrenia patients were shown to possess a higher risk of developing bipolar disorder compared to other relatives. These findings support the genetic link between schizophrenia and bipolar disorder.

Molecular genetic research includes large-scale genome-wide association studies (GWAS), aimed at detecting commonly occurring genetic variants which by themselves have a small effect on the risk for diseases. On the other hand, large chromosomal structural variants, particularly copy number variants (CNV), produce rare but large effects on the risk [8]. GWAS typically deals with more than a million of genetic markers residing in each chromosome, with sample sizes (cases and controls combined) of tens of thousands in recent years [18, 19].

Genetic markers include single-nucleotide polymorphisms (SNPs) that are used to determine whether one of the variants occurs more frequently than expected in affected cases compared with control subjects. An association indicates the presence of a causal

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Table 1. Genome-wide association study (GWAS) findings for schizophrenia and bipolar disorder from the review by Sullivan *et al.* [20]. Based on studies with large samples (minimum of around 10000 cases and 10000 controls) and SNP markers showing associations at genome-wide level of statistical significance ($p<5\times10^{-8}$). Odds Ratio; OR. Copyright (2012), with permission from Springer Nature.

Phenotype	Chromosome where Marker is Located	Nearest Gene	OR
Schizophrenia	1	*MIR137*	1.12
	2	*VRK2*	1.09
	2	*ZNF804A*	1.10
	2	*PCGEM1*	1.20
	6	*MHC*	1.22
	8	*MMP16*	1.10
	8	*CSMD1*	1.11
	8	*LSM1*	1.19
	10	*CNNM2*	1.10
	10	*NT5C2*	1.15
	11	*AMBRA1*	1.25
	11	*NRGN*	1.12
	18	*CCDC68*	1.09
	18	*TCF4*	1.20
Bipolar disorder	11	*ODZ4*	1.14
	12	*CACNA1C*	1.14
	19	*NCAN*	1.17
Schizophrenia and Bipolar disorder	2	*ZNF804A*	1.11
	3	*ITIH3-ITIH4*	1.12
	10	*ANK3*	1.22
	12	*CACNA1C*	1.11

genetic variant nearby or, less commonly, *i.e.,* the genetic marker variant itself may have a causal effect [8]. In a review [20] that summarized major GWAS findings for schizophrenia, bipolar disorder, and both disorders combined, the associations indicate a small effect on risk (ORs around 1.1), consistent with a partial overlap of genetic influences from commonly occurring variants on the two disorders (Table **1**). These findings show that both diseases share a similar genetic sensitivity.

3. ISSUES OF NEUROMETABOLITES

Proton magnetic resonance spectroscopy (^{1}H -MRS) is a non-invasive technique that detects magnetic resonance signals produced by atomic nuclei located within molecules in living tissues and measures their chemical composition, energy metabolism, neurotransmitter levels, and neuronal integrity *in vivo*. ^{1}H -MRS has increasingly been applied to characterize tissue-based chemical or metabolic abnormalities in psychiatric disorders [21]. This is done by evaluating concentrations of N-acetylaspartate (NAA), creatine (Cr), choline (Cho) and related chemicals [21]. NAA is a metabolite thought to reflect neuronal integrity, and is present exclusively in the brain. Cr is a marker of phosphate metabolism, while Cho indicates the breakdown of cell membranes and cellular turnover [22]. Abnormalities of neurometabolites in various regions of the brain have been implicated in the pathophysiology of schizophrenia and bipolar disorder. For example, both mental disorders show decreased.

NAA levels in the hippocampus and frontal lobes (gray and white matter) [23, 24]. A decrease in NAA concentrations is thought to reflect neuronal or axonal loss, or mitochondrial dysfunction [25], indicating structural abnormalities on a molecular level in schizophrenia and bipolar disorder. Both disorders also show decreased Cr levels in the dorsolateral prefrontal cortex (DLPFC), hippocampus and basal ganglia [26-29], suggesting alterations in the cellular energy metabolism. Conflicting results have been reported for Cho levels in the basal ganglia, hippocampus and DLPFC of schizophrenia patients [21]. In bipolar disorder, increased, decreased, or unaltered Cho levels have been reported in the DLPFC, hippocampus and anterior cingulate cortex [21]. Results of meta-analysis indicate schizophrenia and bipolar disorder share a decline of NAA concentrations and steady-state transition of Cho and Cr.

NAA levels in the thalamus and frontal lobes of schizophrenia patients are significantly decreased, while it is so in the basal ganglia of patients with bipolar disorder [21]. These observations sug-

Table 2. Changes in concentrations of neurometabolites in schizophrenia and bipolar disorder [21]. N-acetylaspartate; NAA, Creatine; Cr, Choline; Cho, and dorsolateral prefrontal cortex; DLPFC.

Phenotype	Neurometabolites	Concentration Change	Region
Schizophrenia	NAA	↓↓	Thalamus, Frontal lobe
Bipolar disorder	NAA	↓↓	Basal ganglia
Schizophrenia and Bipolar disorder	NAA	↓	Hippocampus, Frontal lobe
	Cr	↓~±0	DLPFC, Basal ganglia
	Cho	±0	DLPFC, Hippocampus

gest that the changes of several metabolites in the brain may also represent the notion of specificity and continuity pertinent to some psychiatric illnesses (Table **2**).

4. KEY PROTEINS IN POSTMORTEM BRAIN REGIONS

Proteins are major targets for many types of medicine to treat psychiatric disorders [30]. In particular, schizophrenia and bipolar disorder have been associated with aberrant blood cytokine levels. For example, Goldsmith *et al.* [31] performed meta-analysis of blood cytokines in acutely and chronically ill patients with these disorders, and found increased levels of cytokines (interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α)), a cytokine receptor (sIL-2R), and its antagonist (IL-1RA) (Table **3**). Overall, there were cross-diagnostic similarities in the direction of alterations in cytokine levels throughout the course of illness, suggesting common underlying immune dysfunctions. The association between peripheral levels of cytokines and C-reactive protein (CRP) and cognition was also reviewed [32], which indicates worse cognitive performance in schizophrenia patients with higher CRP levels. By contrast, better cognitive functioning was associated with higher concentrations of tumor necrosis factor-α (TNF-α) [32].

Aberrant regulation of synaptic function is thought to play a role in the etiology of schizophrenia and bipolar disorder. Specifically, normal neurotransmitter release is dependent on a complex group of presynaptic proteins that regulate synaptic vesicle docking, membrane fusion and fission, such as synaptophysin, syntaxin, synaptosomal-associated protein-25 (SNAP-25), vesicle-associated membrane protein (VAMP), α-synuclein and dynamin I. In addition, structural and signaling proteins, such as neural cell adhesion molecule (NCAM), maintain the integrity of the synapse [33]. Postmortem brain studies suggest impaired neuroplasticity. Therefore, much attention has been paid to the imbalance of intracellular signaling systems. For example, Ren *et al.* [34] reported that cyclic-AMP (cAMP) response element binding protein (CREB), its mRNA expression levels, and CRE-DNA binding activity were decreased in the nuclear fraction of the dorsolateral prefrontal cortex (DLPFC) and cingulate gyrus (CG) in postmortem specimens from subjects with bipolar disorder. On the other hand, these intracellular indicators were decreased in the CG, but not DLPFC of subjects with schizophrenia. These results indicate region-specific abnormalities of expression and function of CREB in both disorders.

Fragile X mental retardation protein (FMRP) is an RNA binding protein with 842 target mRNAs in the mammalian brain. Silencing of the fragile X mental retardation 1 (FMR1) gene leads to the loss of expression of FMRP and upregulated metabotropic glutamate receptor 5 (mGluR5) signaling, resulting in multiple physical and cognitive deficits associated with fragile X syndrome (FXS). Reduced FMRP expression has been reported in subjects with schizophrenia and bipolar disorder who do not carry the mutation for FMR1. Specifically, Folsom *et al.* [35] investigated the expression of four downstream targets of FMRP-mGluR5 signaling, *i.e.* homer1, amyloid beta A4 precursor protein (APP), ras-related C3 botulinum toxin substrate1 (RAC1), and striatal-enriched protein tyrosine phosphatase (STEP), in the brains of subjects with either disorder. In the frontal cortex, expressions of APP and homer1 were reduced in both disorders, whereas expressions of STEP were reduced only in subjects with schizophrenia. By contrast, expressions of RAC1 in the lateral cerebellum were, increased only in subjects with bipolar disorder. Overall, proteins involved in the FMRP-mGluR5 signaling pathway are altered in both disorders, consistent with the specificity/continuity concept (Table **3**) [35-38].

5. SPECIFICITY AND CONTINUITY IN BRAIN MORPHOLOGY

Schizophrenia and bipolar disorder exhibit considerable overlaps in terms of morphological brain changes including ventricular enlargement and global reduction in the brain volume [39]. For example, whole-brain voxel-based morphometry (VBM) studies report the reduction of grey matter volumes, mainly in bilateral insula and anterior cingulate cortex, in both mental disorders [40]. On the other hand, generalized grey matter deficits are greater in schizophrenia compared with bipolar disorder [41]. Indeed, schizophrenia patients show smaller grey matter volumes than bipolar disorder patients in fronto-temporal cortex, thalamus, hippocampus and amygdala [41], suggesting that morphological changes are subtler in bipolar disorder. In addition, atrophy of the hippocampus, amygdala and thalamus, brain areas associated with cognitive function [43], is more prominent in schizophrenia as compared with bipolar disorder [41, 42]. These characteristics are consistent with abnormal expressions of proteins and neurometabolites in both diseases (Tables **2** and **3**). Especially, morphological changes in the hippocampus and prefrontal cortex are conspicuous in conjunction with the decrease in NAA concentrations, which is thought to reflect neuronal or axonal loss, or mitochondrial dysfunction in these regions [25]. Moreover, the hippocampus and prefrontal cortex constitute key neural circuits responsible for cognitive impairment [54], a clinical manifestation representing specificity and continuity for schizophrenia and mood disorders.

Advances in neuroimaging also support the hypothesis that schizophrenia and bipolar disorder have common changes in a series of functional connectivity. For example, there are some lines of evidence for white matter alterations shared by the two disorders, in contrast to the case for grey matter deficits [44, 45]. Abnormalities of white matter microstructures, identified from diffusion tensor imaging, have been collated in meta-analyses, supporting altered white matter connectivity as one of the shared features [45].

The dysconnectivity hypothesis [46] suggests that both illnesses arise not from the regionally specific focal pathophysiology in the brain, but rather from impaired integration between neuroanatomical regions. For example, results of meta-analyses indicate pervasive reductions in organization among all major brain regions of

Table 3. Abnormal proteins in schizophrenia and bipolar disorders. Brain-derived neurotrophic factor; BDNF, synaptosomal-associated protein-25; SNAP-25, cyclic-AMP response element binding protein; CREB, amyloid beta A4 precursor protein; APP, striatal-enriched protein tyrosine phosphatase; STEP, growth associated protein 43; GAP43, ras-related C3 botulinum toxin substrate1; RAC1, interleukin; IL, tumor necrosis factor-α; TNF-α, acute phase; AP, chronic phase; CP.

Region	Marker	Schizophrenia	Bipolar Disorder
Hippocampus	Reelin	↓↓	↓
	BDNF	↓↓	↓↓
	Complexin1	↓↓	↓↓
	Complexin2	↓	↓
	SNAP-25	-	↓
	Parvalbumin	↓↓	↓
	Glucocorticoid receptor	↓	↓
	Dopamine 5 receptor	-	↑
	Serotonin 2A receptor	↓↓	↓↓
Prefrontal cortex	Reelin	↓↓	↓
	Kainate receptor KA2 subunit	-	↓
	Glucocorticoid receptor	↓	-
	Dopamine D2 receptor	↓	-
	CREB	-	↓
	Homer1	↓	↓
	APP	↓	↓
	STEP	↓	-
Anterior cingulate cortex	Synaptophysin	-	↓↓
	Neuromodulin (GAP43)	-	↓↓
	Complexin2	-	↓
	Calbindin	↓	↓
	CREB	↓	↓
Lateral cerebellum	RAC1	-	↑
Blood	IL-1β	↑ (AP)↑ (CP)	↑ (CP)
	IL-1RA	↑ (AP)	↑ (AP) ↓ (CP)
	sIL-2R	↑ (AP) ↑ (CP)	↑ (AP) ↑ (CP)
	IL-6	↑ (AP) ↑ (CP)	↑ (AP) ↑ (CP)
	TNF-α	↑ (AP) ↑ (CP)	↑ (AP)

white matter of patients with schizophrenia, while patients with bipolar disorder elicit decreased organization, specifically in the left limbic and right temporal-parietal white matter [47-49].

In view of the connectivity in the brain, both psychiatric disorders share white matter alterations incorporating prefrontal, corticothalamic, and callosal fibers this potentially contributes to aberrant executive and cognitive function, a common feature across the psychosis spectrum albeit to a lesser degree in bipolar disorder (Table **4**) [50-53].

In schizophrenia, the hippocampus is supposed to be hyperactive, leading to overdrive in the responsivity of midbrain dopamine (DA) neurons that project to the associative striatum, which is proposed to underlie positive symptoms [54]. Additionally, hyperactivity of the hippocampus may interfere with the function of other circuits. Thus, the hippocampal projection to the prefrontal cortex (PFC) may lead to disruption of activity and rhythmicity of the PFC, leading to cognitive impairment [54]. Moreover, the hippocampal projection to basolateral amygdala (BLA) may interfere with the BLA-limbic cortical control of emotional responses, possi-

Table 4. Brain morphology changes in grey matter volume and white matter (WM) connectivity between schizophrenia (SZ) and bipolar disorder (BP).

Phenotype	Morphology	Volume/Connectivity Change	Region
Schizophrenia	Grey matter	↓↓	Insula
	Grey matter	↓↓	Anterior cingulate cortex
Schizophrenia and Bipolar disorder	Grey matter	↓↓ (SZ), ↓ (BP)	Fronto-temporal cortex
	Grey matter	↓↓ (SZ), ↓ (BP)	Thalamus
	Grey matter	↓↓ (SZ), ↓ (BP)	Hippocampus
	Grey matter	↓↓ (SZ), ↓ (BP)	Amygdala
Schizophrenia	White matter	↓↓	Fronto-temporal WM
Bipolar disorder	White matter	↓	Left limbic WM
	White matter	↓	Right temporal-parietal WM
Schizophrenia and Bipolar disorder	White matter	↓↓ (SZ), ↓ (BP)	Prefrontal WM
	White matter	↓↓ (SZ), ↓ (BP)	Cortico-thalamic WM
	White matter	↓↓ (SZ), ↓ (BP)	Callosal fiber

bly leading to negative symptoms [54]. In this way, altered hippocampal function potentially disrupts multiple interconnected circuits, and causes major symptoms of schizophrenia and bipolar disorders (Figs. **1** and **3**) [54].

6. SPECIFICITY AND CONTINUITY IN BRAIN CONNECTIVITY

The medial prefrontal cortex (MPFC) plays a crucial role in the psychophysiology of schizophrenia and bipolar disorders [55]. The ventral and orbital parts of the MPFC are extensively and reciprocally connected to the limbic circuit and surrounding prefrontal cortical regions [56]. Abnormalities of these neural systems may be responsible for the emotional dysregulation of bipolar disorder [57]. For example, patients with bipolar disorders exhibit increased functional connectivity between MPFC and the amygdala compared with healthy controls [58]. MPFC is also associated with internal, self-referential processing [59], and has been suggested to underlie the impairments in reality monitoring of schizophrenia [60].

The MPFC is a major hub of the default mode network, which is typically more active during the resting state than during the performance on tasks that demand external attention, and thought to mediate internal mental activity [61]. Chai *et al.* [55] examined functional connectivity between MPFC and other brain regions in schizophrenia and bipolar disorder using resting-state functional magnetic resonance imaging (fMRI). The schizophrenia group did not exhibit any resting-state correlations between the MPFC and the ventral lateral prefrontal cortex (VLPFC) or insula. In contrast, the bipolar disorder group exhibited positive correlations between the MPFC vs. insula and VLPFC. Under the same conditions, the control group exhibited negative correlations between these regions. Moreover, the decoupling of dorsal lateral prefrontal cortex (DLPFC) with MPFC in both disorders was observed, consistent with the impaired executive functioning. In sum, functional connectivity between MPFC and insula/VLPFC may distinguish between bipolar disorder and schizophrenia, whereas both diseases share the decoupling DLPFC from MPFC, which may provide a common pathogenesis.

Recent fMRI studies have shown altered brain dynamic functional connectivity (DFC) in mental disorders. Thus, Du *et al.* [62] examined DFC across a spectrum of symptomatically-related disorders, including schizophrenia, schizoaffective disorder and bipolar disorder with psychosis. They conducted group information guided independent component analysis to estimate both group-level and subject-specific connectivity states from DFC, using fMRI data from patients and healthy control subjects. Regarding the dominant state, widespread group differences were found in 166 functional connectivity, which mainly involved the thalamus and cerebellum, as well as frontal, temporal, occipital, fusiform, postcentral, cuneus, supramarginal and calcarine cortices. Specifically, 22 functional connectivity associated with the postcentral, frontal, and cerebellar cortices were weakened across health control, bipolar disorder with psychosis, schizoaffective disorder, and schizophrenia groups, while 34 functional connectivity associated with the insular, temporal, frontal, fusiform, lingual, occipital, supramarginal cortices, as well as thalamus and cerebellum, were strengthened across those groups (Fig. **4**). The degree of these abnormalities, *i.e.,* hypo-connectivity and hyper-connectivity, was in the ascending order of bipolar disorder with psychosis, schizoaffective disorder, and schizophrenia relative to healthy controls. These results are consistent with those in previous studies that observed more severe gray matter deficits [63] and functional impairments [64] in these disorders. These findings support the view that schizophrenia, schizoaffective disorder and bipolar disorder with psychosis are in a continuum of severity, with bipolar disorder with psychosis closer to normality and schizophrenia at the most severe end.

7. SPECIFICITY AND CONTINUITY IN NEUROCOGNITION

Neurocognitive impairment has long been recognized as a core feature of schizophrenia [65]. In contrast, the importance of cognitive problems in bipolar disorder has been recognized more recently [68]. Individuals with bipolar disorder also demonstrate persistent and trait-like cognitive deficits during remission, while there are some effects of mood state on cognition with acute manic or depressed patients demonstrating profound cognitive deficits [66]. The impairment is most notable in attention, verbal learning and executive function [67], with performance falling 0.5-1 standard deviation (SD) below average. Moreover, these cognitive deficits

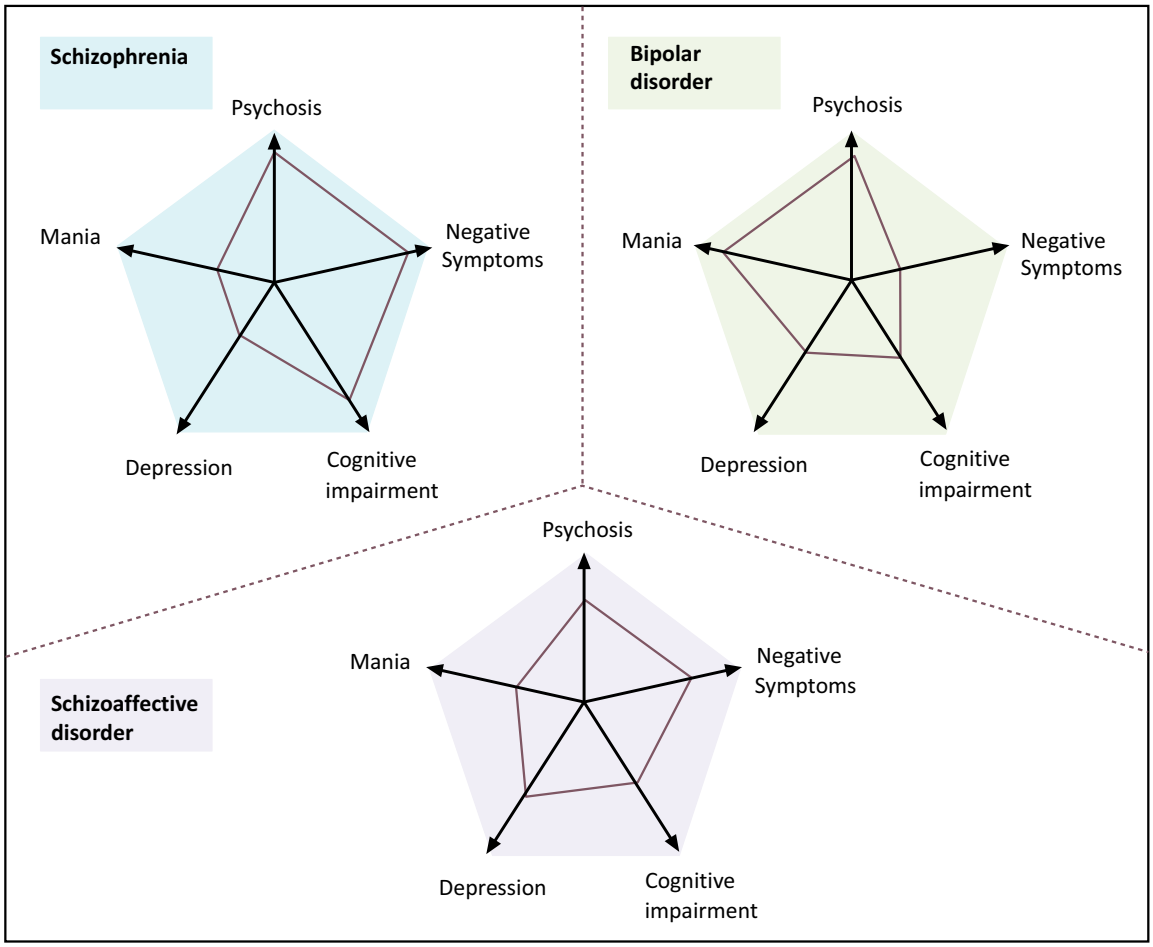

Fig. (1). Typical profile of each disease diagnosed with a combination of psychopathological categories and phenomenological features. Categorical diagnoses of schizophrenia (blue), bipolar disorder (green), and schizoaffective disorder (violet) are accompanied by a patient's quantitative scores (connected by red lines) on five main dimensions of psychopathology [4]. Copyright (2009), with permission from Elsevier.

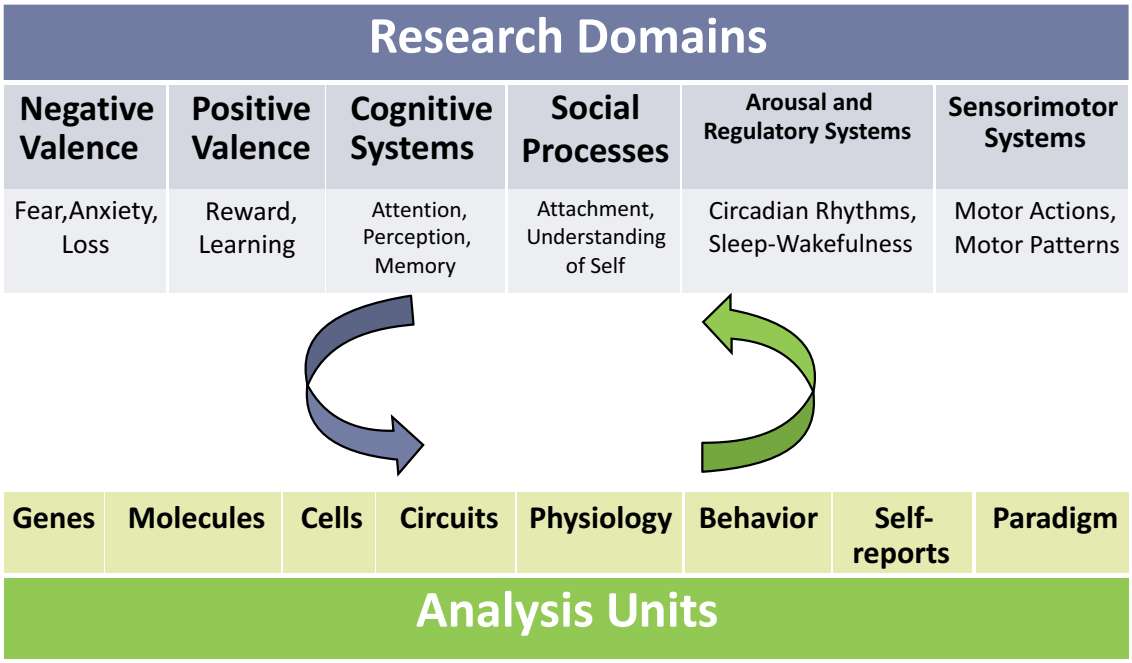

Fig. (2). Schematic diagram of the RDoC framework.

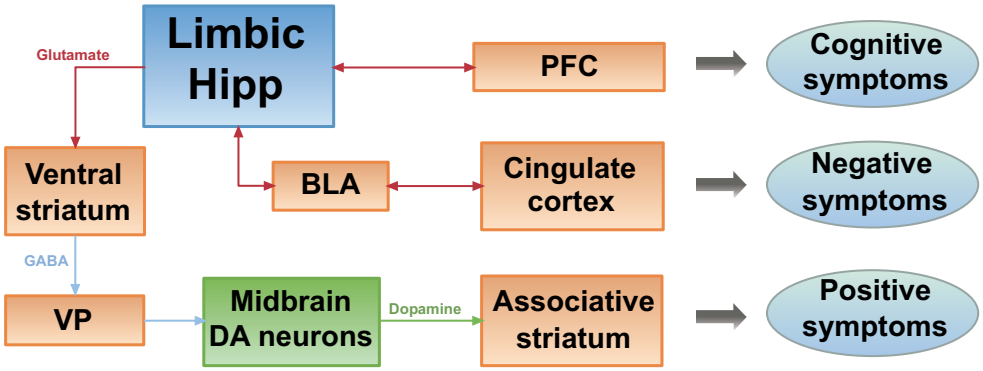

Fig. (3). Circuitry of dopamine system regulation and its disruption in schizophrenia. Hyperactive, dysrhythmic limbic hippocampus potentially disrupts multiple interconnected circuits, and could contribute to all 3 symptom classes of schizophrenia [54]. Hipp: Hippocampus, PFC: Prefrontal cortex, BLA: Basolateral amygdala, VP: Ventral pallidum, DA: Dopamine. Copyright (2019), with permission from Oxford University Press.

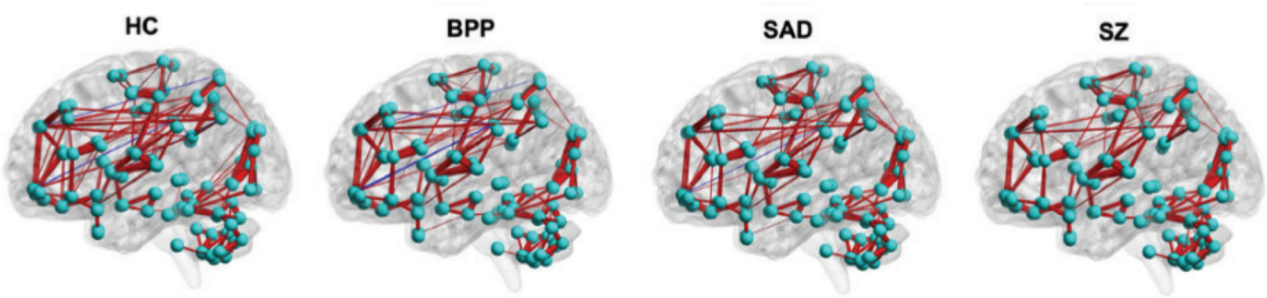

Fig. (4). The mean static functional connectivity matrix across subjects and its visualized pattern for health control (HC), bipolar disorder with psychosis (BPP), schizoaffective disorder (SAD) and schizophrenia (SZ) group, respectively [62]. The red and blue lines represent positive and negative connectivity strengths, respectively. Copyright (2017), with permission from John Wiley and Sons.

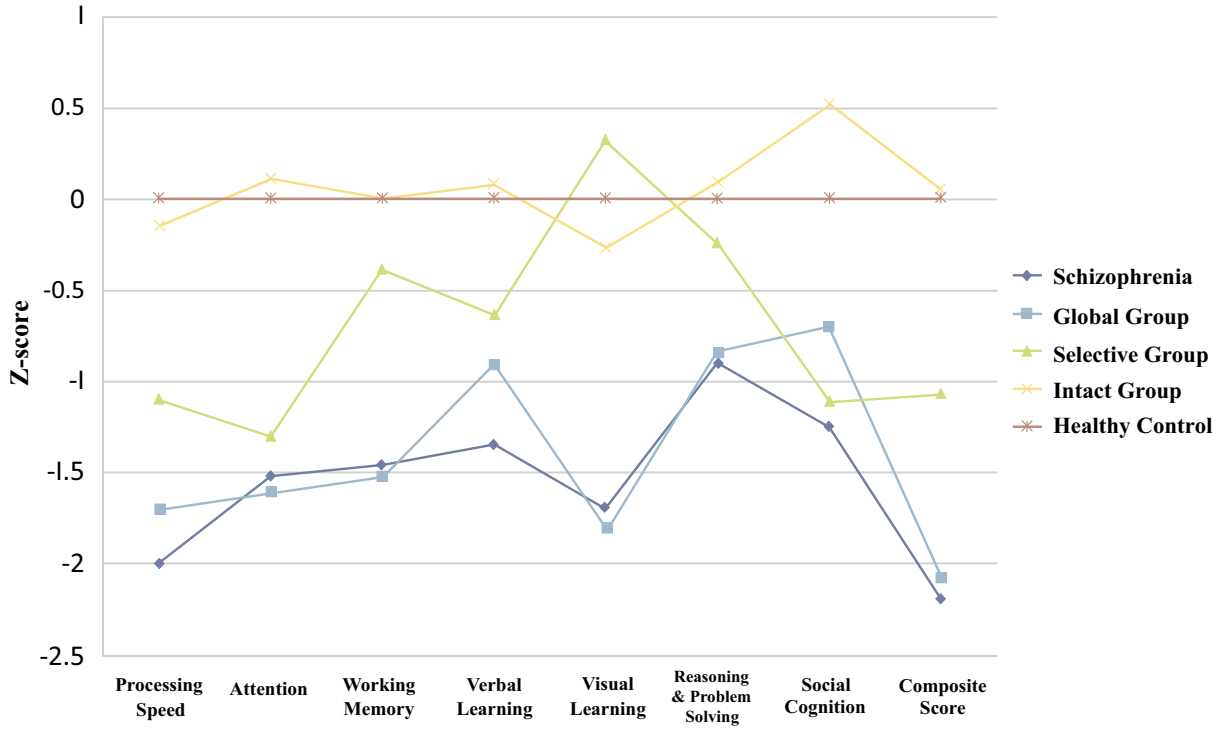

Fig. (5). Neurocognitive profiles of bipolar disorder clusters and the schizophrenia sample. The X-axis indicates the MATRICS Consensus Cognitive Battery (MCCB) domains. The Y-axis depicts a Z-scale score with a mean of 0 and a standard deviation of 1. Z scores were computed based upon the healthy control sample. Patients are divided into lines based on scoring for each cognitive domain [72]. Copyright (2014), with permission from Cambridge University Press.

significantly contribute to functional disability in both schizophrenia and bipolar disorder [65, 68].

Schizophrenia shows cognitive heterogeneity [69], and generally has four subgroups; one with almost normal and one with profoundly impaired cognitive performance, and two intermediate subgroups [70]. Similarly, bipolar disorder has cognitive heterogeneity, with some subgroups whose cognitive deficits are less severe than those reported in schizophrenia [71]. Accordingly, Burdick *et al.* conducted a cluster analysis of data from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) cognitive battery test in 136 bipolar disorder patients, and found three distinct subgroups, as follows [72] (Fig. **5**):

Cluster 1, global impairment group, presenting diffuse and severe cognitive dysfunction, with performance falling between 1 and 2 SD below the mean of healthy controls (Global Group);

Cluster 2, selective impairment group, presenting modest deficits on specific domains, with performance ranging between normal and -1 SD below average (Selective Group);

Cluster 3, intact group, performing comparably to healthy controls on all domains, with superior performance *vs.* healthy controls on social cognition (Intact Group).

In this way, these subtypes of bipolar disorder were based on degree and pattern of cognitive decline, with the Global Group demonstrating cognitive deficits comparable to those of schizophrenia [72]. This supports the concept of continuity between bipolar disorder and schizophrenia on the basis of behavioral paradigms.

CONCLUSION

Information from multiple modalities of measures, herein reviewed, support the notion that schizophrenia and bipolar disorder share several biological substrates responsible for the clinical manifestations. These considerations suggest the utility of dimensional perspectives to develop new therapeutics for unmet needs, such as cognitive dysfunction, which may compensate the limitations of categorical diagnostic classifications for psychiatric disorders.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Pearlson GD, Clementz BA, Sweeney JA, Keshavan MS, Tamminga CA. Does biology transcend the symptom-based boundaries of psychosis?. Psychiatr Clin North Am 2016; 39(2): 165-74. http://dx.doi.org/10.1016/j.psc.2016.01.001 PMID: 27216897

[2] Ebert A, Bär KJ. Emil kraepelin: a pioneer of scientific understanding of psychiatry and psychopharmacology. Indian J Psychiatry 2010; 52(2): 191-2. http://dx.doi.org/10.4103/0019-5545.64591 PMID: 20838510

[3] Kasanin J. The acute schizoaffective psychoses. 1933. Am J Psychiatry 1994; 151(6)(Suppl.): 144-54. http://dx.doi.org/10.1176/ajp.151.6.144 PMID: 8192190

[4] van Os J, Kapur S. Schizophrenia. Lancet 2009; 374(9690): 635-45. http://dx.doi.org/10.1016/S0140-6736(09)60995-8 PMID: 19700006

[5] Insel TR, Cuthbert BN. Endophenotypes: bridging genomic complexity and disorder heterogeneity. Biol Psychiatry 2009; 66(11): 988-9. http://dx.doi.org/10.1016/j.biopsych.2009.10.008 PMID: 19900610

[6] Insel T, Cuthbert B, Garvey M, *et al.* Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry 2010; 167(7): 748-51. http://dx.doi.org/10.1176/appi.ajp.2010.09091379 PMID: 20595427

[7] Clark LA, Cuthbert B, Lewis-Fernández R, Narrow WE, Reed GM. Three approaches to understanding and classifying mental disorder: ICD-11, DSM-5, and the national institute of mental health's research domain criteria (RDoC). Psychol Sci Public Interest 2017; 18(2): 72-145. http://dx.doi.org/10.1177/1529100617727266 PMID: 29211974

[8] Cardno AG, Owen MJ. Genetic relationships between schizophrenia, bipolar disorder, and schizoaffective disorder. Schizophr Bull 2014; 40(3): 504-15. http://dx.doi.org/10.1093/schbul/sbu016 PMID: 24567502

[9] Kendler KS, Diehl SR. The genetics of schizophrenia: a current, genetic-epidemiologic perspective. Schizophr Bull 1993; 19(2): 261-85. http://dx.doi.org/10.1093/schbul/19.2.261 PMID: 8322035

[10] Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D. The roscommon family study. I. methods, diagnosis of probands, and risk of schizophrenia in relatives. Arch Gen Psychiatry 1993; 50(7): 527-40. http://dx.doi.org/10.1001/archpsyc.1993.01820190029004 PMID: 8317947

[11] Lichtenstein P, Yip BH, Björk C, *et al.* Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 2009; 373(9659): 234-9. http://dx.doi.org/10.1016/S0140-6736(09)60072-6 PMID: 19150704

[12] Tsuang MT, Winokur G, Crowe RR. Morbidity risks of schizophrenia and affective disorders among first degree relatives of patients with schizophrenia, mania, depression and surgical conditions. Br J Psychiatry 1980; 137: 497-504. http://dx.doi.org/10.1192/bjp.137.6.497 PMID: 7214104

[13] Maier W, Lichtermann D, Minges J, *et al.* Continuity and discontinuity of affective disorders and schizophrenia. Results of a controlled family study. Arch Gen Psychiatry 1993; 50(11): 871-83. http://dx.doi.org/10.1001/archpsyc.1993.01820230041004 PMID: 8215813

[14] Bertelsen A, Gottesman II. Schizoaffective psychoses: genetical clues to classification. Am J Med Genet 1995; 60(1): 7-11. http://dx.doi.org/10.1002/ajmg.1320600103 PMID: 7485238

[15] Cardno AG, Gottesman II. Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics. Am J Med Genet 2000; 97(1): 12-7. http://dx.doi.org/10.1002/(SICI)1096-8628(200021)97:1<12::AID-AJMG3>3.0.CO;2-U PMID: 10813800

[16] Cardno AG, Marshall EJ, Coid B, *et al.* Heritability estimates for psychotic disorders: the maudsley twin psychosis series. Arch Gen Psychiatry 1999; 56(2): 162-8. http://dx.doi.org/10.1001/archpsyc.56.2.162 PMID: 10025441

[17] Van Snellenberg JX, de Candia T. Meta-analytic evidence for familial coaggregation of schizophrenia and bipolar disorder. Arch Gen Psychiatry 2009; 66(7): 748-55. http://dx.doi.org/10.1001/archgenpsychiatry.2009.64 PMID: 19581566

[18] Ripke S, O'Dushlaine C, Chambert K, *et al.* Multicenter genetic studies of schizophrenia consortium; psychosis endophenotypes international consortium; wellcome trust case control consortium 2. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat Genet 2013; 45(10): 1150-9. http://dx.doi.org/10.1038/ng.2742 PMID: 23974872

[19] Psychiatric GWAS consortium bipolar disorder working group. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. Nat Genet 2011; 43(10): 977-83. http://dx.doi.org/10.1038/ng.943 PMID: 21926972

[20] Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. Nat Rev Genet 2012; 13(8): 537-51. http://dx.doi.org/10.1038/nrg3240 PMID: 22777127

[21] Kraguljac NV, Reid M, White D, *et al.* Neurometabolites in schizophrenia and bipolar disorder - a systematic review and meta-analysis. Psychiatry Res 2012; 203(2-3): 111-25. http://dx.doi.org/10.1016/j.pscychresns.2012.02.003 PMID: 22981426

[22] Keshavan MS, Stanley JA, Pettegrew JW. Magnetic resonance spectroscopy in schizophrenia: methodological issues and findings-part II. Biol Psychiatry 2000; 48(5): 369-80. http://dx.doi.org/10.1016/S0006-3223(00)00940-9 PMID: 10978720

[23] Steen RG, Hamer RM, Lieberman JA. Measurement of brain metabolites by ^{1}H magnetic resonance spectroscopy in patients with schizophrenia: a systematic review and meta-analysis. Neuropsychopharmacology 2005; 30(11): 1949-62. http://dx.doi.org/10.1038/sj.npp.1300850 PMID: 16123764

[24] Yildiz-Yesiloglu A, Ankerst DP. Neurochemical alterations of the brain in bipolar disorder and their implications for pathophysiology: a systematic review of the in vivo proton magnetic resonance spectroscopy findings. Prog Neuropsychopharmacol Biol Psychiatry 2006; 30(6): 969-95. http://dx.doi.org/10.1016/j.pnpbp.2006.03.012 PMID: 16677749

[25] Sager TN, Topp S, Torup L, Hanson LG, Egestad B, Møller A. Evaluation of CA1 damage using single-voxel 1H-MRS and unbiased stereology: Can non-invasive measures of N-acetyl-asparate following global ischemia be used as a reliable measure of neuronal damage?. Brain Res 2001; 892(1): 166-75. http://dx.doi.org/10.1016/S0006-8993(00)03274-1 PMID: 11172761

[26] Deicken RF, Pegues MP, Anzalone S, Feiwell R, Soher B. Lower concentration of hippocampal N-acetylaspartate in familial bipolar I disorder. Am J Psychiatry 2003; 160(5): 873-82. http://dx.doi.org/10.1176/appi.ajp.160.5.873 PMID: 12727690

[27] Ohrmann P, Siegmund A, Suslow T, *et al.* Evidence for glutamatergic neuronal dysfunction in the prefrontal cortex in chronic but not in first-episode patients with schizophrenia: a proton magnetic resonance spectroscopy study. Schizophr Res 2005; 73(2-3): 153-7. http://dx.doi.org/10.1016/j.schres.2004.08.021 PMID: 15653258

[28] Frey BN, Stanley JA, Nery FG, *et al.* Abnormal cellular energy and phospholipid metabolism in the left dorsolateral prefrontal cortex of medication-free individuals with bipolar disorder: an *in vivo* 1H MRS study. Bipolar Disord 2007; 9(Suppl. 1): 119-27. http://dx.doi.org/10.1111/j.1399-5618.2007.00454.x PMID: 17543030

[29] Rüsch N, Tebartz van Elst L, Valerius G, *et al.* Neurochemical and structural correlates of executive dysfunction in schizophrenia. Schizophr Res 2008; 99(1-3): 155-63. http://dx.doi.org/10.1016/j.schres.2007.05.024 PMID: 17616347

[30] Sharif-Barfeh Z, Beigoli S, Marouzi S, Sharif-Rad A, Asoodeh A, Chamani J. Multi-spectroscopic and HPLC studies of the interaction between estradiol and cyclophosphamide with human serum albumin: binary and ternary systems. J Solution Chem 2017; 46: 488-504. http://dx.doi.org/10.1007/s10953-017-0590-2

[31] Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol Psychiatry 2016; 21(12): 1696-709. http://dx.doi.org/10.1038/mp.2016.3 PMID: 26903267

[32] Misiak B, Stańczykiewicz B, Kotowicz K, Rybakowski JK, Samochowiec J, Frydecka D. Cytokines and C-reactive protein alterations with respect to cognitive impairment in schizophrenia and bipolar disorder: a systematic review. Schizophr Res 2018; 192: 16-29. http://dx.doi.org/10.1016/j.schres.2017.04.015 PMID: 28416092

[33] Gray LJ, Dean B, Kronsbein HC, Robinson PJ, Scarr E. Region and diagnosis-specific changes in synaptic proteins in schizophrenia and bipolar I disorder. Psychiatry Res 2010; 178(2): 374-80. http://dx.doi.org/10.1016/j.psychres.2008.07.012 PMID: 20488553

[34] Ren X, Rizavi HS, Khan MA, Bhaumik R, Dwivedi Y, Pandey GN. Alteration of cyclic-AMP response element binding protein in the postmortem brain of subjects with bipolar disorder and schizophrenia. J Affect Disord 2014; 152-154: 326-33. http://dx.doi.org/10.1016/j.jad.2013.09.033 PMID: 24148789

[35] Folsom TD, Thuras PD, Fatemi SH. Protein expression of targets of the FMRP regulon is altered in brains of subjects with schizophrenia and mood disorders. Schizophr Res 2015; 165(2-3): 201-11. http://dx.doi.org/10.1016/j.schres.2015.04.012 PMID: 25956630

[36] Leber SL, Llenos IC, Miller CL, Dulay JR, Haybaeck J, Weis S. Homer1a protein expression in schizophrenia, bipolar disorder, and major depression. J Neural Transm (Vienna) 2017; 124(10): 1261-73. http://dx.doi.org/10.1007/s00702-017-1776-x PMID: 28815330

[37] Torrey EF, Barci BM, Webster MJ, Bartko JJ, Meador-Woodruff JH, Knable MB. Neurochemical markers for schizophrenia, bipolar disorder, and major depression in postmortem brains. Biol Psychiatry 2005; 57(3): 252-60. http://dx.doi.org/10.1016/j.biopsych.2004.10.019 PMID: 15691526

[38] Novikova SI, He F, Cutrufello NJ, Lidow MS. Identification of protein biomarkers for schizophrenia and bipolar disorder in the postmortem prefrontal cortex using SELDI-TOF-MS ProteinChip profiling combined with MALDI-TOF-PSD-MS analysis. Neurobiol Dis 2006; 23(1): 61-76. http://dx.doi.org/10.1016/j.nbd.2006.02.002 PMID: 16549361

[39] Arnone D, Cavanagh J, Gerber D, Lawrie SM, Ebmeier KP, McIntosh AM. Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis. Br J Psychiatry 2009; 195(3): 194-201. http://dx.doi.org/10.1192/bjp.bp.108.059717 PMID: 19721106

[40] Ellison-Wright I, Bullmore E. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. Schizophr Res 2010; 117(1): 1-12. http://dx.doi.org/10.1016/j.schres.2009.12.022 PMID: 20071149

[41] Maggioni E, Bellani M, Altamura AC, Brambilla P. Neuroanatomical voxel-based profile of schizophrenia and bipolar disorder. Epidemiol Psychiatr Sci 2016; 25(4): 312-6. http://dx.doi.org/10.1017/S2045796016000275 PMID: 27095442

[42] Nenadic I, Maitra R, Langbein K, *et al.* Brain structure in schizophrenia *vs*. psychotic bipolar I disorder: a VBM study. Schizophr Res 2015; 165(2-3): 212-9. http://dx.doi.org/10.1016/j.schres.2015.04.007 PMID: 25935815

[43] Brambilla P, Perlini C, Rajagopalan P, *et al.* Schizophrenia severity, social functioning and hippocampal neuroanatomy: three-dimensional mapping study. Br J Psychiatry 2013; 202(1): 50-5. http://dx.doi.org/10.1192/bjp.bp.111.105700 PMID: 23284150

[44] Altamura AC, Bertoldo A, Marotta G, *et al.* White matter metabolism differentiates schizophrenia and bipolar disorder: a preliminary PET study. Psychiatry Res 2013; 214(3): 410-4. http://dx.doi.org/10.1016/j.pscychresns.2013.08.011 PMID: 24144506

[45] O'Donoghue S, Holleran L, Cannon DM, McDonald C. Anatomical dysconnectivity in bipolar disorder compared with schizophrenia: a selective review of structural network analyses using diffusion MRI. J Affect Disord 2017; 209: 217-28. http://dx.doi.org/10.1016/j.jad.2016.11.015 PMID: 27930915

[46] Stephan KE, Friston KJ, Frith CD. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophr Bull 2009; 35(3): 509-27. http://dx.doi.org/10.1093/schbul/sbn176 PMID: 19155345

[47] Ellison-Wright I, Bullmore E. Meta-analysis of diffusion tensor imaging studies in schizophrenia. Schizophr Res 2009; 108(1-3): 3-10. http://dx.doi.org/10.1016/j.schres.2008.11.021 PMID: 19128945

[48] Nortje G, Stein DJ, Radua J, Mataix-Cols D, Horn N. Systematic review and voxel-based meta-analysis of diffusion tensor imaging studies in bipolar disorder. J Affect Disord 2013; 150(2): 192-200. http://dx.doi.org/10.1016/j.jad.2013.05.034 PMID: 23810479

[49] Vederine FE, Wessa M, Leboyer M, Houenou J. A meta-analysis of whole-brain diffusion tensor imaging studies in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 2011; 35(8): 1820-6. http://dx.doi.org/10.1016/j.pnpbp.2011.05.009 PMID: 21624424

[50] Baker JT, Holmes AJ, Masters GA, *et al.* Disruption of cortical association networks in schizophrenia and psychotic bipolar disorder. JAMA Psychiatry 2014; 71(2): 109-18. http://dx.doi.org/10.1001/jamapsychiatry.2013.3469 PMID: 24306091

[51] Bullmore E. Functional network endophenotypes of psychotic disorders. Biol Psychiatry 2012; 71(10): 844-5. http://dx.doi.org/10.1016/j.biopsych.2012.03.019 PMID: 22520728

[52] De Peri L, Crescini A, Deste G, Fusar-Poli P, Sacchetti E, Vita A. Brain structural abnormalities at the onset of schizophrenia and bipolar disorder: a meta-analysis of controlled magnetic resonance imaging studies. Curr Pharm Des 2012; 18(4): 486-94. http://dx.doi.org/10.2174/138161212799316253 PMID: 22239579

[53] Skudlarski P, Schretlen DJ, Thaker GK, *et al.* Diffusion tensor imaging white matter endophenotypes in patients with schizophrenia or psychotic bipolar disorder and their relatives. Am J Psychiatry 2013; 170(8): 886-98. http://dx.doi.org/10.1176/appi.ajp.2013.12111448 PMID: 23771210

[54] Grace AA, Gomes FV. The circuitry of dopamine system regulation and its disruption in schizophrenia: insights into treatment and prevention. Schizophr Bull 2019; 45(1): 148-57. http://dx.doi.org/10.1093/schbul/sbx199 PMID: 29385549

[55] Chai XJ, Whitfield-Gabrieli S, Shinn AK, *et al.* Abnormal medial prefrontal cortex resting-state connectivity in bipolar disorder and schizophrenia. Neuropsychopharmacology 2011; 36(10): 2009-17. http://dx.doi.org/10.1038/npp.2011.88 PMID: 21654735

[56] Ongür D, Price JL. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb Cortex 2000; 10(3): 206-19. http://dx.doi.org/10.1093/cercor/10.3.206 PMID: 10731217

[57] Phillips ML, Ladouceur CD, Drevets WC. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol Psychiatry 2008; 13(9): 829-57. http://dx.doi.org/10.1038/mp.2008.82 PMID: 18574483

[58] Versace A, Thompson WK, Zhou D, *et al.* Abnormal left and right amygdala-orbitofrontal cortical functional connectivity to emotional faces: state versus trait vulnerability markers of depression in bipolar disorder. Biol Psychiatry 2010; 67(5): 422-31. http://dx.doi.org/10.1016/j.biopsych.2009.11.025 PMID: 20159144

[59] Gilbert SJ, Spengler S, Simons JS, *et al.* Functional specialization within rostral prefrontal cortex (area 10): a meta-analysis. J Cogn Neurosci 2006; 18(6): 932-48. http://dx.doi.org/10.1162/jocn.2006.18.6.932 PMID: 16839301

[60] Vinogradov S, Luks TL, Schulman BJ, Simpson GV. Deficit in a neural correlate of reality monitoring in schizophrenia patients. Cereb Cortex 2008; 18(11): 2532-9. http://dx.doi.org/10.1093/cercor/bhn028 PMID: 18321870

[61] Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 2008; 1124: 1-38. http://dx.doi.org/10.1196/annals.1440.011 PMID: 18400922

[62] Du Y, Pearlson GD, Lin D, *et al.* Identifying dynamic functional connectivity biomarkers using GIG-ICA: Application to schizophrenia, schizoaffective disorder, and psychotic bipolar disorder. Hum Brain Mapp 2017; 38(5): 2683-708. http://dx.doi.org/10.1002/hbm.23553 PMID: 28294459

[63] Ivleva EI, Bidesi AS, Keshavan MS, *et al.* Gray matter volume as an intermediate phenotype for psychosis: bipolar-schizophrenia network on intermediate phenotypes (B-SNIP). Am J Psychiatry 2013; 170(11): 1285-96. http://dx.doi.org/10.1176/appi.ajp.2013.13010126 PMID: 24185241

[64] Argyelan M, Ikuta T, DeRosse P, *et al.* Resting-state fMRI connectivity impairment in schizophrenia and bipolar disorder. Schizophr Bull 2014; 40(1): 100-10. http://dx.doi.org/10.1093/schbul/sbt092 PMID: 23851068

[65] Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia?. Am J Psychiatry 1996; 153(3): 321-30. http://dx.doi.org/10.1176/ajp.153.3.321 PMID: 8610818

[66] Daban C, Martinez-Aran A, Torrent C, *et al.* Specificity of cognitive deficits in bipolar disorder versus schizophrenia. A systematic review. Psychother Psychosom 2006; 75(2): 72-84. http://dx.doi.org/10.1159/000090891 PMID: 16508342

[67] Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. J Affect Disord 2009; 113(1-2): 1-20. http://dx.doi.org/10.1016/j.jad.2008.06.009 PMID: 18684514

[68] Burdick KE, Goldberg JF, Harrow M. Neurocognitive dysfunction and psychosocial outcome in patients with bipolar I disorder at 15-year follow-up. Acta Psychiatr Scand 2010; 122(6): 499-506. http://dx.doi.org/10.1111/j.1600-0447.2010.01590.x PMID: 20637012

[69] Reichenberg A, Harvey PD, Bowie CR, *et al.* Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. Schizophr Bull 2009; 35(5): 1022-9. http://dx.doi.org/10.1093/schbul/sbn044 PMID: 18495643

[70] Hill SK, Ragland JD, Gur RC, Gur RE. Neuropsychological profiles delineate distinct profiles of schizophrenia, an interaction between memory and executive function, and uneven distribution of clinical subtypes. J Clin Exp Neuropsychol 2002; 24(6): 765-80. http://dx.doi.org/10.1076/jcen.24.6.765.8402 PMID: 12424651

[71] Burdick KE, Goldberg TE, Cornblatt BA, *et al.* The MATRICS consensus cognitive battery in patients with bipolar I disorder. Neuropsychopharmacology 2011; 36(8): 1587-92. http://dx.doi.org/10.1038/npp.2011.36 PMID: 21451499

[72] Burdick KE, Russo M, Frangou S, *et al.* Empirical evidence for discrete neurocognitive subgroups in bipolar disorder: clinical implications. Psychol Med 2014; 44(14): 3083-96. http://dx.doi.org/10.1017/S0033291714000439 PMID: 25065409