

Schizophrenia, Bipolar Disorder and Pre-Attentional Inhibitory Deficits

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Abstract: According to recent findings schizophrenia and bipolar disorder as separate disease entities manifest similarities in neuropsychological functioning. Typical disturbances in both disorders are related to sensory gating deficits characterized by decreased inhibitory functions in responses to various insignificant perceptual signals which are experimentally tested by event related potentials (ERP) and measured P50 wave. In this context, recent findings implicate that disrupted binding and disintegration of consciousness in schizophrenia and bipolar disorder that are related to inhibitory deficits reflected in P50 response may explain similarities in psychotic disturbances in both disorders. With this aim, this review summarizes literature about P50 in both schizophrenia and bipolar disorder.

Keywords: bipolar disorder, neural synchrony, event related potentials, inhibition, P50, schizophrenia

Introduction

According to recent findings schizophrenia and bipolar disorder as separate disease entities manifest similarities in neuropsychological functioning profile¹⁻³ and accumulating evidence also indicates an overlap in various neurobiological changes such as genetic susceptibility, neurochemical markers and other neurophysiological parameters.^{1,4-7} Current findings also indicate that significant clinical similarities between both disorders frequently occur.⁸⁻¹⁰ For example, frequent manifestations of psychotic symptoms such as hallucinations, delusions and other symptoms of thought disorders were reported in patients with bipolar illness.¹⁰⁻¹² On the other hand in patients with schizophrenia may manifest typical bipolar symptoms.^{9,13} Recent findings strongly suggest that both disorders are specifically linked to basic changes in neural correlates of consciousness and integrated cognitive functioning closely related to EEG activities typically presented as synchronous neural oscillations mainly in gamma frequency band which is critical for large-scale integration of distributed neural assemblies.^{14,15} These EEG findings are also in agreement with brain imaging studies that reported various structural abnormalities mainly in prefrontal cortex, temporal lobe and limbic structures in schizophrenia as well as bipolar disorder.¹⁶⁻¹⁸

Recent data indicate that large scale synchronization related to gamma activity is related to global connections of large groups of neurons reflecting activities of interneural excitations in the GABAergic systems.¹⁹⁻²¹ These characteristic changes reported in mental disorders such as bipolar disorders or schizophrenia^{15,22} link GABA deficits with perceptual and cognitive disturbances.²³⁻²⁵ GABA systems specifically influence neural networks involved in cognitive and emotional processing and modulates noradrenergic, dopaminergic and serotonergic neural activities.²⁶ In pathological conditions GABAergic interneurons through cortico-limbic connections influence inhibitory processes in cerebral cortex, which are typically disrupted in schizophrenia and bipolar patients.²⁷⁻²⁹ In addition connections between both disorders possible might be explained also by reciprocal relationships between GABAergic and dopaminergic systems.^{27,30}

These findings also indicate that typical changes in neural oscillations and synchronization are specifically linked to inhibitory deficits that may be measured using event-related potentials (ERP). In addition reported ERP studies of evoked

responses also show that the P50 inhibitory (suppression) deficits may be specifically related to schizophrenia and bipolar disorder with psychotic symptoms.^{31,32}

P50 and Inhibitory Deficits

Recent findings indicate that P50 wave is related to brain processes linked to large scale neural binding mainly in prefrontal and temporo-parietal cortices.³³ These processes are reflected by ERPs mainly in early stages of the information processing at about 50 msec after a stimulus presentation³² in the process of active gating when the S1 stimulus tends to inhibit and “filter out” the response to following identical stimulus (S2).^{34–40} For example, Volkov and Galazyuk³⁹ “in a more general context proposed that synchronous activations of large number of cortical neurons by a short stimulus result in coordinated release of large amount inhibitory transmitters into the synaptic connections, which enables a relatively prolonged hyperpolarization of post-synaptic neurons. As a consequence, repeated stimulus leads to a constant release of a small amount of the transmitter into the synaptic cleft which may explain the process of continued inhibition”. These mechanisms enable to distinguish non-identical perceptual signals mainly via processing by different neurons which enable “unhabituated response”.^{41–43}

Basic role in this inhibitory processes and habituation to repeated stimuli play CA3-CA4 areas of the hippocampus and its cholinergic inputs from the septal nucleus mediated by low-affinity nicotinic receptors affecting CA3-CA4 interneurons and these GABAergic interneurons transiently inhibit pyramidal neurons, and mediate gating of the second stimulus during sensory stimulation usually used in ERP experiments.^{27,44–46} These pyramidal neurons of the CA3 region of the hippocampus were therefore identified as sources of brain evoked potentials responding for “habituation” related to repeated perceptual signals processed via cholinergic inhibitory interneurons in the hippocampus. Further findings show that activities of these interneurons may lead to “bursts” activities releasing GABA molecules (gamma aminobutyric acid) which enables to activate presynaptic GABA-B receptors in CA3 pyramidal neurons that block excitatory glutamate release and the CA3 pyramidal neurons are not available for response to the second stimulus.^{20,21,47–53}

However, other brain regions are also indispensable for the pre-attentional inhibitory deficits, the pulvinar nucleus in the thalamus in particular. Previous studies have shown that the pulvinar nucleus is mutually and extensively connected with the prefrontal cortex, sensory cortex, superior colliculus and amygdala,⁵⁴ and plays very important roles in the contextual bottom-up inhibitory multi-sensory gating.^{55–57} It is also involved in the cortico cortical synchronization and attention.⁵⁸ In addition, the dysfunction of the pulvinar nucleus has been reported to be associated with the sensory and cognitive deficits in schizophrenia.^{59,60}

P50 in Schizophrenia

Sensory processing deficits in schizophrenia due to disturbances in attentional filtering of “meaningful” signals^{61,62} were reported by studies utilizing “auditory evoked potentials” and mainly reflected by P50 wave^{63,64} which might help to explain relationships between clinical symptoms and the brain insufficiency to inhibit “unsignificant” sensory signals.^{49,51,65,66} One of the possible consequences of these “sensory gating deficits” reported in schizophrenia may lead to neural hyper-excitability^{67,68} reflecting P50 gating disturbances.^{69,70}

These findings indicate that schizophrenia patients manifest typical disturbances of dishabituation mechanisms which determine that schizophrenia patients experience “overload” of information.^{71,72} In this context, many studies have shown that the P50 sensory gating ratio in a paired click task is higher in patients with schizophrenia compared to healthy control subjects indicating more effective sensory gating.³² Meta-analysis by Patterson et al⁶¹ shows that the differences between patients and controls in P50 latency were no significant.⁶¹ Based on these findings Patterson et al⁶¹ concluded that their meta-analysis confirms the existence of ERP deficits in schizophrenia with significance similar to the most robust findings reported in neuroimaging studies of schizophrenia. Similar conclusions found also several others meta-analyses or reviews, which have shown that sensory gating impairments in early stages of schizophrenia become more prominent in chronic stages of the disease.^{61,63,73} For example, meta-analytical study by Chang et al⁷³ also confirmed that sensory gating deficits in schizophrenia patients are well-documented and that future studies need to clarify more detailed mechanisms of “gating”- related disturbances and their links to the disease progression^{73–75} suggesting that P50 disturbances might reflect deficits in neural connectivity.⁷⁶

P50 in Bipolar Disorder

In schizophrenia typical inhibitory disturbances and deficits in executive functions are linked to information overload in neural processing, on the other hand in bipolar disorder similar inhibitory deficit is related to deficits in action planning that disables coordinated responses which represent typical clinical characteristics of bipolar disorder.⁷⁷ In this process impulsivity likely represents a predisposition toward rapid unplanned reactions to internal or external stimuli resulting from impaired neural information processing and executive dysfunctions.⁷⁸ Impulsivity mainly is linked to pre-attentional and early attentional neural information processing and impulsive behavior increases probability of action without conscious reflection with excessive spontaneous “context independent” behavior.^{79,80} Level of impulsivity may also specifically characterize mania, depression, and anxiety, and recent findings show that these neurophysiological changes associated with impulsivity and attentional deficits related to disturbed executive functions in bipolar disorder are also typically linked to disinhibition of P50 and disturbed sensory gating.^{78,80,81}

These findings also show that diminished P50 suppression in bipolar disorder subjects with a history of psychosis might represent a mediating indicator of vulnerability in both trait- and state-like components. In this context several researchers suggest that abnormal P50 sensory gating deficit might represent state markers correlated with symptoms of mood disorders.^{82,83} For example, Baker et al⁸² found negative relationship between P50 ratios and Brief Psychiatric Rating Scale (BPRS) rating in depressive patients and several studies also found larger P50 ratios in bipolar groups with a history of psychosis.^{31,84} Another study³¹ focused on associations between psychosis and auditory P50 suppression in bipolar disorder reported that bipolar patients with a history of psychosis manifested significantly decreased P50 suppression in comparison to healthy controls, but significantly higher levels of suppression than patients with schizophrenia. These findings show that bipolar patients without history of psychosis exhibit P50 suppression ratios similar to healthy controls³¹ which suggests that vulnerability to psychosis may represent a common psychophysiological mechanism that might connect bipolar disorder and schizophrenia.

Conclusion

According to recent findings recognition process related to stimuli received from the external world in its principle most likely is based on repeated multilevel comparisons of various competitive neural patterns representing possible interpretations of the received information during selective attentional processing and selected interpretation from this competition and its neural pattern represents the output of the recognition process.^{85–88} The brain mechanisms that enable multilevel information processing are likely regulated within the framework of contextual understanding which strictly determines what details of the information are important for the whole coherent context.^{89–93}

These findings suggest that typical deficits and “mental disintegration” in cognitive processing in schizophrenia and bipolar disorder might be related to executive signals that in the framework of required context determine sensitivity to various details needed for contextual processing the so-called “cognitive bias” which seems to be important for various mental disorders.^{94–100} In this sense “mental disintegration” in both schizophrenia and bipolar disorder are linked to disturbances in synchronized oscillations dynamically linking neurons into assemblies through the process of “binding” mainly at gamma frequencies (30–100 Hz) that are closely associated with sensory processing, attentional selection, effective sensory-motor integration and also play an important role in working and long-term memory.^{101–106}

According to recent findings disruptions of consciousness and “mental integration” in schizophrenia are related to disturbances of “neural binding”^{14,22} and similar disturbances were reported also in bipolar disorders.^{27,107,108} In this context, major supportive findings strongly suggest a link between gamma activity and GABAergic postsynaptic excitation.^{19–21} In this overall context, disrupted binding and disintegration of consciousness in schizophrenia and bipolar disorder likely are related to inhibitory deficits reflected in P50 response that may explain similarities in psychotic disturbances in both disorder. Nevertheless this review cannot claim that P50 disturbance is really a similarity that is unique to those disorders as it might be a feature that is present also in other disorders that manifest psychotic symptoms (for example PTSD, substance use and others as described diagnostic manuals DSM-V or ICD-10). Similarly, the role of impulsivity in bipolar disorder and its link to P50 may mean that P50 disturbance might not be unique to psychotic symptoms. Furthermore, there are other psychiatric disorders that are associated with high impulsivity (such as ADHD or

borderline personality disorders, please see DSM-V or ICD-10), so the question might be whether these other disorders also share same features as bipolar disorder and schizophrenia. To resolve these limitations needs other detailed analyses of available published findings and further research which could provide more detailed knowledge about neurobiological basis of cognitive-affective processes related to mental disorders.

Acknowledgments

This publication was supported by the project „National Institute of Mental Health (NIMH-CZ)“, grant number CZ.1.05/2.1.00/03.0078 (and the European Regional Development Fund) and by the Charles University project Cooperation SVV.

Disclosure

The authors declare that there are no conflicts of interest.

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