

Sensory disturbances, inhibitory deficits, and the P50 wave in schizophrenia

Premysl Vlcek¹Petr Bob^{1,2}Jiri Raboch¹

¹Center for Neuropsychiatric Research of Traumatic Stress, Department of Psychiatry and UHSL, First Faculty of Medicine, Charles University, Prague, Czech Republic;

²Central European Institute of Technology (CEITEC), Masaryk University, Brno, Czech Republic

Abstract: Sensory gating disturbances in schizophrenia are often described as an inability to filter redundant sensory stimuli that typically manifest as inability to gate neuronal responses related to the P50 wave, characterizing a decreased ability of the brain to inhibit various responses to insignificant stimuli. It implicates various deficits of perceptual and attentional functions, and this inability to inhibit, or “gate”, irrelevant sensory inputs leads to sensory and information overload that also may result in neuronal hyperexcitability related to disturbances of habituation mechanisms. These findings seem to be particularly important in the context of modern electrophysiological and neuroimaging data suggesting that the filtering deficits in schizophrenia are likely related to deficits in the integrity of connections between various brain areas. As a consequence, this brain disintegration produces disconnection of information, disrupted binding, and disintegration of consciousness that in terms of modern neuroscience could connect original Bleuler’s concept of “split mind” with research of neural information integration.

Keywords: event-related potential, information overload, inhibition, P50 wave, schizophrenia, splitting

Introduction

Sensory disturbances in schizophrenia are often described as an inability to filter meaningful sensory stimuli.^{1–9} In experimental settings, this filtering inability has been examined most often using auditory evoked potentials to repeated sounds with the main aim of testing the brain’s ability to inhibit (or gate) its response to repeated stimuli that in schizophrenic patients typically manifest as an inability to gate neuronal responses related to the P50 wave.^{10–12}

According to recent findings, sensory gating abnormalities represent early clinical symptoms of schizophrenia, typically characterized as a decreased ability of the brain to inhibit various responses to insignificant stimuli.^{1,5,7,13–18} Typical symptoms manifest as hypervigilance and difficulty in focusing attention, most likely due to disturbances of inhibitory neuronal activity in the hippocampus related to deficits of nicotinic cholinergic modulation.^{7,17,19,20} Typically, the gating related to the P50 wave is linked to widely distributed neuronal activities involving the temporoparietal and prefrontal cortical networks, mainly during the early phases of processing, in which a very significant role is played by the CA3–CA4 area of the hippocampus and its cholinergic inputs from the septal nucleus mediated by low-affinity nicotinic receptors affecting CA3–CA4 interneurons.^{21–24} These gamma aminobutyric acid (GABA)ergic interneurons transiently inhibit pyramidal neurons and mediate gating of the second stimulus during sensory stimulation usually used in event-related potential experiments.^{25–28} In this context, the basic experimental finding in research of auditory P50 sensory gating is typically suppression of the response to the second identical

Correspondence: Petr Bob
Center for Neuropsychiatric Research of Traumatic Stress, Department of Psychiatry and UHSL, First Faculty of Medicine, Charles University, Prague, Czech Republic
Email petrbbob@netscape.net

(S2) stimulus presented shortly after the first (S1) stimulus. This event-related potential response manifests very early in information processing (about 50 milliseconds) and most likely represents an adaptive mechanism preventing from becoming overloaded by redundant sensory information from the environment.^{29–31}

These typical inhibitory deficits related to activity of pyramidal neurons in the CA3 region of the hippocampus were therefore identified as important contributors to the cerebral evoked responses that play a significant role in habituation of repeated stimuli depending on cholinergic stimulation of hippocampal inhibitory interneurons.²⁷ Because of this cholinergic stimulation, those interneurons manifest bursts of activity that release a sufficient amount of GABA to activate presynaptic GABA-B receptors on CA3 pyramidal neurons, and due to this release, the excitatory neurotransmitter glutamate is blocked, so that the CA3 pyramidal neurons cannot respond to the second stimulus.^{27,28,32}

Current experimental and theoretical findings of normal responses to repeated auditory stimuli at the single neural level in animal models have provided some direct insights into the basic mechanisms of the sensory gating deficits.²¹ Basic observations show that acetylcholine receptors on hippocampal interneurons are very sensitive to alpha bungarotoxin, a nicotinic antagonist.^{23,32} Specific roles for these low-affinity nicotinic receptors in the P50 gating abnormalities in schizophrenia are supported by various recent physiological, pharmacological, and genetic studies.^{17,19,33–41} For example, these data show that the flow of sensory information from the cortex to the hippocampus is controlled by nicotinic cholinergic input from the septum to the hippocampus.^{32,42} These findings are also supported by genetic studies indicating that nicotinic receptors (produced by the specific alpha-7-nicotinic acetylcholine receptor subunit gene, *CHRNA7*) influence inhibition of responses to repeated auditory stimuli.^{7,21,23,35,43,44} In addition, several studies show that these sensory gating disruptions are also influenced by alpha-2-selective noradrenergic antagonists (eg, yohimbine) and 3-methoxy-4-hydroxyphenylglycol.^{45–49} Altogether, these findings indicate that specific inhibitory deficits play a major role in sensory gating deficits that can be observed in event-related potential studies focused on the P50 wave.

P50 and inhibitory theory

According to physiological theory, the main events enabling a decreased evoked response due to repetition of identical stimuli are linked to active inhibitory/excitatory mechanisms and passive habituation/dishabituation mechanisms. A basic

explanation of this active gating theory suggests that local neuronal inhibitory activity of the S1 stimulus specifically inhibits and filters out the response to the S2, representing the second identical stimulus (the same as the previous one).^{50–54}

The second stimulus therefore has no new information and is inhibited. The inhibitory effect of the stimulus, which usually lasts several hundred milliseconds, develops inhibitory postsynaptic potentials at about 96% of neurons in the primary auditory cortex in the early period of the inhibitory response (20–200 msec). During this period of inhibitory postsynaptic potentials, neural membrane resistance is reduced to 60%–90% of its initial value. In the subsequent periods, the efficiency of inhibitory reactions typically decreases for periods lasting longer than 200 msec. In this context, it is likely that the decreased neuronal sensitivity to auditory stimuli repeated every 500 msec is caused by inhibitory processes in cortical neurons per se rather than their blocking due to “in-flow” of afferent excitatory impulses during the refractory period.^{55,56}

Any following inputs reset the cortical dynamics with a delay that ranges from 10 to several hundred milliseconds, enabling cortical mechanisms to process rapidly changing successive information in short time intervals.^{57–59} For example, Volkov and Galazyuk⁵⁷ in a more general context proposed that synchronous activations of a large number of cortical neurons by a short stimulus resulted in coordinated release of a large amount of inhibitory transmitters into the synaptic connections, enabling relatively prolonged hyperpolarization of post-synaptic neurons.

As a consequence, a repeated stimulus leads to constant release of a small amount of neurotransmitter into the synaptic cleft, which may explain the process of continued inhibition. To explain this mechanism, it has also been proposed that the S1 stimulus may influence the initial evoked response that excites the hippocampal pyramidal neurons and also activate the inhibitory neurons that act as a comparator, and via this mechanism, the subsequent identical S2 stimulus produces diminished responses, when pyramidal neurons acting as the comparator are still active. On the other hand, when a subsequent nonidentical stimulus is presented, different sets of neurons are stimulated that were not stimulated before, resulting in an unhabituated response.^{60–66}

The current evidence also suggests that the main generators of P50 are located in the temporal lobes, but the main neuronal activities contributing to amplitude reduction in the P50 time range are localized in the frontal lobe.⁶⁷ These processes are closely linked to those of memory reconsolidation,

typically involving the medial temporal and frontal lobes that interact closely to allow successful remembering of and responses to sensory stimuli. Whereas the medial temporal lobe is predominantly associated with encoding, storage, and retrieval of long-term memories, the prefrontal cortex is closely related to cognitive control processes such as selection, engagement, monitoring, and inhibition.⁶⁸

P50 in schizophrenia

Recent findings indicate that schizophrenia is characterized by typical disturbances in cognitive processes that predominantly manifest as deficits of perceptual and attentional function.^{69–75} In this context, the data suggest that these deficits are characterized by an inability to inhibit, or “gate”, irrelevant sensory inputs, leading to the sensory and information overload typical of individuals with schizophrenia.^{1,76–82} This sensory gating deficit may result in neuronal hyperexcitability due to disturbances of neuronal inhibition at the subcortical and cortical levels.^{5,33,60,83} Accordingly, typical cognitive and sensory processing deficits in schizophrenia are closely related to deficits in P50 auditory gating which are linked to nicotinic cholinergic-mediated disinhibitory processes, representing a new potential opportunity for therapeutic intervention in schizophrenia.^{40,41,43,44,84–89}

The data presented above strongly suggest that patients with schizophrenia manifest typical disturbances of habituation mechanisms linked to information overload, leading to disruption of information processing.^{90–94} In this context, many studies have shown that the P50 sensory gating ratio in a paired click task is higher in patients with schizophrenia than in healthy controls, indicating more effective sensory gating processes.^{37,47,61,88,89,95–113}

A detailed meta-analysis⁸ rejected the possibility of the null hypothesis that these studies showed no effect, and also found that the differences were not the same across all studies. In this meta-analysis, the mean ratios in 45 of 46 group comparisons were smaller for controls than for patients. Patterson et al⁸ have also shown that the observed differences in means were significant in 35 of these studies. They identified 46 studies suitable for analysis of P300 measures, including 1,443 patients and 1,251 controls. There were 20 P50 studies, including 421 patients and 401 controls. The pooled standardized effect size (the difference between the means of the two groups divided by the common standard deviation) for the P50 ratio was -1.56 (95% confidence interval $-2.05, -1.06$; $P < 0.001$). There were no significant differences between patients and controls in P50 latency. Across-study variations in filters, task difficulty, antipsychotic medication,

and duration of illness did not influence the pooled standardized effect size significantly. Patterson et al⁸ concluded that their meta-analysis confirms the existence of event-related potential deficits in schizophrenia, with significance similar to the most robust findings reported in neuroimaging and neuropsychology in schizophrenia. Similar conclusions found also several others meta-analytic or detailed review studies which show sensory gating impairments in early stages of schizophrenia that become more prominent in chronic stages of schizophrenia.^{8,11,13,15,114} Further meta-analytical data by Chang et al¹¹⁵ confirm that the sensory gating deficit in patients with schizophrenia is well documented; nevertheless, certain findings raise doubts about the validity and utility of the S2/S1 ratio as a measure of sensory gating. The meta-analytical results confirm that the S2/S1 ratio and the repeating (S2) stimulus discriminate effectively between patients with schizophrenia and healthy controls, in contrast with the consistent but smaller effect size for the S1 amplitude, and these findings likely reflect inhibitory deficits related to repeated redundant input. Future studies are needed to clarify in detail the variables modifying sensory gating processes related to progression of schizophrenia and genetic predisposition to the illness.^{13,113,116}

In this context, recent findings also show that schizophrenia is associated with impairments of functional brain connectivity, which in principle may be studied using the P50 suppression paradigm in close relationship with the functional integrity of connections between brain areas involved in cross-sensory processing. According to a study reported by Magnee et al¹¹⁷ the typical filtering deficits studied as P50 deficits may be secondary to earlier sensory dysfunctions due to deficits in the integrity of connections between brain areas involved in low-level cross-sensory processing. In principle, this finding is in agreement with data suggesting that the main generators of P50 are located in the temporal lobes but that the neuronal activities predominantly contributing to amplitude reduction in the P50 time range are localized in the frontal lobe.⁶⁷

This relationship between connectivity and P50 in schizophrenia is also in agreement with the finding that gamma and beta activity, which are likely to be specifically linked to neural synchrony, connectivity, and integration of information, are related to P50. In this context, the initial response to S1 is observed as a high gamma band oscillatory activity that after about 200 msec switches to beta frequency oscillations, which may reflect an encoding of the sensory perception.^{118–121} There is also some interesting evidence showing that this post-S1 beta frequency response

is inversely correlated with the S2 response in patients with schizophrenia.^{100,106,122} This suggests that P50 is basically linked to rhythmic activity of neural assemblies that code information processing within and across cortical circuits and modulate neuronal excitability.^{120,123–126}

Based on these findings, sensory gating deficits related to schizophrenia might be explained by disconnection of information, mainly between temporal lobe generators and the frontal lobe, which may account for the diminished inhibitory activity of the frontal cortex linked to the P50 deficit.

Conclusion

There is now growing evidence that disruption of coherent neural binding is related to disintegration of consciousness in schizophrenia,^{127–130} and that this could be related to sensory gating disturbances.¹²⁷ In this context, sensory gating research might yield new findings connecting neuroscientific and psychological research of schizophrenia that could connect “split mind” according to original Bleuler’s concept with research of disturbed integration in neural information processing. Together these findings suggest that mental disintegration in schizophrenia could be described as sensory and information disturbance related to disinhibition and neural disintegration.

Major findings supporting the need for future research in this area include data indicating that long-range synchrony of gamma oscillations reflecting neural connectivity that depends on excitatory postsynaptic potentials of GABAergic interneurons is also closely related to sensory gating processes.^{28,32,126} This relationship between gamma oscillations and GABAergic interneurons is especially important for investigation of schizophrenia, given that there is now evidence indicating disturbance of GABAergic interneurons in schizophrenia.^{127–129} Further, convergent findings indicate that a signaling deficiency leads to reduced GABA synthesis and disrupted coordination of neural representations and related changes in perception and cognition in patients with schizophrenia.^{127,129,130} There is also evidence that these GABAergic abnormalities play an important role in schizophrenia and that the changes in neural synchrony in schizophrenia are most likely linked to dysregulation of multiple neurochemical systems, also including glutamate, dopamine, and other neurotransmitter molecules.

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Disclosure

The authors report no conflicts of interest in this work.

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