A Brief Review of a Brain Model for Schizophrenia and Other Psychotic Disorders Which Might Suggest Novel Treatment Modalities

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Here I will briefly describe a suggested pathogenic cycle which might lead to the formation of positive psychotic symptoms and discuss its therapeutic application. In a model presented in another paper (1), I proposed that defective sensory gating in the hippocampus may cause the schizophrenic brain to use the means of pattern completion to understand the ambiguous environment presented to it.

In a world where we are simultaneously bombarded with a great deal of stimulation, we are able to focus our attention on important stimuli, while filtering out, or gating, less relevant stimuli (2). Sensory gating (SG) creates habituation to repetitious and unimportant stimuli so that the brain may reserve its limited resources to focus on important stimuli that need processing. In a schizophrenic brain, sensory gating, which takes place in the hippocampus, is defective, and the brain is bombarded by a huge amount of stimuli that enters the patient's consciousness and needs to be processed. SG is assessed by the study of auditory-evoked potential P50 response, which is a sum of the electrophysiological neuronal response detected after stimulation by an auditory signal. The stimulus is repeated after 80 to 120 milliseconds, and the auditory-evoked response to the paired stimuli is detected. In normal people, because of habituation to the repeated stimulus, the response to the second stimulus is significantly diminished by at least fifty percent, while schizophrenic patients lack much of this inhibition. This results in an overflow of stimuli into the schizophrenic brain (3, 4).

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While the schizophrenic brain is bombarded by a huge amount of sensory stimuli due to defective gating in the hippocampus, because of the structural and functional defects of the amygdala, it also can encode fewer amounts of the input data than that of a normal brain. In other words, the schizophrenic brain has access to fewer clear and understandable data because of defective sensory gating, plus defective amygdala-hippocampal salience coding circuits. Since the amygdala is defective itself, understanding the emotional salience of the input data is difficult for the brain, and it has to complete the ambiguous data into an understandable format.

Pattern completion, as a function involved in memory retrieval, helps the brain to retrieve a complete pattern from an incomplete perceived pattern (5). When the brain encounters a vague and incomplete visual or auditory stimulus, it refers to its previously memorized visual or auditory patterns and attempts to match the new stimulus with the one complete pattern closest to it. Then the pattern is locked, and the person will perceive the vague pattern as the locked complete pattern. Through pattern completion

in thalamocortical and hippocampal circuits, both of which are defective in schizophrenia, the schizophrenic brain tries to understand the internal and external stimuli as much as possible (6). However, these abnormally completed patterns appear in the form of the hippocampal memories most relevant to the emotional situation of the brain. In other words, a schizophrenic person with oedipal conflicts might hear the criticizing voice of the father or might have delusions about someone trying to harm his or her father. The same happens to the psychotic manic brain that produces grandiose psychotic products that are related to the inflated state of mind. In the same way, the hippocampal-amygdala complex of a person with post traumatic stress disorder (PTSD) produces the most relevant patterns to the anxious state of the mind that are related to the traumatic experience. It is important to note that sensory gating is defective both in psychotic, but not non-psychotic, bipolar disorder and PTSD.

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Interestingly, it is clear that at least visual pattern completion is performed in the CA3 part of the hippocampus, which is the same place where sensory gating takes place (7, 8). From anatomical and electrophysiological data it is understood that in schizophrenia CA1 to CA3 regions are abnormal, and this leads to defective sensory gating (9, 10). It should be noted that the same region is defective functionally in both post traumatic stress disorder and psychotic, but not non-psychotic, bipolar disorder. It is already suggested that increased mesolimbic-dopamine levels in schizophrenia, despite the shrinkage and abnormality of the amygdala, might be due to a compensatory function of the amygdala to be able to code and understand the salience of the high amount of vague sensory data introduced to it by the defective hippocampus (1). The schizophrenics' desire for dopamine-increasing substances like cocaine and amphetamines might also show their need for dopamine excess to help the amygdala perform better on sensory, especially auditory, inputs. It has been suggested that this compensatory dopamine production might make the dopamine-producing cells burn out during time, the same as what happens to pancreatic insulin-producing cells in diabetes mellitus type II, which can explain why schizophrenic people lose more of their positive symptoms from aging, as well as having their negative symptoms increase (1). However, these two phenomena might put the amygdala-hippocampal circuits into a positive-reinforcing cycle of descending levels of sensory gating and ascending levels of dopamine production.

This defective gating in a schizophrenic brain also might be applicable to internal inputs that are thought contents. One form of such defective internal gating happens in obsessive compulsive disorder (OCD). Although the defects in OCD are mostly related to caudate dysfunction, sensory gating deficits are also found in OCD (8). In schizophrenic people one can assume that, since there is no proper gating of primary process thoughts, the large amount of vague thoughts creates a situation in which there is a higher need by the brain for pattern completion, which may lead to the production of delusions. Furthermore, the border between severe OCD and schizophrenia is not clear, and these disorders sometimes are two sides of the same spectrum, a fact that has caused authors to coin the term obsessive schizophrenia (11, 12).

Although the above defects are present in a schizophrenic brain before the onset of the psychotic phase, positive psychotic symptoms do not appear until early adulthood. This can be explained by the phenomenon of excessive frontal-cortical pruning, which has been related to the etiology of psychosis by many authors (13-15). Based on the model proposed here, one can assume that before the prefrontal cortex is damaged by excessive pruning, it can omit and correct the irrelevant and false productions of the pattern completion in lower areas of the brain and can also help in understanding the vague, large amount of input stimuli. When excessive pruning takes place in early adulthood, this control of the prefrontal cortex over the lower areas is diminished, and false memories and completed patterns may show up in the form of delusions and hallucinations. The imbalance between frontal and limbic systems as a reason for production of psychotic symptoms is discussed in another paper (16).

As is already known, one of the reasons for the high rate of tobacco use among schizophrenic people is the effect of smoking in diminution of hallucinatory symptoms for a brief period of time (17). Noting the model presented above, this fact can be related to the temporary enhancement of sensory gating by the effect of nicotine on (α7N) receptors. Furthermore, since sensory gating is highly dependent on the normal function of α7 nicotinic (α7N) receptors in the hippocampus, in the near future nicotinic cholinergic medications may play an important role in treatment of psychotic disorders, PTSD, psychotic mood disorders, and even OCD. Those agents that can stimulate (α7N) receptors might enhance sensory gating and interrupt the cycle explained above in order to decrease positive psychotic symptoms. In other words, while dopamine antagonists break the pathogenic cycle of psychosis in the amygdala, nicotinic cholinergic drugs can do the same in the hippocampus.

Serotonin-dopamine antagonists, which are novel effective antipsychotics, are distinct from typical antipsychotics in their inhibitory effects on different types of dopamine receptors and 5HT2A serotonin receptors. 5HT2A is an anxiogenic receptor (its activation is responsible for the generation of some anxiety disorders) which can impair normal emotional function of the amygdala and also interfere with normal sensory gating through afferent pathways from the raphe nucleus to the hippocampus. So, one effect of novel antipsychotics can be assumed to be the correction of sensory gating and the stabilization of amygdalic irregular and inappropriate function. This may also suggest the use of specific 5HT2A blocking agents for the treatment of such disorders as PTSD, bipolar psychotic mania, and OCD.

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References

1. Javanbakht A. Sensory gating deficits, pattern completion, and disturbed fronto-limbic balance, a model for description of hallucinations and delusions in schizophrenia. Med Hypotheses 2006;67(5):1173-1184.
2. Panksepp J. Textbook of biological psychiatry. Hoboken (NJ): Wiley-Liss; 2004. p.285.
3. Light GA, Braff DL. Human and animal studies of schizophrenia-related gating deficits. Curr Psychiatry Rep 1999;1(1):31-40.
4. Clementz BA, Geyer MA, Braff DL. Multiple site evaluation of P50 suppression among schizophrenia and normal comparison subjects. Schizophr Res 1998;30(1):71-80.
5. Samura T, Hattori M. Hippocampal memory modification induced by pattern completion and spike-timing dependent synaptic plasticity. Int J Neural Syst 2005;15(1-2):13-22.
6. Peláez JR. Towards a neural network based therapy for hallucinatory disorders. Neural Netw 2000;13(8-9):1047-1061.
7. Mizumori SJ, McNaughton BL, Barnes CA, Fox KB. Preserved spatial coding in hippocampal CA1 pyramidal cells during reversible suppression of CA3c output: evidence for pattern completion in hippocampus. J Neurosci 1989;9(11):3915-3928.
8. Freedman R. Schizophrenia: sensory gating deficits and translational research. In: Sadock BJ, Sadock VA, editors. Kaplan and Sadock's comprehensive textbook of psychiatry. 8th ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2004. p.1450.
9. Nelson MD, Saykin AJ, Flashman LA, Riordan HJ. Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study. Arch Gen Psychiatry 1998;55(5):433-440.
10. Waldo MC, Cawthra E, Adler LE, Dubester S, Staunton M, Nagamoto H, et al. Auditory sensory gating, hippocampal volume, and catecholamine metabolism in schizophrenics and their siblings. Schizophr Res 1994;12(2):93-106.
11. Gross-Isseroff R, Hermesh H, Zohar J, Weizman A. Neuroimaging communality between schizophrenia and obsessive compulsive disorder: a putative basis for schizo-obsessive disorder? World J Biol Psychiatry 2003;4(3):129-134.
12. Kwon JS, Shin YW, Kim CW, Kim YI, Youn T, Han MH, et al. Similarity and disparity of obsessive-compulsive disorder and schizophrenia in MR volumetric abnormalities of the hippocampus-amygdala complex. J Neurol Neurosurg Psychiatry 2003;74(7):962-964.
13. Keshavan MS, Anderson S, Pettegrew JW. Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? The Feinberg hypothesis revisited. J Psychiatr Res 1994;28(3):239-265.
14. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? J Psychiatr Res 1982-1983;17(4):319-334.
15. Hoffman RE, Dobscha SK. Cortical pruning and the development of schizophrenia: a computer model. Schizophr Bull 1989;15(3):477-490.
16. Javanbakht A. The theory of bowl and bugs: a model for the explanation of the coexistence of psychological and biological etiologies in the psychosis. J Am Acad Psychoanal Dyn Psychiatry 2005;33(2):363-375.
17. Adler LE, Hoffer LD, Wiser A, Freedman R. Normalization of auditory physiology by cigarette smoking in schizophrenic patients. Am J Psychiatry 1993;150(12):1856-1861.