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Sensory gating deficits, pattern completion, and disturbed fronto-limbic balance, a model for description of hallucinations and delusions in schizophrenia

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Summary Schizophrenia, if not the most difficult, is one of the most difficult mysterious puzzles for psychiatrists, psychologists, and neuroscientists to solve. In this paper, based on the previously known pathologies of schizophrenia, a new model is proposed for explanation of the formation of positive psychotic symptoms of hallucinations and delusions. This model can be used for understanding psychotic or psychotic-like positive symptoms of bipolar mood disorder, posttraumatic stress disorder, obsessive compulsive, and amphetamine and drug-induced psychotic disorders. Based on the postulated model, a spectral view on these disorders with psychotic features is also proposed.

These pathologies include auditory sensory gating deficits in hippocampus, abnormal emotional coding in amygdala, pattern completion in thalamic and cortical areas, and disturbed fronto-limbic balance. This model includes anatomical and neurotransmitter defects of hippocampus, amygdala, thalamus, cingula, and prefrontal cortex and their interconnections. A role for hippocampal sensory gating deficits in the pathogenesis of positive psychotic symptoms and interrelation between amygdala and its dopamine level with hippocampus is speculated. This model also hires the interesting function of pattern completion in thalamus and cortical areas for a better explanation of the pathogenesis of hallucinations and delusional psychotic symptoms.

Furthermore, there is also explanation for the polygenic etiology of the schizophrenic and psychotic disorders and relation between schizophrenia and bipolar mood disorder in anatomy and neural systems involved. A spectral view is proposed that explains the absence of clear cut border between different psychotic or psychotic-like disorders in their form and severity based on the involved genes and brain functional systems. Including excessive prefrontal pruning, there is also explanation for the appearance of positive psychotic symptoms in early adulthood.

An explanation for the high dopamine level of amygdala despite its decreased size and abnormal anatomy is also suggested as a compensatory function which might explain the decline in positive psychotic symptoms when schizophrenics age according to amygdala burn out.

Based on this model, speculations are provided for: late onset of the effects of antipsychotics on positive psychotic symptoms, mechanism for the therapeutic effect of serotonin type 2A receptor blockers and GABAergic medications

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in psychosis, role of smoking in diminution of psychotic symptoms, and relationship between biological and psychological issues in the formation of psychotic symptoms.

Finally, based on this model, a new role for nicotinic cholinergic drugs (such as galantamine) for treatment of schizophrenia and other psychotic or psychotic-like disorders is proposed.

Introduction

Schizophrenia, as a spectrum of deficits in many brain areas and neural networks, has been one of the most difficult puzzles for neuroscientists, psychiatrists, psychologists and psychoanalysts to solve. However, there has yet not been a comprehensive and definite model for explanation of all the psychotic phenomena and signs and symptoms observed in schizophrenic people. By the emergence of impressive technological developments in brain imaging, we have a big amount of neuroanatomical and neurotransmitter data about schizophrenia that need to be understood, interpreted, and related to each other in order to suggest more acceptable and comprehensive models for explanation of how the changes in brain macroscopic and microscopic anatomy end in clinical symptoms observed in schizophrenic patients. While there is less ambiguity in understanding the etiology of negative symptoms of schizophrenia, that are mostly related to deficits in cognitive systems especially frontal lobe, there are more controversies about the etiology of positive psychotic symptoms of hallucinations and delusions. In this paper, I suggest a new model to explain the appearance of psychotic symptoms of hallucinations and delusions in schizophrenic patients. This model is mainly based on sensory gating deficits, dysregulation of amygdala, pattern completion, and disturbed frontal-limbic balance. In neuroanatomical level it mainly includes prefrontal cortex especially dorsolateral prefrontal cortex (DLPFC), hippocampal and amygdala limbic formations, thalamus, and their interconnections. I will first have an overview of anatomical changes in these regions that I need for my model and then briefly describe sensory gating deficits, pattern completion, and frontal-limbic imbalance in schizophrenia, and will finally describe my model based on these defects.

Sensory Gating deficits in schizophrenia

In a world where we are simultaneously bombarded with a great deal of stimulation, we learn to focus our attention on important stimuli, while filtering out (gating) less relevant stimuli [1]. Sensory gating (SG) is a way of habituation to repetitious and unimportant stimuli for the brain to reserve its limited resources to focus on important stimuli that need processing. In a schizophrenic brain, sensory gating is defective and the patient is bombarded with many stimuli that enter his/her consciousness and all need processing. 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—120 ms 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 50% while schizophrenic patients lack much of this inhibition. This results in an overflow of stimuli into the schizophrenic brain [2,3].

SG is mostly related to hippocampal formation of limbic system which is a main area of malfunction and anatomical defects in schizophrenia. Hippocampus is not a primary sensory processing area. Rather, it is concerned with interpreting the significance of sensory stimuli, to orient the organism to its environment [4]. The primary auditory cortex in temporal lobe projects to entorhinal cortex and that has perforant projections to CA3 portion of hippocampus as well as direct projections to dentate gyrus and CA3 through cholinergic neurons decides what data are worth to be processed by CA1 [5].

In schizophrenic patients there are clear macroscopic and microscopic defects in hippocampus that can be responsible for disturbed sensory gating. Studies have revealed a decrease in the size of hippocampus and entorhinal cortex [6] and also neuronal disarray in both the areas in schizophrenia. There are reports of decreased neuronal density in all CA1—CA4 regions along side a decline in axonal markers and dendritic connections [7]. There is also decreased metabolism in hippocampus especially in left hemisphere. GABA and glutamate neurotransmitter systems that are both defective in schizophrenia, are needed for the

CA3 region to perform its SG function properly [8]. From the cholinergic system, α7 nicotinic (α7N) receptors exert an inhibitory effect in hippocampus and thalamus. In hippocampus, these receptors are responsible for inhibition of response to the second stimulus in P50 sensory gating. A 50% decrease in α7N receptors in schizophrenic brains is thought to be mainly responsible for SG deficits [9,10]. There are also other neurotransmitters involved in modulation of sensory gating. Dopamine increases the response of cortical neurons to incoming stimuli, so that more of their activity is transmitted to the hippocampus while serotonin through 5HT2A receptors increases the release of glutamate onto the pyramidal interneurons of hippocampus [5]. Finally, norepinephrine interferes with the calcium influx produced by α7N and NMDA receptors that leads to decreased sensory gating [5,11]. This means, dysregulation in any of these systems might lead to disturbed sensory gating. It is needed to mention that schizophrenia is not the only disease with sensory gating deficits and SG is also defective in amphetamine psychosis, post traumatic stress disorder (PTSD), psychotic mania, and obsessive compulsive disorder (OCD) [12,13].

Pattern completion, a means of the brain to understand vague stimuli

Peláez, in an interesting paper describes the phenomenon of pattern completion in neural networks such as thalamus and suggests it to be a probable cause of hallucinatory and delusional phenomena [14]. Pattern completion in thalamus is the key concept used in this paper for analyzing some cognitive disorders that involve hallucinations of several kinds: visual hallucinations in the Charles Bonnet syndrome and psychedelic drugs consumption, somatic hallucination in phantom limbs, hallucinations in schizophrenia and multiple personality disorders. In his view, thalamic architecture is very similar to a folded autoassociative neural network in which the hidden layer acts as a hinge [15]. A neural network is a collection of neurons, that can consist of a few to a few billion neurons connected in an array of different methods. Autoassociative networks take input and output the *same* vector. Usually, autoassociative neural networks are used for pattern completion: during the phase of training of an autoassociative network, equal patterns are presented to its input and output layers. Once an autoassociative network is trained, a noisy, damaged or incomplete testing pattern can be input to the network so that the network will output a noise-free and complete pattern. During this testing phase, the autoassociative network outputs an idealized version of the testing input pattern. This idealized output is a blend of the *Principal Components* extracted by means of the hidden layer. In this blend, irrelevant data are not recalled and, in this way the output can be considered an ''idealized'' version of the input. The author proposed that the thalamus is also able to complete noisy or damaged patterns by means of the PC that are extracted in its reticular layer [15]. Peláez agrees that this idealized pattern completion may be the consequence of a top-down process from high level cortical areas but he suggests the site of pattern completion might also be at the thalamus instead. The proposed model of computation at the thalamus corroborates experimental data in which feedback signals from cortex are capable of making the thalamus reconstruct and anticipate a pattern that will be presented to it at the next instant [16]. He brings an example: if an image is stabilized in the retina so that relative movements between the retina and the image are no possible any more, a remarkable fact takes place: the image soon fades and disappears and, after a while, fragments of the image appear again. For example, a monogram formed of the letters H and B breaks into recognizable letters and numbers that come successively into view [17]. In other words, a distorted figure is transformed into a more rounded one!

Important for our work, Peláez finally suggests that schizophrenia might be a result of pattern completion in a cortically deafferented thalamus. Neuroimaging studies confirm an abnormal small size of the thalamus and adjacent white matter in schizophrenic subjects and there are reports of a loss of cortico-thalamic inputs especially that of prefrontal to medial dorsal thalamus in schizophrenics [18–20]. Besides, target cells in medial dorsal thalamus are decreased and there is decreased dopamine in cortico-thalamic feedback loops [21]. Interestingly, treatment with haloperidol in schizophrenic people leads to a decrease in thalamic metabolism and also frontal and cingular metabolism [22].

Finally, noting that there are also defects in thalamo-limbic and thalamo-prefrontal connections; Peláez suggests that delusion might be the result of thalamic deprivation of cortical and limbic inputs that make the process of thought. He also suggests that, just like other syndromes discussed above, auditory and visual hallucinations of the schizophrenic patients might be a result of pattern completion in a sensory deprived thalamus!

Fronto-limbic imbalance in schizophrenia, the theory of bowl and bugs

In another paper, I have discussed the prefrontal dominance over limbic system (especially amygdala and hippocampus) and have suggested the positive delusional and hallucination symptoms of schizophrenic people to be related to the disturbed balance between the two brain areas [23,24]. Inner experiences, traumatic and pathological memories, and repressed fears are the bugs that, by dysfunction or weakening of the ego bowl, come out of the bug hole (hippocampus) and take the energy of limbic system (hyperdopamine state of amygdala) to overcome the prefrontal dominance and show off as delusional and hallucinational symptoms. In schizophrenia, the damage in prefrontal bowl is clearly understood and it has been mostly related by other authors to negative cognitive symptoms and signs [25]. Besides, the role of PFC in control and overriding of emotions is known [26]. There are also disturbed reciprocal fronto-limbic pathways that impair prefrontal dominance and control over the hyperactive limbic system [27].

On the bugs' side, amygdala, that is responsible for recognition of emotional significance of external stimuli and coordination of cortical responses is in a hyperdopaminergic state. Limbic dopamine, that determines emotional importance of the received internal or external stimuli [28], is interestingly usually increased only in the psychotic state of schizophrenics but not in remission. It is also increased in psychotic manic patients but not in non-psychotic ones [29]. Furthermore, dopaminergic drugs such as amphetamines can produce psychotic symptoms in some people or worsen schizophrenic symptoms in patients [30]. Hippocampus, as the third element of the frontal-amygdala-hippocampus model for schizophrenia, is both a source of unconscious traumatic memories and experiences and producer of bizarre memories that, by the force of heightened dopamine level of amygdala, pass the barrier of PFC and become real to the patient. They become real delusions or hallucinations that are merged with the reality as a result of dysfunction of PFC to discriminate them from real experiences and dominating them. In this psychobiological model, the manic psychotic state is an escape of the hyperactive limbic system from the PFC dominance in which the elated emotion-congruent positive memories of hippocampus take the form of pleasant delusions and hallucinations.

The model

Defective sensory gating and abnormal limbic dopamine level, beginning of the pathogenic cycle

As it was noted above, there are clear evidences of decreased sensory gating in schizophrenia due to disruption in architecture, function, and neurotransmitters of hippocampus. Because of this defect, the schizophrenic hippocampus and amygdala (that are responsible for development of emotional significance and response to environmental and internal contexts) are bombarded by a big amount of auditory sensory data that is more than the capacity of the defective limbic system to handle [31]. Besides, auditory sensory processing areas are also defective due to well understood decreased volume and function of left temporal lobe [32]. As a result, patient's limbic system has to deal with many unfiltered auditory sensory data. Hippocampus, receives auditory sensory inputs from primary auditory cortices through the entorhinal cortex [4] and as an associative area of the brain, interacts with amygdala in the development of emotional response to environmental stimuli. For this to happen, auditory stimuli need to be conceptually understood and amygdala is supposed to detect the emotional salience of incoming stimuli and relate proper emotional value to each stimulus [31,33]. While amygdala itself is defective and small in size, its bombardment by many stimuli that it has to work on, may lead it to function in a more chaotic manner. Since it is proven that in many schizophrenics amygdala dopamine level is increased in acute psychotic phase [34], this dopamine rise might be related to increased need for amygdala function of emotional salience coding of the enormous unnecessary inputs from hippocampus. However, dysfunctional amygdala may also fail to relate proper emotional values to all the stimuli because of its own disturbed architecture and function. In this view, hyperdopamine state of amygdala might be both primary, and secondary to highly increased need forced on a defective amygdala. On the other hand, as it was noted above, increased limbic dopamine level might also increase sensory input by decreasing the gating of sensory stimuli in hippocampus [35]. So, one can suggest these dysfunctions in hippocampus and amygdala can be causatively interrelated. This interrelation is evidenced by a decrease in psychotic hallucinations after smoking that is one reason for the high rate of smoking in schizophrenics [36]. As it was noted above, nicotine, by activation of α7N receptors, potentiates

sensory gating for a short period and corrects it to some extents. Besides, one distinct action of novel antipsychotic drugs is blockade of serotonin receptor 5HT2A. As it happens in vigilant state that is observed in anxiety disorders and PTSD, 5HT2A receptors activation weakens sensory gating in order to let more sensory data enter the individual's consciousness [37]. In a normal person, this can be easily understood as a function of the brain to receive as much sensory stimuli as possible in a danger situation to save the organism from environmental insults [38]. However, this protective measure results in pathology in anxiety disorders [39]. The antipsychotic effect of serotonin dopamine antagonists might be in part because of the correction of sensory gating deficit by blockade of the negative effect of 5HT2A on it. On the other hand, while raised levels of dopamine and norepinephrine are proved to interfere with the effects of α7N receptors and lead to impaired sensory gating in hippocampus, it has been shown that dopamine antagonist antipsychotics help sensory gating to return to near normal level [13,40,41]. These evidences support the idea of interrelation between the disturbed sensory gating in hippocampus and rise of dopamine level in amygdala. Interestingly, in psychotic manic patients (but not non-psychotic ones), both the limbic dopamine level and sensory gating are abnormal. Limbic dopamine level in psychotic manic patients is shown to be high while sensory gating is also impaired in those patients [4]. Again, in amphetamine-induced psychosis, both the phenomena are present: limbic system dopamine is increased by the direct effect of the drug, and sensory gating is also defective [12]. In some other researches, dopamine or LSD injection into rat's brain has lead to disturbed sensory gating [42]. These evidences again support a correlation between these two defective systems in hippocampus and amygdala.

In another psychotic-like state, PTSD, in which patients reexperience the traumatic memories in vivid hallucinatory and dreamlike forms, sensory gating has proven to be defective. Interestingly, in these people, because of a high level of anxiety, there is higher amount of norepinephrine (dopamine-like and dopamine increasing effects of norepinephrine are known) and 5HT2A activation present [43,44].

Another evidence for the high dopamine level of amygdala to be (at least to some extent) secondary to other malfunctions of the brain (here the sensory bombardment) is the observed decrease in active psychotic symptoms in chronic schizophrenic patients. As the patient gets older, positive psychotic symptoms diminish and what remain are mostly negative symptoms. Interestingly, this happens along side a decline in the increased level of limbic dopamine in the old age chronic schizophrenic patients. If we consider the hyperdopaminergic state of amygdala to be in response to defective amygdala function and structure, and to some extent to an increased need for sensory processing as a result of defective sensory gating, the diminution of its dopamine level in chronic patients can be understood as an exhaustion and burn out of dopamine producing cells. This might also explain in part the rise of negative symptoms in schizophrenics as they age. As amygdala loses its function more and more, it fails more to give least proper emotional response to environmental and social stimuli which leads to deterioration of negative symptoms. A similar exhaustion is evidenced in the endocrine disease of type II diabetes mellitus. In type II diabetes mellitus, the pancreas gland has to increase its insulin production over the normal level to respond to increased need for insulin due to decreased sensitivity of adipose cells to insulin. In that disease, after some time pancreatic insulin-producing cells burn out and pancreas loses its ability of insulin production.

Furthermore, as it will be noted later, while hippocampus is responsible for filtering the unnecessary sensory inputs from entering the higher conceptual and emotional processing areas, presence of a gating for the internal stimuli especially those that come through afferent fibers from cortical and limbic areas is not impossible [5]. Since there are many thoughts that rise from the lower intellectual areas, most of them are filtered out in order to provide a goal directed and meaningful process of thought formed. An example of the defect in such a gating is found in obsessive compulsive disorder (OCD) in which many absurd and unnecessary ideas and thoughts enter the consciousness and impair the normal process of thinking. It is interesting to note that another disorder that is shown to have defective sensory gating is OCD! In another paper I have suggested the OCD to be on a spectrum on the other side of which schizophrenia lies [23].

Pattern completion compensates limbic system malfunction

We have yet discussed a malfunction in the filtering (hippocampal sensory gating) and emotional understanding and coding (amygdala-hippocampal dysfunction) of the auditory sensory stimuli. This results in an overload of auditory sensory data that although is handled by primary sensory areas and can be heard, is more than what limbic system can handle to code and value emotionally and

conceptually. So, a big amount of sensory data with inaccurate emotional value is relayed to upper cognitive areas, especially prefrontal cortex. These data that are not processed properly (because of the lack and inaccuracy of resources with highly increased stimuli), are vague and are not understood well because of inappropriate emotional coding (defective amygdala with increased dopamine). Because of this conceptual ambiguouity, pattern completing circuits (of thalamus and frontal cortical areas) have to use the means of pattern completion to understand the surrounding world.

As an example, when a schizophrenic patient begins to become symptomatic (I will discuss this process of beginning of the disease later), in a so called *trema* phase, he or she experiences severe anxiety with the ambiguity of the environment. The patient experiences severe anxiety because of a surge in limbic dopamine level (as an indicator of acute psychosis) and feels something must be wrong about the environment (because of that raised dopamine level and also bombardment by a big amount of sensory data along side the erroneous emotional coding and conceptual understanding of these data that makes them very difficult for him or her to understand). At this time, in order to relate the ambiguous data to the high emotional state of the patient, pattern completion devices (especially thalamus and higher frontal areas) refer to the past experiences to fill the empty space in understanding of the world. So, memories those are compatible with the present anxious level of limbic system revive in the form of delusional ideas or hallucinatory experiences. In other words, in order to be able to know what is wrong about the environment that is presented chaotically to it, the brain refers to its old bugs that match with the emotional state of the patient. In a schizophrenic patient with oedipal conflicts, these bugs will be persecutory delusions about father or auditory hallucinations commanding him or her to kill the father. For a manic patient, due to the very positive emotional load circulating in limbic system, the brain faces the puzzle of the sensory mismatch this way: I am very happy (A). I have always been very happy because of something (B). That something is not known (C). Only being a saint can let someone to be this much happy (D). To solve the problem, memories about the saints arise to complete the pattern in the most appropriate manner. In simple words: A + B + C + D = I am a saint.

Finally in PTSD, appropriate to the very high level of anxiety, patterns of a previous state with that level of anxiety (the traumatic event) are completed and the patient only hallucinates those highly emotional experiences.

However, as it was mentioned before, the gating (hippocampus) and emotional understanding and processing can be also defective for internal stimuli and as like as sensory stimuli, internal stimuli and thoughts may be also referred to pattern completing systems and make them create unreal experiences according to those internal feelings, thoughts, and emotions.

Interestingly, schizophrenic patients usually have meaningful voices as their auditory hallucinations not nonsense and monotonic sounds. It is because the problem is not in hearing of voices and sound (that is a task of primary sensory areas). The problem is with emotional and conceptual understanding of those auditory stimuli because of the overload and defective function of the associative and secondary sensory areas. All the stimuli are heard, but they are more than what the processing areas can handle to understand. Because of the resulting conceptual and emotional vagueness of the stimuli, pattern completion will be of conceptual and emotional kind. Besides, since according to the bowl and bugs theory those are traumatic and conflictual memories and thoughts that are used as means of pattern completion, it will not be surprising for the hallucinations to be of meaningful kind.

Prefrontal pruning, the last hit to flare up the fire

As a result of dysfunctional subcortical areas in schizophrenia, the prefrontal cortex receives a big amount of irrelevant and unnecessary data and completed patterns. A normal prefrontal (especially DLPFC) can eliminate this big load of irrelevant data. In other words, it can correct the products of defective hippocampus, amygdala, and thalamic pattern completion especially through its dominance over these areas through cingulate gyrus. If the prefrontal cortex is normal, it can filter these data as a second barrier level and can eliminate unnecessary, incorrect, or invalid data that are relayed from limbic and secondary auditory areas. This is what happens in PTSD and bipolar disorder. For example, bipolar patients do not always hallucinate, but the times that increased dopamine level of limbic system rises as so much as it can pass the normal barrier of PFC. In a bowl and bugs language, only very strongly boosted bugs (by amygdala dopamine) can pass the sane barrier of frontal. In PTSD also, only emotionally very traumatic and strong experiences can pass through the hippocampal-amygdala limbic system to the PFC and show off as vivid hallucinatory reexperiences while the patient does not hallucinate about other

experiences and memories (weaker bugs). Another example is for amphetamine abuse. A normal person becomes psychotic only when the amygdala and limbic dopamine is high enough to overcome a normal PFC dominance.

The near normal PFC in people, who will be schizophrenic in future, protects them from the products of limbic dysfunction and pattern completion in their younger age before the beginning of the disease. There has always been a question about why schizophrenia begins in adulthood and whether it is congenital or developmental as a field of great controversy. Many scholars believe the problem to be defects in neuronal migrations in embryonic stages, birth traumas, hypoxias, or congenital defects of the brain [45,46], while pros of developmental theories lie on the later changes in brain that cause the patient to become psychotic usually in adulthood and not in the childhood age [47,27]. They have strong evidence of the emergence of psychotic symptoms in adult age. In my theory, these two ideas can join and both can be validated. While the defects in subcortical areas appear sooner, failure in dominance of frontal lobe happens later when the process of excessive *pruning* takes place!

Opposed to the early model, late developmental model postulates that at least some of the crucial developmental abnormalities occur during adolescence to explain why schizophrenic psychotic symptoms appear in adolescence not in childhood. While normal pruning of neuronal dendritic connections take place in adolescence in order to let functional and appropriate neural circuits form and shape, Keshavan suggests that schizophrenia might result from an excessive synaptic pruning [48]. Since human brain pruning is under genetic regulation, schizophrenia producing genes might exert some of their effect by compromising cortical maturation [49,50].

In the theory proposed here, as it was noted above, I suggest that defects in function of limbic system and compensatory pattern completion are eradicated and corrected by near normal prefrontal functioning. Especially, DLPFC that volitionally controls the lower areas and is responsible for self monitoring helps to discriminate real environmental experiences from inner experiences and products of limbic system and pattern completion. In adolescence, the time in which abnormal and excessive pruning takes place, this last frontier of reality testing gets destroyed and the anarchism in subcortical areas finds the opportunity to show off. In a bowl and bugs language, bugs get out of the control of the broken bowl of PFC. This explains why although malfunctions such as hippocampal defective sensory gating or thalamic or amygdala abnormalities are present from earlier ages, symptoms of the disease appear later in adolescence.

To summarize the theory, hippocampal defective sensory gating lets a high amount of sensory data be presented to the previously defective and abnormal amygdala for emotional and conceptual processing. The result is an overload on hippocampus-amygdala system that might end in a compensatory rise in amygdala dopamine level and abnormal and irrelevant emotional coding by amygdala. Although both the defective sensory gating and amygdala dysfunction and high level of dopamine can be primary, they can also affect each other as described above and worsen each others' defective function through the interconnective circuits. Sensory gating and emotional coding might also be defective in a similar pattern for internal stimuli. Besides, defective limbic system with an overload of sensory data coming from the primary sensory areas also fails to discriminate memories of the inside world (the bugs) from real external experiences. However, until the PFC and especially DLPFC functions are near normal, these errors are mostly corrected by higher cortical areas responsible for reality testing and pattern correction. When the prefrontal system fails to do so because of excessive pruning in adolescence, the brain is bombarded by a high amount of sensory data with abnormally high, irrelevant, and inappropriate emotional and conceptual labeling by amygdala. This vagueness of sensory data that are more than what the defective brain (especially PFC and limbic system) can handle, forces the brain to use its pattern completion defense which might be performed both by thalamus and PFC. Since auditory sensory data are relayed both to thalamus and hippocampus, when hippocampus-amygdala circuits fail to understand the incoming data appropriately and the data are vague with an inappropriately high emotional value, brain refers to its memory resources in order to complete the vague and irrelevant received patterns to understand the defective, blurred, and chaotic environment presented to it. The result is emergence of memory bugs related to the same emotional situation of amygdala due to its high dopamine level. When patterns match the dopamine level and can complete the vague sensory incomings in presence of a defective PFC and DLPFC that fails to eradicate erroneous patterns and irrelevant incoming sensory and internally emerged data, the brain (thalamus or PFC) locks the new pattern and a delusion or a hallucination forms. If the patient is schizophrenic and feels severe anxiety due to high limbic dopamine level

and irrelevant coding of the high amount of incoming sensory data in an acute psychotic episode, the patterns that will lock with this emotional state are memories (especially traumatic and of persecutory theme) that have been related closest in anxiety level to the present emotional state of the patient. However, these memories can also be unreal without any previous experiences because of the dysfunctional hippocampus as the bug hole.

If the patient is bipolar in an acute psychotic manic episode, patterns of intense happiness will be completed according to the emotional state in the limbic system and finally, in a patient with PTSD, related to heightened level of norepinephrine and dopamine in limbic system, the most anxiogenic experience (the traumatic event) is the big bug that comes out of the hole. However, in such anxiety disorders as PTSD and OCD, since the PFC and DLPFC are most intact and amygdala dopamine level is not as high as in schizophrenia and bipolar disorder, reality testing is the least disturbed and the brain does not fail to discriminate between inner products of pattern completion and external reality most of the times.

Interestingly, it is shown that during an auditory hallucinatory state, there is activation in Broca and Wernicke areas that are related to speech and verbal memories [25]. This activation can be because of the brain need for these areas during the task of pattern completion while producing its hallucinatory patterns. In other words, pattern completing circuits take the bugs from these areas in order to understand the vague and emotionally irrelevant world.

From an energy saving point of view, while during vagueness of the bombarding sensory stimuli the brain has to expend a high level of energy in the defective limbic system to handle the incoming data, when the pattern completion takes place and the completed pattern is locked, brain facilitates that circuit of the completed pattern by its repetition and later it will become automatic and facilitated through fixation of the delusions. As like as other learned patterns of behavior, that after a proper times of repetition become automatic with less expenditure of higher brain areas energy, the fixated delusions and hallucinations can be repeated more easily with lower expense of energy for the brain and these psychotic features become more fixed and stabilized during the time of psychotic progression. They may also become a locus that pattern completion can more easily relate other vague and blurred phenomena and environmental cues presented to the brain to it and form a systematized complex of delusions around this primary locus.

Finally, defects and malfunctions in hippocampus, amygdala, and PFC hand in hand with the pattern completing defense of the brain, correspond for the formation of hallucinatory and delusional phenomena in psychotic states. There are also many evidences of dysfunction of cingula in schizophrenic brains and also its activation during a hallucinatory experience [51]. While cingula is the gateway between higher cortical areas and the limbic system, its top-down function of modulating ascending emotions fails in schizophrenia as another subset of damaged cortical dominance on subcortical areas.

Implications and conclusion

The model presented here, is a suggested explanation for the formation of positive psychotic symptoms of hallucinations and delusions in schizophrenic patients but it has also some to say about other psychotic or psychotic-like disorders such as PTSD, psychotic bipolar disorder, amphetamine psychosis, and OCD.

In this model, that tries to suggest an understanding of the psychogenic process of schizophrenia, dysfunctions of hippocampus, amygdala, thalamus, and prefrontal cortex are postulated to form a pathogenic circle. While most of the previous models had put defective prefrontal cortex on the negative symptoms side of schizophrenia, I here propose it to be involved in the process of production of positive psychotic symptoms by its defective function and lack of mastery on lower brain areas. However, it can also be involved in pathologic process of pattern completion that leads to formation of delusions and hallucinations.

Besides as a provider and producer of traumatic and pathologic memories, this model suggests an explanation for the little known role of hippocampal sensory gating deficits in the pathogenesis of positive psychotic symptoms. An interrelation between amygdala and its dopamine level with hippocampus is also included in this model. For amygdala, since it is smaller than normal in schizophrenic patients, one cannot expect it to be hyperactive. But its dopamine level is high and in this model, at least in part, this hyperdopaminergic state might be understood as its compensatory strive for processing of the high rate of incoming stimuli due to defective sensory gating alongside its (amygdala) primary anatomical and functional defects. In this view, a decline in both positive psychotic symptoms and amygdala dopamine level during the chronic course of illness when the patient

becomes older and the disease is more chronic, can be related to amygdala exhaustion and burn out. This burn out can also explain the increased degree of negative symptoms and emotional blunting of the more chronic schizophrenic patients. This model also hires the interesting function of pattern completion in thalamus and cortical areas for a better explanation of the pathogenesis of hallucination and delusional psychotic symptoms.

Furthermore, this model has suggestions for how the disorder begins in a previously non-psychotic person. As it was noted above, there are different congenital, early, and late developmental models suggested for schizophrenia. The present model is based on pathologies related to both early and late changes in the brain. It hires the early dysfunctions and anatomical defects of temporal lobe, hippocampus, and amygdala that are mostly present from younger ages and might be due to genetic or environmental influences. On the other hand, it explains how the late developmental model of excessive cortical and especially prefrontal pruning lets the pathologies in lower subcortical areas find an opportunity to flare up and form the positive psychotic symptoms in an adolescent schizophrenic patient. Since defects in sensory gating, amygdala function, and prefrontal are also found in non-psychotic relatives of schizophrenic patients [52—54], based on this model, one can think that all these defects are required simultaneously for the formation of psychotic symptomatology. In other words, in a family with genetic loading for schizophrenia, the one member who has abnormal genes responsible for defective formation and function of all these systems becomes schizophrenic while others, who own genes related to only one of these defects, survive and live with no prominent psychotic disorder. Since more than one defect is needed for production of schizophrenic psychosis, one person with only some of these genes will not become schizophrenic. In this polygenic view, the extended spectrum of schizophrenia can be also understood better. As it was noted before, schizophrenia cannot be understood as a distinct disorder with unique features and degree of symptoms in all schizophrenic patients and there are many differences between patients in the spectrum of their symptoms and their severity [54]. If we consider these genes to be gathered differently in different schizophrenic people, we can have a spectral view on schizophrenia and other psychotic disorders. In this view, people with other disorders such as schizotypal personality disorder, their short psychotic episodes, and even their change to schizophrenia might be included in the spectral model [55].

By considering the presence of sensory gating deficits in other psychotic or psychotic-like states such as bipolar psychotic mania, PTSD, and amphetamine use, this model explains why this defect is present in all these disorders. It also suggests and explanation for how these patients experience psychotic symptoms similar to those of schizophrenics. It includes dopamine and norepinephrine abnormalities of those disorders in the pathogenic complex and explains the reason why psychotic manic patients have increased level of limbic dopamine. With some modification, there might be also some to say about sensory gating deficits and anxious emotional dysregulation in OCD alongside a normal frontal reality testing.

Similarities between the circuits involved in formation of psychotic symptoms in schizophrenia and bipolar disorder as suggested in this model, might explain the concept of schizoaffective disorder. If we do not look for one specific gene for bipolar disorder and schizophrenia, gathering of different genes that affect different parts of the proposed pathogenic cycle can produce different degrees and kinds of psychosis or make schizophrenia and bipolar disorder overlap in some patients. In a very simplified example, a bipolar patient might have hippocampal sensory gating and amygdala dysfunction and dysregulation without late defects in prefrontal cortex (pruning) because of lacking the genes responsible for excessive frontal pruning. This patient will have psychotic episodes of mania while another bipolar patient without these genetic characteristics may not become psychotic in the course of his/her manic episodes. However, if the genes responsible for excessive prefrontal pruning are also present in a psychotic bipolar patient, based on the degree of genetic dysfunction, the duration and extent of psychotic symptoms may be longer and it may even lead to a schizoaffective disorder.

Some therapeutic effects can also be explained by employment of this theory. The eliminating effects of dopamine antagonist antipsychotics on psychotic symptoms are well known. Alongside their effect on amygdala dopamine level, as increased dopamine level disturbs sensory gating, these drugs are also proved to be effective in correction of sensory gating. By considering a role for sensory gating deficits in the cycle of production of psychotic symptoms, it might be explained why dopamine antagonists do not have an acute effect on delusions and hallucinations. The long time that is needed for their effect contrasts the idea that all their antipsychotic action is in amygdala because they decrease its dopamine level fast but not the psychotic symptoms. When we consider that their

corrective effect on sensory gating needs more time, this long course of their therapeutic function is better understood. However, correction of stabilized abnormal pattern completions that are results of defects in hippocampus and amygdala can be also a matter of time.

By consideration of sensory gating deficits as an important component of psychosis producing pathology, neurotransmitters that affect this system might be also included in the model. Because of the inhibitory effects of $\alpha 7$ nicotinic receptors in hippocampus, the corrective effect of activation of these receptors on sensory gating can be related to the decreased experience of hallucination with smoking and a very high rate of smoking in schizophrenic patients [36]. This may let us suggest a search for effective nicotinic cholinergic medications as a novel method for treatment of schizophrenia. In other words, while dopamine antagonists break the pathogenic cycle of psychosis in amygdala, nicotinic cholinergic drugs can do the same in hippocampus. Since GABA is another neurotransmitter with inhibitory function that attenuates both amygdala activation and sensory gating deficits [8], the effect of high doses of GABAergic benzodiazepines in decreasing psychotic symptoms can be related to the limbic system.

Serotonin-dopamine antagonists, that 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 generation of some anxiety disorders) that can impair normal emotional function of amygdala and it also interferes with normal sensory gating. Its hyperactivity gives an anxious load of emotion to limbic system in a psychotic patient that, alongside the defective prefrontal reality testing function, can activate pattern completing components of the brain to find a proper experience or thought in order to understand the reason for that heightened level of anxiety. However, it also impairs sensory gating through afferent pathways from raphe nucleus to hippocampus. So, we can assume an effect of novel antipsychotics to be correction of sensory gating and stabilization of amygdala 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.

Another measure for management of hallucinatory symptoms of schizophrenics is making them try to concentrate on some strong stimulus. For example, listening to a loud music through a headphone decreases a schizophrenic patient's hallucinations to some extent and helps them be more relaxed. This can be a result of a loud auditory stimulus that, by masking other incoming auditory stimuli, does an artificial sensory gating and inhibit other sounds from entering the patient's consciousness through the defective hippocampal sensory gating. This will result in a more understandable and less stimulus presented to the hippocampal-amygdala system so that there will be no need for pattern completion to take place.

Finally, the model presented here, is an explanation for the coexistence of psychological and biological, and congenital and developmental etiologies in psychotic disorders. It also proposes a wide spectrum that covers many heterogeneous psychotic or psychotic-like disorders based on the level and extent of coexistence of pathologies of different areas of the brain. Besides describing the longitudinal process of schizophrenia, it also suggests new therapeutic methods for psychotic disorders, mainly schizophrenia.

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