Dysmodulation of Synapse Formation and Pruning Hypothesis of Schizophrenia

Ersin ESEN PhD[1]

Abstract

Schizophrenia is a devastating disease that affects at least 1% of humanity. Current understanding is focused on two different hypotheses: excessive dopamine and excessive pruning. Both hypotheses are not totally compliant with observations and are inadequate to provide a unifying framework that explains the cause, mechanism, and symptoms. In this hypothetical work, we propose a unifying hypothesis of schizophrenia. The proposed dysmodulation occurs as a result of growth factor deficiency and any impairment in the related endocrine circuitry. Consequently, synapse formation and pruning processes are regionally and temporally dysmodulated. This dysmodulation results in irregular wiring that contains residual unrelated connections and altered signaling pathways after maturation. We show that available evidence supports the proposed hypothesis, which can explain all the symptoms in a unified framework. If the proposed hypothesis is true, risk group identification and prevention will be straightforward. However, intervention should be performed earlier than currently thought. Unfortunately, after irregular wiring reaches an irreversible steady-state, treatment may not be possible. Nonetheless, even in that case severity of symptoms can be attenuated if the mechanism of synapse formation and pruning is fully understood.

Keywords: altered signaling pathway; dysmodulation hypothesis; growth factors; neurodevelopmental deficiency; synapse formation; synapse pruning; residual unrelated connection; schizophrenia

1. INTRODUCTION

The widely acknowledged excessive dopamine hypothesis of schizophrenia [1] is not the cause, but a result. We come to this conclusion because we believe that the mechanism of schizophrenia can be understood from a connectionist perspective and accumulated knowledge hitherto is adequate to propose a unifying hypothesis.

Schizophrenia is a lifelong disorder that occurs generally in early adulthood [2]. It is well known that there is a significant genetic tendency and also environmental factors play a significant role.

Schizophrenia encompasses negative symptoms, positive symptoms, and cognitive impairments. However, basic faculties (memory, orientation, autonomous subsystems, etc.) remain generally intact. This fact points to a defect in the interconnection of subsystems and hierarchical organization of perceptions, feelings, and ideas as Blueler thought [3]. Bleuler [4] wrote: “In every case, we are confronted with a more or less clear-cut splitting of psychic functions. If the disease is marked, the personality loses its unity; at different times different psychic complexes seem to represent the personality. ... one set of complexes dominates the personality for a time, while other groups of ideas or drives are split off and seem either partly or completely impotent.” These considerations direct us to believe that the mechanism of schizophrenia is a higher-level issue and its cause lies in neurodevelopmental abnormalities.

Synapse pruning is investigated since the early times and still attracts attention [5]. Recent findings that show combinations of genetic and environmental factors that result in disturbances in the neurodevelopmental process can be associated with schizophrenia [2]. Accumulated evidence indicates that schizophrenia is a neurodevelopmental disease and promising direction lies within this perspective [6]. In one of the early neurodevelopmental

approaches, Feinberg [3] proposed that fault in programmed synaptic elimination during adolescence may be the cause of schizophrenia. However, he states that both excessive and reduced synapse pruning may cause the same results. He also speculates this faulty elimination process can be triggered or entirely controlled by neuroendocrine mechanisms [3].

Another preeminent connectivity-based theory is the dysconnection (bad, ill connection) hypothesis [7,8], which states that there is abnormal (not necessarily decreased) integration among brain regions in schizophrenia as a result of aberrant synaptic plasticity caused by neuromodulatory transmitters. Friston states that “anatomical and neurodevelopmental characteristics of schizophrenia are consequences not causes of the underlying pathophysiology” because “psychosis can be induced by simply changing neuromodulatory status of synaptic integration” [7]. We think only this fact is not sufficient to conclude which one is the cause. Because, stationarity of positive symptoms may be due to overly activated subnetworks with aberrant connections, which will require the usage of more neurotransmitters and cause abnormalities in synapse plasticity.

We believe that the correct cause and mechanism lie within the connectionist perspective. With the help of recent findings, we propose a unifying hypothesis. For this purpose, we approach the issue at the system level and propose a simple neurodevelopmental framework that contains the cause and mechanism of schizophrenia and explains all the symptoms in a unified manner.

2. HYPOTHESIS

Human babies are born with almost all neurons [9]. The brain develops at a fast pace and makes excessive numbers of connections. Before adolescence, synapse pruning starts and

settles in a steady state in adulthood [10]. This pruning occurs in accordance with the environment through various forms of interactions and then personality forms. At least, this is what happens in healthy individuals. Any defection from this development path can cause psychiatric disorders.

The development of the brain is a region-dependent and temporally varying process. All regions of the brain do not mature at the same time [11]. Gray Matter (GM) volumes (an indicator of synaptic density) increase during childhood, reach peak levels around adolescence, and decline in the frontal and parietal lobes but not in the temporal lobes [12]. The observations indicate that phylogenetically older brain areas mature earlier than newer ones [11]. There is a temporal hierarchy in the maturation of the regions: "Higher-order association cortices mature only after lower-order somatosensory and visual cortices are developed" [11]. Even within the prefrontal cortex (PFC), there is a dependency between different regions and hence they mature at different times [13]. All these findings suggest that brain maturation occurs according to a program that involves a regional and temporal hierarchy.

We claim that schizophrenia is the result of an abnormal development process that distorts the regional hierarchy. In this perspective, we state dysmodulation of synapse formation and pruning hypothesis (DMH) as follows:

Cause: Genetic variants cause deficiency in growth factors and related endocrine circuits.

Mechanism: Growth factor deficiency results in the alteration of the maturation of the brain regions. The amount of deficiency and change in temporal modulation alters the synapse formation process. The maximum level is attained with a time delay and possible attenuation in synapse count. Hierarchically dependent regions experience an exaggerated amount of distortion. Hence region-dependent and temporally varying modulation process is broken.

The resultant dysmodulation will be a superposition of each altered modality. The dysmodulation will depend on the amount and temporal variation of the growth factor deficiency and will show higly diverse characteristics between patients.

Result: Early maturated regions will have stronger connections. Because the delay in the process will yield more time to be excited and due to Hebb's rule their connections will become stronger and more robust to pruning. On the other hand, late maturated regions will have less time to strengthen their connections and will be more fragile to synapse pruning. Finally, in adulthood, the brain of schizophrenia patients will have an irregular wiring structure that is composed of hyper and hypo connected regions.

The irregular wiring has two important and discriminative characteristics that finally leads to schizophrenia. The first one is the existence of unrelated but unpruned connections that would be normally pruned in healthy subjects. These *residual unrelated connections* distort the functional connectivity. The second one is the *altered signaling pathways*. Hyper and hypo connected regions distort the signaling pathways and hence the signal transmission times will be altered. This alteration will be between the regions of the brain as well as with respect to healthy subjects.

2.1. Supporting Observations Related to Growth Factors

There are various works [14-18] that point to growth factor involvement in psychiatric disorders and schizophrenia. Specifically, Van Beveren et al. [14] find a statistically significant negative correlation between growth factors and schizophrenia. Growth factors and related endocrine circuits form a complex system and they are responsible for many processes. They are also effective in the regulation of synapse pruning. For instance, IGF-1

mediates EPHRINB1 activation [19], which is observed to be effective synaptogenesis and synapse pruning [20]. Furthermore, reduced peripheral blood nerve growth factor (NGF) levels are also observed [21].

Recent genetic studies also indicate an apparent relation between psychiatric disorders and the pathways that regulate the growth and plasticity of synapses [10]:

> "Since the advent of genomic technologies, genetic risk factors for neuropsychiatric disorders are being identified at an unprecedented rate, providing a window into the molecular basis of disease. Remarkably, the pathways that are being uncovered intersect with mechanisms regulating the growth and structural plasticity of synapses, which may be important for understanding the nature of these disorders."

As a specific example, CACNA1C, which is effective in synaptic plasticity, is reported to be a significant risk factor [22] and in a recent work it is found to behave differently during embryonic development and adulthood [23]:

> "... embryonic deletion of CACNA1C in forebrain glutamatergic neurons promotes the manifestation of endophenotypes related to psychiatric disorders ... depletion of CACNA1C during embryonic development also increases the susceptibility to chronic stress ... Remarkably, this was not observed when CACNA1C was deleted in glutamatergic neurons during adulthood ..."

This ineffectiveness in adulthood is very interesting. We think it coincides with our hypothesis in the following manner: depletion in adulthood has no effect since synapse count that is already converged to the normal level.

2.2. Supporting Observations Related to Abnormal Connectivity

Structural and functional connectivity is significantly disturbed in schizophrenia [24]. Gray matter reduction in schizophrenia is a consistent observation and supported by longitudinal MRI studies [25]. Especially, structural connectivity is reduced in the prefrontal cortex (hypofrontality) [26]. These abnormalities do not arise as co-morbidities associated with schizophrenia or a result of the treatments [27].

Post-mortem gray matter reduction observations are also supported by in vivo observations of postsynaptic elements with positron emission tomography (PET). Observation of synaptic vesicle glycoprotein 2A (SV2A) levels indicated significantly lower connectivity in the frontal and anterior cingulate cortices whereas there was no significant difference in the hippocampus [28].

Heterogenous functional connectivity patterns are also found. For instance, increased connectivity in the cerebello–thalamo–cortical circuitry is observed [29]. Hyper and hypo connectivity are observed in different regions of the brain: Thalamocortical hypoconnectivity in middle frontal, cingulate, and thalamic regions, and hyperconnectivity in motor, somatosensory, temporal, occipital, and insular cortical regions [30]. Similarly, temporal-thalamic hyperconnectivity and cingulo-opercular hypoconnectivity are observed [31].

Interestingly, these heterogeneous connectivity disturbances coincide with the maturation order of the regions: hypoconnectivity in cortical regions and hyperconnectivity in temporal and temporal-thalamic regions. Therefore they are perfectly in line with DMH.

3. EXPLANATION OF SYMPTOMS

A hypothesis of schizophrenia should explain all symptoms in a unified framework. In the following subsections, we provide our explanations according to DMH.

3.1. Dopamine aberration

The initial idea of hyperdopaminergia as the etiology of schizophrenia was transformed to subcortical hyperdopaminergia and prefrontal hypodopaminergia [1]. Dopamine metabolites were not universally elevated in the cerebrospinal fluid (CSF) and post-mortem and in vivo imaging data revelated differences between cortical and subcortical regions [1]. Most of the antipsychotic drugs block striatal dopamine D2 receptors [1], which are found mainly in the subcortical regions [32].

Aberrant dopamine levels totally comply with the hyper and hypo connectivity that is expected as a result of DMH.

We should note that expected irregular wiring is not specific to dopaminergic networks. There should be alterations in all neurotransmitter levels. However, they are not as apparent as dopamine. We think the main reason is the role of the dopaminergic D2 receptor networks. Dopamine is involved in motivation, long-term planning, and learning which require feedback. The recurrent structure of these subnetworks results in the secretion of an excessive amount of dopamine when activated continuously or for a longer period. Conflicting ideas for which consciousness (prefrontal cortex) can not settle on one of them result in longer activation of these networks. Excessive connectivity and residual unrelated connections keep these subnetworks active. Because unrelated inputs can excite and keep them active without any reason that consciousness can resolve. This in turn keeps recurrent subnetworks active and yields excessive dopamine secretion.

3.2. Multiple Inner voices

Consciousness attaches a single, compact inner voice to itself. The identification of his own voice necessitates temporal coherence. Irregular wiring can alter the networks in which ideas form. The time required to reach the frontal cortex may deviate from the main voice as a result of altered signaling pathways. In that case, temporal coherence is broken and consciousness can not associate the voice with itself. In order to provide a complete understanding, it generates a plausible narrative and associates them with other persons or beings. According to this explanation, there is no need for a corollary discharge [33] like mechanism.

The association of voices may alternate between subnetworks depending on the activation power of the subnetwork. The most activated one can surpass the others and be recognized as the main voice.

3.3. Thought Disorganization

One of the severe positive symptoms of schizophrenia is the disorganization of thoughts. The relation between thoughts can not be established correctly. A consistent structure between thoughts can not be built. This situation can easily arise in an irregular wiring structure that can be excited with unrelated inputs due to residual unrelated connections. These irrelevant excitations may occur in an incoherent way temporally. This in turn prevents the formation of stationary and consistent thoughts.

3.4. Delusions

Delusions are permanent beliefs or thoughts that humans stick to even if they contradict facts. Delusions can be triggered by real facts. Even healthy individuals can adhere to their delusions for a certain period of time. But they can refute the delusion with the help of substantial evidence. On the other hand, schizophrenics can not refute it easily as a result of residual unrelated connections that have no relation with that specific belief or thought. Irrelevant connections feed it with irrelevant excitations. Once schizophrenics can not resolve the delusion by means of reasoning, they start to reflect on it more. Because it contradicts reality and there is no way to settle down. This incessant contemplation makes the subnetwork of the delusion and its synapses stronger. Hence, it becomes permanent and never vanishes.

The delusional disorder was previously considered as a member of the schizophrenia spectrum. We believe the same mechanism is also valid for it.

3.5. There are no blind schizophrenics

Several works indicate that congenital or early blindness may serve as a protective factor against schizophrenia [34]. The same is not valid for blindness developed later in life. This is very important. Because neurotransmitters do not have any effect on congenital blindness. On the other hand, it can be explained from a connectionist perspective.

Silverstein et. al. [34] mention pruning as a possible cause of the difference in visual cortex thickness:

> “Schizophrenia is typically characterized by cortical thinning [35] and it has been hypothesized that excessive neuronal pruning takes place during adolescence [5]. In

> contrast, the visual cortex of C/E blind people ... is thicker than in sighted people, and is thought to be characterized by a less than normal amount of pruning, due to deprivation of visual experience [36]. A consequence of this thickening is that, even if genes related to schizophrenia cause excessive pruning in someone with C/E blindness, the remaining number of neurons may still be greater than normal in some areas. This ... may protect blind people against crossing the threshold needed for psychotic symptoms to emerge (i.e. an adequate number of neurons devoted to specific types of processing may be present even if pruning is excessive)."

Excessive pruning can not be the cause. Because Shultz et al. [37] observed cortical thinness in only a certain area and more importantly, they observed hypergyrification. Then, how can early blindness protect from schizophrenia? We claim that congenital or early blind people can not form as many synapses as sighted people. Therefore, even if they have the genetic variants that may cause growth factor deficiency, they do not have enough number of synapses to form irregular wiring. We base our claim on the high entropy of the visual input. Its high entropy yields more activations and hence it is the main factor for the proliferation of synapse formation.

3.6. Psychedelics excite similar positive symptoms

It is well known that psychedelics and some drugs cause temporary hallucinations in healthy individuals [38]. They achieve this by exciting the receptors without pre-synaptic activations.

When the drug diminishes it can no more activate the receptors and hallucination disappears. The drugs do not form synapses and hence their effect is temporary. We think this is totally compliant with the persistent existence of irregular wiring.

3.7. Negative symptoms

Negative symptoms like blunted affect, alogia, avolition, asociality, and anhedonia accompany schizophrenia, although not specific to it [39]. We think these negative symptoms can be easily explained according to DMH. First of all, we think that they are precursors or alarming signs in the path to psychosis. In the beginning, when conflicting ideas and rival subnetworks emerge due to residual unrelated connections, the brain starts to focus on them. If the consciousness can not cope up with these conflicts, the brain enters into an alarming state and starts to take control by activating precautions. Social withdrawal or similar introversions are protection mechanisms of the subconscious brain against the outside world. As a protection strategy brain tries to minimize the interaction with the outer world to avoid the risks to which consciousness can not respond. In schizophrenia, consciousness can never resolve the problems as the negative symptoms deepen and this protection mechanism may even evolve to more severe symptoms eventually.

3.8. Different response to antipsychotics

Patients show different responses to antipsychotics. We think this is because every individual has a unique network structure. The connectivity, required activation energy of subnetworks, amount of hypo and hyper-connectivity are all specific to the individual. Therefore, receptor blocking agents behave differently in each person. Furthermore, connectivity aberrations are not limited to dopaminergic networks. For those connections, antipsychotics will have no use.

4. DEDUCTIONS

4.1. Minor Physical Anomalies

Even if not conclusive, minor physical anomalies (for instance small head size) are reported [2]. Growth factor deficiency should yield such physical anomalies. Even infinitesimal, it should even be distinguishable in a physical feature that is a result of the interaction of many factors such as height. We expect to observe distinguishable distributions as in Figure 1. The discrepancy should be more apparent towards the tails. Towards gigantism end, excessive growth factors prune synapses drastically and eliminate the risk of schizophrenia. On the other hand, towards the dwarfism end, the brain can not form a normal amount of synapses and this also should decrease the risk of schizophrenia.

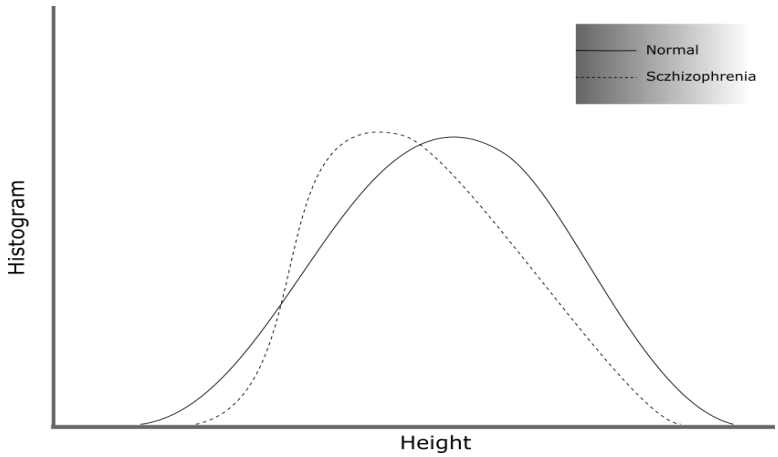

Figure 1. Expected height distributions of groups of the same gender, age, and geography.

4.2. Less cancer

Inspired by Laron syndrome [40], in which congenital IGF-1 deficiency protects from cancer, we claim that schizophrenics should have a lower incident rate than the normal population. Although there are reports indicating such a possibility, the literature is not conclusive [41]. For instance, Kisely et al. [41] report that the male cancer incidence rate with respect to the healthy population is 79%, whereas the same rate is 97% in females. The lung cancer

incidence rate appears to be higher. Heavy smoking, alcohol, or drug usage in schizophrenia might play a significant role here. Therefore, if the effect of substance usage can be canceled out, we would expect a smaller incidence rate and late onset in schizophrenia.

4.3. Abundance of genetic variants related to growth factors

There are dozens of genes related to growth factors and associated endocrine circuits. Probably, there are also undiscovered related genes. We believe that genome-wide association studies should reveal a significantly higher amount of genetic variants in the growth factor related genes with respect to a healthy population, whereas there should not be any apparent discrimination in the rest of the genome.

4.4. Altered Energy Metabolism

It is evident that energy metabolism is altered in schizophrenia [42]. Impaired energy production can be associated with impaired neural connectivity [43]. “Schizophrenic patients appear to be at an increased risk for diabetes mellitus and hyperglycemia, however, there is little genetic overlap with diabetes and schizophrenia” [44]. Schizophrenic patients also show a failure of deactivation in the prefrontal cortex [45], which may lead to more energy consumption. We claim that this altered energy metabolism is a consequence of irregular wiring and incessant activation of rival subnetworks.

This fact may also explain the short life expectance in schizophrenia. The brain uses a significant portion of its resources for the interplay of the rival subnetworks and can not reserve resources to autonomous systems as much as the healthy subjects do. This in turn results in the early aging of all subsystems.

We also expect a similarly altered energy metabolism in the whole body. Because, growth factors are negatively correlated with the HPA axis, which regulates the metabolism rate by modulating cortisol levels. For instance, children with growth hormone deficiency experienced a significant reduction in cortisol levels after recombinant human growth hormone therapy [46]. Similarly, schizophrenics should have higher metabolism rates during childhood due to growth factor deficiency as well as any impairment in related endocrine circuitry including the HPA axis. Interestingly, larger pituitary volume, suggesting activation of the HPA axis, is correlated to the onset of psychosis [47].

5. DISCUSSION

The idea of faulty synapse pruning of Feinberg [3] led to a consensus of excessive pruning hypothesis, even though he stated that both excessive and reduced pruning can be possible. Apart from the excessive pruning hypothesis, reduced synapse formation is also considered as a possible cause [48]. Either way can not explain the heterogeneous structural and functional connectivity in schizophrenia. Furthermore, the excessive pruning hypothesis alone can not explain excessive dopamine secretion or aberrations in any other neurotransmitters. It should be complemented with additional dysfunctional neurotransmitter modulation schemes that are specific to each region.

Another observation that contradicts the excessive pruning hypothesis but can be explained by DMH is pyrotherapy (fever therapy), which dates back to antiquity [49]. Even Hippocrates and Galen mentioned the curative effect of pyrotherapy on mental diseases [49]. Many similar positive reports followed thereafter. In the previous century, Wagner-Jauregg was awarded the Nobel prize for medicine for his malaria therapy for the treatment of mental diseases. However, the therapy was very dangerous and yielded inconsistent results. It was abandoned

especially after the discovery of the neuroleptics. We think that the high-grade fever induced by pyrotherapy excites the autoimmune system. The autoimmune system attacks all the synapses and exacerbates synapse pruning. Since this attack is made blindly, the beneficial results are obtained by just coincidence. While the positive effect, achieved by chance, cannot occur according to the idea of excessive synapse pruning, it is plausible in the framework DMH, since residual unrelated connections can be pruned in this way.

In order to explain the inner workings of the proposed mechanism, we make some conceptual definitions. One of the key definitions is *rival subnetworks*. They are contradicting subnetworks that are activated by residual unrelated connections. They provide conflicting feedback and hence consciousness can not resolve the situation and settle on one of them. As a result, they enter a loop where they are incessantly excited. This incessant activation strengthens the inner connections and makes them permanent. In this regard, we define *psychosis* as the clash of these rival subnetworks after which consciousness collapses onto the one that contradicts reality. Depending on the environmental conditions and changes in excitation, consciousness may alternate between the rival subnetworks. Usage of neuroleptics suppresses the activation of these rival subnetworks. In this regard, their early usage may be more beneficial. Because the interconnectivity and strength of the rival subnetworks increase with time as a result of Hebb's rule.

Actually, every human experience the rival subnetworks phenomenon. Even if the subnetworks are not fed with unrelated connections, when the multiple input sources contradict the previously trained models, healthy subjects also experience a similar phenomenon. McGurk effect [50] is an interesting example in this respect. Speech recognition is not a pure auditory process, visual information is also utilized. When these two input sources conflict, the consciousness is confronted with an unusual situation that needs to be

resolved. However, in this case, incessant activation does not occur, because there are no unrelated feedback connections between auditory and visual inputs.

Another definition is the *temporal coherence* that we make use of during the explanation of multiple inner voices. We think consciousness associates a temporal coherency margin for each inner voice and recognizes filtered out ones as distinct voices. This temporal incoherence is caused by the altered signaling pathways that result in different propagation times of signals between subnetworks. These temporally incoherent subnetworks and pathways form different clusters. The emergence and continuous activation of these clusters make their discrimination stronger and result in a state of orthogonality. In this way, the existence of totally conflicting inner voices becomes possible.

We think the disruption in the temporal coherence is the main cause of abnormalities in the self-monitoring mechanism of schizophrenia. They fail to discriminate between self-produced and externally produced stimuli [51]. For instance, some schizophrenics can tickle themselves, unlike healthy individuals. This is because, when temporal coherence is impaired self-produced stimuli can not be associated with the perceived input signal. Hence, the received signal is recognized as an external stimulus.

6. CONCLUSIONS

We believe accumulated knowledge on schizophrenia is adequate to propose a unifying hypothesis. DMH is such an attempt that contains the cause, mechanism, and explanation of all the symptoms in a consistent framework. If DMH holds true, identification of risk groups and prevention will be easily possible. However, intervention should be performed earlier than thought. On the other hand, after irregular wiring reaches a steady-state it may be

irreversible even if the mechanism of synapse formation and pruning is completely understood.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Consent statement/Ethical approval

Not required.

Funding Statement

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

REFERENCES

[1] Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III—the final common pathway. Schizophrenia bulletin. 2009 May 1;35(3):549-62.

[2] Lewis DA, Levitt P. Schizophrenia as a disorder of neurodevelopment. Annual review of neuroscience. 2002 Mar;25(1):409-32.

[3] Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence?. Journal of psychiatric research. 1982 Jan 1;17(4):319-34.

[4] Bleuler, E. Dementia praecox or the group of schizophrenias. New York (International Universities Press) 1958.

[5] Boksa P. Abnormal synaptic pruning in schizophrenia: Urban myth or reality?. Journal of psychiatry & neuroscience: JPN. 2012 Mar;37(2):75.

[6] Insel TR. Rethinking schizophrenia. Nature. 2010 Nov;468(7321):187-93.

[7] Friston K, Brown HR, Siemerkus J, Stephan KE. The dysconnection hypothesis (2016). Schizophrenia research. 2016 Oct 1;176(2-3):83-94.

[8] Stephan KE, Friston KJ, Frith CD. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophrenia bulletin. 2009 May 1;35(3):509-27.

[9] Nowakowski RS. Stable neuron numbers from cradle to grave. Proceedings of the National Academy of Sciences. 2006 Aug 15;103(33):12219-20.

[10] Forrest MP, Parnell E, Penzes P. Dendritic structural plasticity and neuropsychiatric disease. Nature Reviews Neuroscience. 2018 Apr;19(4):215-34.

[11] Gogtay N, Vyas NS, Testa R, Wood SJ, Pantelis C. Age of onset of schizophrenia: perspectives from structural neuroimaging studies. Schizophrenia bulletin. 2011 May 1;37(3):504-13.

[12] Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL. Brain development during childhood and adolescence: a longitudinal MRI study. Nature neuroscience. 1999 Oct;2(10):861-3.

[13] Wood SJ, De Luca CR, Anderson V, Pantelis C. Cognitive development in adolescence: cerebral underpinnings, neural trajectories and the impact of aberrations. Neurodevelopment and schizophrenia. 2004 Nov 18:69-88.

[14] Van Beveren NJ, Schwarz E, Noll R, Guest PC, Meijer C, de Haan L, Bahn S. Evidence for disturbed insulin and growth hormone signaling as potential risk factors in the development of schizophrenia. Translational psychiatry. 2014 Aug;4(8):e430-.

[15] Åberg ND, Brywe KG, Isgaard J. Aspects of growth hormone and insulin-like growth factor-I related to neuroprotection, regeneration, and functional plasticity in the adult brain. TheScientificWorldJournal. 2006 Jan 18;6:53-80.

[16] Laryea G, Arnett MG, Muglia LJ. Behavioral studies and genetic alterations in corticotropin-releasing hormone (CRH) neurocircuitry: insights into human psychiatric disorders. Behavioral sciences. 2012 Jun;2(2):135-71.

[17] Nawa H, Takahashi M, Patterson PH. Cytokine and growth factor involvement in schizophrenia—support for the developmental model. Molecular psychiatry. 2000 Nov;5(6):594-603.

[18] Venkatasubramanian G, Chittiprol S, Neelakantachar N, Naveen MN, Thirthall J, Gangadhar BN, Shetty KT. Insulin and insulin-like growth factor-1 abnormalities in

antipsychotic-naive schizophrenia. American Journal of Psychiatry. 2007 Oct;164(10):1557-60.

[19] Matsumura S, Quispe-Salcedo A, Schiller CM, Shin JS, Locke BM, Yakar S, Shimizu E. IGF-1 mediates EphrinB1 activation in regulating tertiary dentin formation. Journal of dental research. 2017 Sep;96(10):1153-61.

[20] Hanna SA. Role of Astrocytic Ephrin-B1 in Synaptogenesis in the Developing Hippocampus. 2017.

[21] Qin XY, Wu HT, Cao C, Loh YP, Cheng Y. A meta-analysis of peripheral blood nerve growth factor levels in patients with schizophrenia. Molecular psychiatry. 2017 Sep;22(9):1306-12.

[22] Ripke S, O'dushlaine C, Chambert K, Moran JL, Kähler AK, Akterin S, Bergen SE, Collins AL, Crowley JJ, Fromer M, Kim Y. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nature genetics. 2013 Oct;45(10):1150-9.

[23] Dedic N, Pöhlmann ML, Richter JS, Mehta D, Czamara D, Metzger MW, Dine J, Bedenk BT, Hartmann J, Wagner KV, Jurik A. Cross-disorder risk gene CACNA1C differentially modulates susceptibility to psychiatric disorders during development and adulthood. Molecular psychiatry. 2018 Mar;23(3):533-43.

[24] Karlsgodt KH, Sun D, Cannon TD. Structural and functional brain abnormalities in schizophrenia. Current directions in psychological science. 2010 Aug;19(4):226-31.

[25] Dietsche B, Kircher T, Falkenberg I. Structural brain changes in schizophrenia at different stages of the illness: a selective review of longitudinal magnetic resonance imaging studies. Australian & New Zealand Journal of Psychiatry. 2017 May;51(5):500-8.

[26] Andreasen NC, O'Leary DS, Flaum M, Nopoulos P, Watkins GL, Ponto LL, Hichwa RD. Hypofrontality in schizophrenia: distributed dysfunctional circuits in neuroleptic-naive patients. The Lancet. 1997 Jun 14;349(9067):1730-4.

[27] Moyer CE, Shelton MA, Sweet RA. Dendritic spine alterations in schizophrenia. Neuroscience letters. 2015 Aug 5;601:46-53.

[28] Onwordi EC, Halff EF, Whitehurst T, Mansur A, Cotel MC, Wells L, Creeney H, Bonsall D, Rogdaki M, Shatalina E, Marques TR. Synaptic density marker SV2A is reduced in schizophrenia patients and unaffected by antipsychotics in rats. Nature communications. 2020 Jan 14;11(1):1-1.

[29] Cao H, Chén OY, Chung Y, Forsyth JK, McEwen SC, Gee DG, Bearden CE, Addington J, Goodyear B, Cadenhead KS, Mirzakhanian H. Cerebello-thalamo-cortical hyperconnectivity as a state-independent functional neural signature for psychosis prediction and characterization. Nature communications. 2018 Sep 21;9(1):1-9.

[30] Ramsay IS. An activation likelihood estimate meta-analysis of thalamocortical dysconnectivity in psychosis. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2019 Oct 1;4(10):859-69.

[31] Culbreth AJ, Wu Q, Chen S, Adhikari BM, Hong LE, Gold JM, Waltz JA. Temporal-thalamic and cingulo-opercular connectivity in people with schizophrenia. NeuroImage: Clinical. 2021 Jan 1;29:102531.

[32] Missale C, Nash SR, Robinson SW, Jaber M, Caron MG. Dopamine receptors: from structure to function. Physiological reviews. 1998 Jan 1;78(1):189-225.

[33] Sperry RW. Neural basis of the spontaneous optokinetic response produced by visual inversion. Journal of comparative and physiological psychology. 1950 Dec;43(6):482.

[34] Silverstein SM, Wang Y, Keane BP. Cognitive and neuroplasticity mechanisms by which congenital or early blindness may confer a protective effect against schizophrenia. Frontiers in Psychology. 2013 Jan 21.

[35] Cobia DJ, Smith MJ, Wang L, Csernansky JG. Longitudinal progression of frontal and temporal lobe changes in schizophrenia. Schizophrenia research. 2012 Aug 1;139(1-3):1-6.

[36] Jiang J, Zhu W, Shi F, Liu Y, Li J, Qin W, Li K, Yu C, Jiang T. Thick visual cortex in the early blind. Journal of Neuroscience. 2009 Feb 18;29(7):2205-11.

[37] Schultz CC, Wagner G, Koch K, Gaser C, Roebel M, Schachtzabel C, Nenadic I, Reichenbach JR, Sauer H, Schlösser RG. The visual cortex in schizophrenia: alterations of gyrification rather than cortical thickness—a combined cortical shape analysis. Brain Structure and Function. 2013 Jan 1;218(1):51-8.

[38] Gonzalez-Maeso J, Sealfon SC. Psychedelics and schizophrenia. Trends in neurosciences. 2009 Apr 1;32(4):225-32.

[39] Correll CU, Schooler NR. Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. Neuropsychiatric disease and treatment. 2020;16:519.

[40] Laron Z. Lessons from 50 years of study of Laron syndrome. Endocrine Practice. 2015 Dec 1;21(12):1395-402.

[41] Kisely S, Crowe E, Lawrence D. Cancer-related mortality in people with mental illness. JAMA psychiatry. 2013 Feb 1;70(2):209-17.

[42] Prabakaran S, Swatton JE, Ryan MM, Huffaker SJ, Huang JJ, Griffin JL, Wayland M, Freeman T, Dudbridge F, Lilley KS, Karp NA. Mitochondrial dysfunction in schizophrenia:

evidence for compromised brain metabolism and oxidative stress. Molecular psychiatry. 2004 Jul;9(7):684-97.

[43] Song X, Chen X, Yuksel C, Yuan J, Pizzagalli DA, Forester B, Öngür D, Du F. Bioenergetics and abnormal functional connectivity in psychotic disorders. Molecular Psychiatry. 2021 Jan 4:1-0.

[44] Henderson DC, Ettinger ER. Schizophrenia and diabetes. International review of neurobiology. 2002 Jan 1;51:481-501.

[45] Pomarol-Clotet E, Salvador R, Sarro S, Gomar J, Vila F, Martinez A, Guerrero A, Ortiz-Gil J, Sans-Sansa B, Capdevila A, Cebamanos JM. Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network?. Psychological medicine. 2008 Aug;38(8):1185-93.

[46] Wang L, Wang Q, Li G, Liu W. Dynamic changes in the hypothalamic-pituitary-adrenal axis during growth hormone therapy in children with growth hormone deficiency: a multicenter retrospective study. Journal of Pediatric Endocrinology and Metabolism. 2015 Sep 1;28(9-10):975-9.

[47] Garner B, Pariante CM, Wood SJ, Velakoulis D, Phillips L, Soulsby B, Brewer WJ, Smith DJ, Dazzan P, Berger GE, Yung AR. Pituitary volume predicts future transition to psychosis in individuals at ultra-high risk of developing psychosis. Biological psychiatry. 2005 Sep 1;58(5):417-23.

[48] Bennett MR. Synapse formation and regression in the cortex during adolescence and in schizophrenia. Medical journal of Australia. 2009 Feb;190(S4):S14-6.

[49] Whitrow M. Wagner-Jauregg and fever therapy. Medical history. 1990 Jul;34(3):294-310.

[50] McGurk H, MacDonald J. Hearing lips and seeing voices. Nature. 1976 Dec;264(5588):746-8.

[51] Blakemore SJ, Smith J, Steel R, Johnstone EC, Frith CD. The perception of self-produced sensory stimuli in patients with auditory hallucinations and passivity experiences: evidence for a breakdown in self-monitoring. Psychological medicine. 2000 Sep;30(5):1131-9.