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Some Ideas on Schizophrenia Research

JA Ure[1]*, L Alba-Ferrara[3], EH Wainwright[4], R Caccuri[2]

[1]Chair of Neurology, Borda Hospital, Buenos Aires, Argentina. [2]Chair of Pathology, Borda Hospital, Buenos Aires, Argentina. [3]Functional MRI Department, El Cruce Hospital, Florencio Varela, Buenos Aires, Argentina. [4]Psychiatry Service, Hospital Moyano Hospital and British Hospital. Buenos Aires, Argentina.

**Corresponding author: JA Ure.*

Abstract

Objective: To characterize the symptoms of patients with schizophrenia by identifying patterns linked to brain dysfunction.

Methods: Three systems of neural circuits and connections are analyzed with their neurobiochemical repercussions: 1) Thalamocortical and thalamosubcortical connections, 2) Glutamate deficiency in granule cells in the hippocampal dentate gyrus causing increased activity in pyramidal neurons in the sector, and; 3) Extensive disconnections of the network extending between the anterior insula (AI, associated with the default mode network –DMN-) and the dorsal anterior cingulate cortex (dACC, linked to the important central executive network, CEN).

Results: The decrease or loss of functional efficiency of important thalamocortical projections (hypoconnectivity mediodorsal thalamus-dorsolateral and dorsomedial prefrontal cortices) added to the anterior thalamic nuclei with the anterior cingulate gyri (bilateral or asymmetric) are potential causes of important cognitive deficits. In addition, hyperconnectivity between the ventrolateral thalamic nuclei and the sensorimotor, auditory and visual regions and extensive subcortical projections are responsible for psychotic symptoms. Besides these derangements, hypofunction can be noted in the granular cell of the dentate gyrus linked to hyperactivity of the pyramidal neurons and causing misperceptions. On the other hand, the dysfunction is made more complex by a disconnection between the anterior insula and the dorsal anterior cingulate cortices (salience network, SN) as well as regional sectors of the central executive (CEN) and the default mode network (DMN), causing functional imbalances between networks with serious compromise in the awareness of oneself.

Conclusion: Three circuits linked to the pathophysiology of schizophrenia are considered. Functional disorders of thalamocortical connections regarding cognitive while hippocampal hyperactivity would be linked to the generation of psychotic content and disconnection of the anterior insula leads to states of confusion between external and inner world.

Keywords: schizophrenia; glutamate, hippocampus; dentate gyrus; thalamic nuclei; salience networks

Introduction

Interconnections between cerebral regions are being reviewed in order to elucidate the physiopathology of chronic psychosis. So, functional connectivity (FC) is under scope at the synaptic level by neurochemical studies and spectroscopy MRI, at the neuroanatomical circuitry level by tract-tracing with DWI tractography and structural MRI and at the functional level testing behavior or cognitive tasks together with functional MRI (fMRI). Neurochemical studies have been focused on neurotransmitters and receptors concentration. Neuroanatomical studies map the different connectivity between various nuclei or areas and functional studies evaluate brain networks operations and possible alterations at this level. Pathological disruption may appear in any or various of these levels thus psychotic behavior emerges. Another factor that must be borne in mind is the compartmentalization between neurons and astrocytes, this is required so as to maintain stable neurotransmitter function.

Schizophrenia is a chronic psychiatric illness characterized by failures in the continuity of information processing, the ability to make contact with reality, and perception of personal identity. In recent years we have published two articles regarding three major hypotheses in this field: 1) hypoactivation of prefrontal cortices from thalamic nuclei impairing the normal streaming of working memory and ulterior cognitive disorder, 2) hyperactivation of hippocampal pyramidal neurons provoking hyperdopaminergic subcortical outbursts linked to positive symptoms as a consequence of glutamatergic insufficiency at the dentate gyrus and 3) inefficiency of salience network linked to diminished cell numbers in dorsal anterior cingulate cortex and altered connectivity and reduction in gray matter in the anterior insula associated with negative symptoms

and modifications in default-mode network (Ure, Corral & Wainwright, 2018; Ure, Corral & Wainwright, 2019) . In this paper we present further evidence in this same direction.

Imbalance Of Thalamocortical Connections

The medial dorsal and anterior nuclei of the thalamus project to the dorsolateral prefrontal cortex (dlPFC), whereas the lateral nuclei project mainly to sensorimotor regions, with similar findings in functional brain connectivity studies in humans. A large body of evidence has shown reduced connectivity from bilateral thalamic regions, medial dorsal and anterior nuclei in particular, to the bilateral dlPFC, dorsal anterior cingulate, parts of the striatum, and bilateral cerebellum in schizophrenia (SZ) and increased connectivity between the thalamus lateral nuclei and motor, visual, and/or auditory sensory regions (Barch, 2021). Thalamic resting-state networks were studied through structural and functional MRI scans in SZ patients and healthy controls. Reduced thalamic connectivity in SZ patients was found in bilateral superior frontal gyrus, anterior cingulate cortex, inferior parietal lobe, and cerebellum. In comparison with controls, patients exhibited enhanced thalamic connectivity with bilateral precentral gyrus, middle occipital gyrus, and lingual gyrus (Wang et al., 2015).

According to Woodward and Heckers (2016), studying 148 psychotic patients through resting-state fMRI, reduced PFC-thalamic connectivity was found in both chronic and early-stage patients, the authors also found motor cortex hyperconnectivity. The hypoconnectivity affected dorsolateral PFC, medial PFC and cerebellar areas (central executive network, CEN) and was related to cognitive impairment, in line with Andreasen hypotheses of cerebellar involvement in schizophrenia (Andreasen & Pierson, 2008). In another work, Ferri et al. (2018) studying resting-state functional connectivity (rsFC), in SZ patients showed reduced thalamic connectivity with bilateral ACC and CBL and found enhanced connectivity with sensorimotor cortices. Thalamus to middle temporal gyrus connectivity was positively correlated with hallucinations and delusions while thalamus to cerebellar connectivity was negatively correlated with delusions and bizarre behavior.

Patterns of cortico-subcortical hypo/hyper connectivity extend from thalamus to basal ganglia nuclei and might link distinctively between psychotic and cognitive impairment. The salience network covering PF-limbic cortices showed decreased connections with mediodorsal (MD) thalamus and ventral part of striatum and thalamus causing cognitive deficits. In contrast, the auditory-sensorimotor network covering primary sensorimotor cortices showed increased connections with the anterior ventral nucleus of the thalamus and dorsal parts of striatum and pallidum and this pattern was correlated with psychotic symptoms. So, PF-limbic hypo-connectivity and primary sensorimotor hyper-connectivity was present consistently across subcortical nuclei and specifically across distinct symptom dimensions (Avram et al., 2018).

Yao et al. have studied 42 patients or siblings compared with 44 healthy controls using DWI probabilistic tractography cross-thalamic and voxel-wise approach. Thalamoprefrontal interconnectivity (IC) was reduced in SZ and siblings relative to controls and showed an increase in thalamo-motor structural connectivity in SZ but not in siblings or the control group. So, altered thalamoprefrontal IC is a marker of vulnerability but altered thalamomotor IC could be expression of the illness (Yao et al., 2020). Xi et al. arrived at similar conclusions, the thalamic-prefronto-cerebellar dysconnectivity showed a significant gradient reduction in patients and siblings comparing to controls. This decreased thalamic dysconnectivity was found at the MD nucleus while increased thalamic sensorimotor connectivity were related to clinical symptoms in patients and was located in the caudal temporal thalamic subregion anchoring at the dorsal and ventral lateral nuclei (Xi et al., 2020).

Decreased thalamic-prefrontal-connectivity may be related to high genetic risk in schizophrenia while increased sensorimotor-thalamic connectivity can be a neural biomarker of the illness. One early-onset group (EOS) showed the same pattern as the adult onset did: increased sensorimotor-thalamic connectivity and decreased prefrontal-cerebello-thalamic connectivity circumscribed to the medial PC. Sensorimotor thalamic hyperconnectivity is critical for the expression of schizophrenia phenotype irrespective of the age of onset, raising the possibility of aberrant but accelerated functional network maturation in EOS (Zhang et al., 2021). Based on working memory (WM) tasks and resting state (rs) fMRI, data was collected from 172 SZ patients and 103 controls, regarding thalamocortical circuit imbalance. SZ patients showed reduced connectivity between thalamus and PF and cerebellar cortices, but hyperconnectivity with sensorimotor cortices, both related to poorer WM performance, lower task accuracy, longer response

time and difficulties in discriminating target from non-target. The results of WM task and the rsfMRI were well correlated showing the imbalance of thalamic cortical connections contributed to WM deficits (Wu et al., 2022).

Studies using genetic neuromodulator technology linked to circuit-specific interventions in primates has shown the role of DLPFC and MD and dorsal caudate nucleus (dCN) in working memory and decision-making. Researchers have observed resting-state FC significantly reduced between DLPFC and MD and dCN in SZ patients but not in healthy controls, or in autistic or major depressive patients (Yahata, Hirabashi & Minamimoto, 2023). So, a large body of evidence has shown reduced connectivity from bilateral thalamic regions, medial dorsal and anterior nuclei in particular, connecting to CEN (central executive network), mainly bilateral dlPFC, dorsal anterior cingulate, parts of the striatum, and bilateral cerebellum in schizophrenia linked with cognitive and WM deficits while hyperconnectivity between thalamus and sensorimotor, auditive and visual cortices can be directly related to psychotic symptoms.

Hypoglutamatergic Activity in Dentate Gyrus and Enhanced Hippocampus Activity

Glutamate and dopamine systems play distinct roles in terms of neuronal signalling, yet both systems have been proposed to contribute significantly to the pathophysiology of schizophrenia. McCutcheon, Krystal & Howes (2020) have implicated both systems in the etiology of the disorder. They examined evidence from post-mortem, preclinical, pharmacological and in vivo neuroimaging studies. Converging evidence indicates that genetic and environmental risk factors for schizophrenia underlie disruption of glutamatergic and dopaminergic function. However, while genetic influences may directly underlie glutamatergic dysfunction, few genetic risk variants directly implicate the dopamine system, indicating that alterations in dopamine signaling are probably due to other factors. Inversly, the dopaminergic dysfunction is more likely to develop downstream abnormalities in other systems, including the glutamatergic system. However, in contrast to dopamine, recent genetic findings do provide support for the view that glutamatergic abnormalities may play a major role in schizophrenia pathophysiology. Unlike dopamine neurons, which are restricted to relatively well circumscribed anatomical pathways, glutamate signaling occurs ubiquitously throughout the brain and, as a result, dysfunction of this system has the potential to cause a wide range of impairments. The balance between excitability and inhibition is crucial for normal physiological function, and NMDA receptors can play a critical role in this. Disruption of this balance has been proposed to result in the EEG abnormalities observed in schizophrenia associated with increased resting gamma oscillations, proposed to be linked with cognitive symptoms (Uhlhaas & Singer, 2010). Disruption of normal oscillatory activity mirrors what has been observed when ketamine (NMDA antagonist) administrated to healthy volunteers. It has also been proposed that in schizophrenia, NMDA hypofunction may mainly affect interneurons (Coyle, 2006) which would in turn lead to greater activity in pyramidal neurons. This uncoordinated increased activity may underlie disruptions to the normal oscillatory activity mentioned above, acting as a noise, and impairing the ability of coordinated activity to be passed down to subcortical regions (Moghaddam & Javitt, 2012).

According to McHugh et al. (2007) the formation of distinct representations of multiple contexts, places, and episodes is a crucial function of the hippocampus. The dentate gyrus subregion has been suggested to fulfill this role. The authors tested this hypothesis by generating and analyzing a mouse strain that lacks the gene encoding the essential subunit of the N-methyl-d-aspartate (NMDA) receptor NR1, specifically in dentate gyrus granule cells (DG). The mutant mice performed normally in contextual fear conditioning, but presented impaired ability to distinguish two similar contexts. A significant reduction in the context-specific modulation of firing rate was observed in the CA3 pyramidal cells when the mutant mice were transferred from one context to another. These results provide evidence that NMDA receptors in the granule cells of the dentate gyrus play a crucial role in the process of pattern separation. Hippocampal imaging studies in schizophrenia have identified two alterations in medial temporal lobe: increases in baseline blood perfusion and decreases in task-related activation. These observations along with converging postsynaptic hippocampal protein changes suggest that homeostatic plasticity mechanisms might be altered in schizophrenia. If hippocampal pattern separation is diminished due to partial dentate gyrus functional failure (resulting in 'spurious associations') and also if pattern completion is accelerated and increasingly inaccurate due to

increased CA3 associational activity, then it is conceivable that associations could be false (psychotic contents) and driven by anxiety or stress, the mistaken associations are laid down as a valid memory, despite their psychotic content, provoking delusions and thought disorder (Tamminga et al., 2012).

DG mediates mnemonic processing of spatial information. The processes subserved by dorsal DG include: (a) the operation of group encoding of multiple sensory inputs, implying an integration of sensory inputs to determine a spatial representation, (b) pattern separation of spatial (specially metric) information, involving the reduction of interference between similar spatial locations, (c) pattern separation of context, (d) importance of context in object recognition, and (e) temporal integration and remote memory and spatial pattern separation based in part on neurogenesis. Additionally. the ventral dentate gyrus (vDG) mediates mnemonic processing of odor information as indicated by odor pattern separation (Kesner, 2013).

Converging lines of evidence have suggested that there are abnormalities of glutamate transmission in schizophrenia. Glutamatergic neurotransmission involves numerous molecules that facilitate glutamate release, receptor activation, glutamate reuptake, and other synaptic activities. Evidence for glutamatergic abnormalities in schizophrenia primarily has implicated the NMDA and AMPA subtypes of the glutamate receptor. The expression of these receptors and other molecules associated with glutamate neurotransmission has been systematically studied in the brain in schizophrenia. These studies have generally revealed region and molecule specific changes in glutamate receptor transcription and protein expression in this illness (Rubio, Drummond & Meadow-Woodruff, 2012). In the hippocampal region, reduced MK801 binding (NMDA blocker) suggested NMDA receptor abnormalities in schizophrenia (Beneyto, et al., 2007). Supporting this line, a study on pan and isoform specific GluN1 proteins reported a decrease in total GluN1 and GluN1-4b isoform expression in the left hippocampus, and of the GluN1-2b isoform in the right hippocampus (Vrajova, et al., 2010). AMPA receptor binding in hippocampal subregion CA2 was significantly less in schizophrenia. The level of mRNA for the NMDA receptor subunits NR1 and NR2B was significantly different between groups; in several hippocampal subregions, the level of NR1 mRNA was lower and the level of NR2B mRNA was higher in schizophrenia. Because the NR1 subunit of the NMDA receptor is critical to full receptor activity, a reduction of NR1 in hippocampus in schizophrenia suggests a functional impairment in glutamatergic transmission at the NMDA receptor, resulting in reduced glutamatergic transmission within and possibly efferent from the hippocampus in schizophrenia. This defect could underlie a hypoglutamatergic state in regions of the limbic cortex, consistent with published results from other lines of research in schizophrenia (Gao, et al., 2000).

Law and Deakin (2001) found reductions in left-sided hippocampal NMDAR1 gene expression. Using in situ hybridization histochemistry (ISHH), they measured mRNA for the NMDAR1 subunit of the NMDA glutamate receptor in post-mortem samples of the hippocampus from schizophrenic, depressive, bipolar patients and normal controls. A significant main statistic effect was observed in the dentate gyrus and a trend in the CA3 region, with all psychiatric groups having reduced NMDAR1 mRNA levels compared to normal controls. In contrast to the affective patient groups, the reductions in the schizophrenia group were more pronounced in the left side compared to the right. Expression of poly A mRNA also showed left-sided losses in the dentate gyrus in schizophrenia and reductions in NMDAR1 remained significant when expressed as a ratio of poly A. These findings confirm a recent report of reduced hippocampal NMDAR1 mRNA in schizophrenia. Recent findings from in vivo-imaging and human post-mortem tissue studies in schizophrenic psychosis, have demonstrated functional and molecular changes in hippocampal subfields that can be associated with hippocampal hyperexcitability. Segev et al. (2020) used a subfield-specific GluN1 knockout mouse with a disease-like molecular perturbation expressed only in dentate gyrus (DG) and assessed its association with hippocampal physiology and psychosis-like behaviors demonstrating a remarkably similar behavioral profile when CA3 hyperactivity was induced. These hippocampal subfield changes could provide the basis for the observed increase in human hippocampal activity in schizophrenia, based on the shared G-specific GluN1 reduction. Probably, the prevalent alterations may be found on NMDA receptor NR1 subunit, mainly in the left hippocampus at the DG level.

Anterior Insula Connective Alterations

The disruption of the salience network (SN) has been consistently found in patients with schizophrenia and

thought to casue specific symptoms. However, the functional disconnection pattern of the SN remains unclear in first-episode schizophrenia (FES). Sixty-five patients with FES and sixty-six healthy controls were enrolled in a study by Huang et al. (2020) and underwent resting-state functional magnetic resonance imaging (rsfMRI). Eleven regions of interest (ROIs) within SN were derived from the peaks of the group independent component analysis (gICA). ROI-based whole-brain functional connectivity (FC) analyses were performed with all SN ROIs as the ROI. Both hyper- and hypo-connectivity of SN were found in the FES. Specifically, the increased FC mainly existed between the SN and cortico-cerebellar sub-circuit and prefrontal cortex, while the reduced FC mainly existed within cortico-striatal-thalamic-cortical (CSTC) sub-circuit. These findings suggest that FES is associated with pronounced dysregulation of SN, characterized prominently by hyperconnectivity of SN-prefrontal cortex and cerebellum, as well as hypoconnectivity of CSTC sub-circuit of the SN.

Rossler et al. (2020) investigated dopamine-induced changes in functional connectivity of the right anterior insula (rAI), a central SN hub, and their association with psychotic-like experiences. Psychotic-like experiences were assessed using the revised Exceptional Experiences Questionnaire (PAGE-R). They then received either placebo (n = 32) or 200 mg L-DOPA (n = 33), a dopamine precursor, orally and underwent rsfMRI. In a ROI-to-voxel approach were analyzed dopamine-induced changes in functional connectivity of the rAI and assessed the relationship between functional connectivity changes and PAGE-R score. L-DOPA reduced functional connectivity between the rAI and the left auditory cortex planum polare. In the placebo group, they found a strong negative correlation between PAGE-R score and rAI to planum polare functional connectivity; in the L-DOPA group, there was a strong positive correlation between PAGE-R score and functional connectivity between rAI and planum polare. The authors concluded that psychotic-like experiences are associated with dopamine-induced disruption of auditory input to the SN, which may lead to aberrant attribution of salience.

White et al. (2010) presented a functional network connectivity (FNC) analysis of spatial networks identified during somatic sensations in order to test the hypothesis that Salience Network connectivity is disturbed during information processing in schizophrenia. Significantly reduced FNC was observed in schizophrenia compared to controls between the insula and ACC (anterior cingulate cortex), insula and ventromedial frontal cortex, and left dorsolateral frontal and parietal with posterior cingulate and angular gyrus. Reduced salience network connectivity during information processing in schizophrenia suggests disturbances to the system which effects changes between contextually-relevant functional brain states. This alteration may provide a mechanistic explanation of several clinical features of the disorder.

In another study, searching for differences in SN, functional and structural connectivity were examined using a ROI-based approach and tract-based spatial statistics. Subject-level functional connectivity measures and diffusion indices of disrupted regions were correlated with scores and compared between ARMS (At Risk Mental State) with and without transition to psychosis. ARMS subjects exhibited reduced FC between the left ventral anterior insula and other SN regions. Reduced fractional anisotropy (FA) and axial diffusivity were also found along white-matter tracts in close proximity to regions of disrupted functional connectivity, including frontal-striatal-thalamic circuits and the cingulum. FA measures extracted from these disrupted white-matter regions correlated with individual symptom severity in the ARMS group. Furthermore, functional connectivity between the bilateral insula and FA at the forceps minor bundle were further reduced in subjects who transitioned to psychosis after 2 years. These findings support the insular disconnectivity hypothesis in the early stages of psychosis (Wang, et al., 2016). Mallikarjun et al. try to elucidate the intrinsic functional connectivity in patients presenting with first episode psychosis (FEP). rsfMRI data were available from 18 FEP patients, 9 of whom also experienced auditory verbal hallucinations (AVH) of sufficient duration in the scanner allowing symptom capture in functional MRI compared to 18 healthy controls. Symptom capture results were used to accurately identify specific brain regions active during AVH; including the superior temporal cortex, insula, precuneus, posterior cingulate and parahippocampal complex. Using these as ROI, patients with FEP and AVH showed increased resting FC between parts of the SN and the DMN (default mode network) and between the SN and the cerebellum, but reduced FC between the claustrum and the insula, compared to healthy controls. It is possible that aberrant activity

within the DMN and SN complex may be directly linked to impaired salience appraisal of internal activity provoking AVH (Mallikarjun, et al., 2018).

Limongi, et al. (2020) tested the hypothesis in core nodes of the salience network (the dorsal anterior cingulate cortex [dACC] and the anterior insula) of 20 patients with first-episode psychosis and 20 healthy control subjects and established 3-way correlations between the magnetic resonance spectroscopy measures of glutamate, effective connectivity of rsfMRI, correlations between measures of this connectivity and estimates of precision (inherent in evidence accumulation in the Stroop task) and psychopathology. Glutamate concentration in the dACC was associated with higher and lower inhibitory connectivity in the dACC and in the anterior insula, respectively. Crucially, glutamate concentration correlated negatively with the inhibitory influence on the excitatory neuronal population in the dACC of subjects with first-episode psychosis. Furthermore, aberrant computational parameters of the Stroop task performance were associated with aberrant inhibitory connections. Finally, the strength of connections from the dACC to the anterior insula correlated negatively with severity of social withdrawal. These findings support a link between glutamate-mediated cortical disinhibition, effective connectivity deficits, and computational performance in psychosis.

Bolton et al. substantiate the pivotal role of the right anterior insula in governing CEN-to-DMN transitions, which appear dysfunctional prior to the onset of psychosis, especially when first attenuated psychotic symptoms occur. In subthreshold delusional and hallucinating subjects, it is a prolonged activation in concert with the DMN and there is a loss of competition between a SN/DMN state, and a state with insula/CEN activation paralleled by DMN deactivation. These features suggest that abnormal network switching disrupts the capacity to distinguish between internal world and external environment, which is accompanied by a loss in flexibility and an excessive awareness to internal processes reflected by prolonged expression of the right anterior insula-default mode co-activation pattern (Bolton, et al., 2020).

Schiwy et al. (2022) chose two approaches for cognitive assessment, first the MATRICS Consensus Cognitive Battery (MCCB) combined with a global score and the disorganization factor derived from a five-factor model of the Positive and Negative Syndrome Scale (PANSS) known to be relevant for cognitive performance. DMN and SN were identified using independent component analysis on rsfMRI data, the authors found significantly decreased connectivity within the right supplementary motor area (SMA) and bilateral putamen in patients with psychosis compared to controls. Within patients, linear regression analysis revealed that aberrant SMA connectivity was associated with impaired global cognition, while dysfunctional bilateral putamen connectivity predicted disorganization. These results support the hypothesis that SN dysfunctional connectivity is important in the pathobiology of cognitive deficits in psychosis. Some relevant findings are summarized: 1) psychotic-like experiences are associated with dopamine-induced disruption of auditory input to the salience network, which may lead to aberrant attribution of salience, and 2) reduced salience network connectivity during information processing in schizophrenia suggests disturbance to the system which effects changes between contextually-relevant functional brain states. These findings support insular altered proximal connectivity in the Salience Network hypothesis in the early stages of psychosis.

Discussion

Genetically determined glutamate receptor expression can be a common deficit in schizophrenic patients in different areas like dentate gyrus and hippocampus (Beneito, et al., 2007; Vrajova, et al., 2010; Tamminga, et al., 2012), mediodorsal thalamic nuclei (Ibrahim, et al., 2000), anterior cingulate cortex (Taylor et al., 2015; Wang, et al., 2019; Reid, et al., 2019), prefrontal cortices (Smucny, Carter & Maddock, 2021) and cerebellum (Yeganeh-Doost, et al., 2011). Three nodal hubs can contribute to the overall mental dysfunction in schizophrenia (Ure et al., 2024): 1) Imbalance of thalamocortical projections including reduced connectivity between mediodorsal thalamus and dorsolateral and dorsomedial prefrontal cortices and anterior thalamic nuclei with anterior cingulate gyri causing cognitive deficits together with hyper-connectivity between ventrolateral thalamic nuclei and sensorimotor, auditive and visual regions and subcortical extensions causing psychotic symptoms. 2) Psychotic contents emerged from the dentate-hippocampal region through enhanced pyramidal neurons activity following disinhibition secondary to glutamate receptor deficits at the dentate gyrus granule cell. 3)

Disconnection of anterior insula with dorsal anterior cingular cortices (salience network, SN) and some regions of the central executive (CEN) and default mode network (DMN) can provoke aberrancies and coactivation of networks causing difficulties in distinguishing the inner from the outside world.

Conclusion

A large bulk of recent experimental studies support the hypothesis of three nodal hubs in the physiopathology of schizophrenia. Imbalance of thalamocortical connections in line with cognitive disturbances, enhanced hippocampal activity linked with generation of psychotic contents and disconnectivity of anterior insula leading to confusion between external and internal world and in some cases alterations in awareness of personal identity.

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