REVIEW

Schizophrenia as a disorder of disconnectivity

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Abstract Schizophrenia is considered as a neurodevelopmental disorder with genetic and environmental factors playing a role. Animal models show that developmental hippocampal lesions are causing disconnectivity of the prefrontal cortex. Magnetic resonance imaging and postmortem investigations revealed deficits in the temporoprefrontal neuronal circuit. Decreased oligodendrocyte numbers and expression of oligodendrocyte genes and synaptic proteins may contribute to disturbances of micro- and macro-circuitry in the pathophysiology of the disease. Functional connectivity between cortical areas can be investigated with high temporal resolution using transcranial magnetic stimulation (TMS), electroencephalography (EEG), and magnetoencephalography (MEG). In this review, disconnectivity between different cortical areas in schizophrenia patients is described. The specificity and the neurobiological origin of these connectivity deficits and the relation to the symptom complex of schizophrenia and the glutamatergic and GABAergic system are discussed.

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Introduction

Schizophrenia is a severe psychiatric disorder with unknown etiology. Currently, a combination of genetic and environmental factors underlying the development of this disorder is discussed. Genetic association and genome-wide association studies revealed several risk genes of schizophrenia, among them are neuregulin1, DISC1, D-amino-acid oxidase activator (DAOA/G72), zinc finger protein 804A (ZNF804A), transcription factor 4 (TCF4) [32]. Environmental factors such as obstetric complications with hypoxia [37], prenatal infection, season of birth, drug abuse, and migration [29] may interact with genetic factors, influencing onset and progression of the disease. This gene-environmental interaction may comprise epigenetic alterations like DNA methylation and histone acetylation [35, 41]. An interaction between metabotropic glutamate receptor (GRM3) gene variants and severe obstetric complications on hippocampus volume has been reported, but this finding was not specific for schizophrenia [22]. Furthermore, it is assumed that these risk factors may affect brain tissue during perinatal neurodevelopment and may lead to the onset of psychotic symptoms in early adulthood during the synaptic pruning process of the prefrontal cortex [43]. In early adulthood, animal models of neonatal hippocampal lesions show behavioral deficits comparable to schizophrenia symptoms and reveal neurobiological deficits in the prefrontal cortex [17, 39], suggesting prefrontotemporal disconnectivity in the pathophysiology of the disease.

MRI and post-mortem findings of disconnected circuits in schizophrenia

Meta-analyses of structural magnetic resonance imaging (sMRI) studies reveal gray matter volume deficits in different brain regions in schizophrenic patients. Affected regions are the medial temporal lobe including the hippocampus, the heteromodal association cortex including the prefrontal, anterior cingulate, superior temporal and parietal cortex as well as the thalamus. The degree of gray matter reduction is in the range of 5–10% in the frontotemporal and basal ganglia-thalamocortical network [10, 13, 16].

Beside effects of environmental factors like cannabis abuse and trauma on cortical thickness in schizophrenia patients [19] or on reduced hippocampal volumes in patients and relatives with obstetric complications [8], schizophrenia susceptibility genes like neuregulin1 variants have shown impact on hippocampus volume [18], white matter density, and integrity in the anterior limb of the internal capsule [30]. A ZNF804A risk variant was associated with reduced cortical gray matter thickness in several regions [42].

sMRI and postmortem schizophrenia studies have shown volume loss in the medial temporal lobe, especially in the hippocampus, as one of the most consistent structural abnormalities [1]. A meta-analysis of diffusion tensor imaging (DTI) studies shows reductions in the myelin membranes and decreased white matter anisotropy in the deep left prefrontal and temporal cortex in schizophrenia and supports the hypothesis of structural and functional disconnectivity [9]. Neuronal axons traversing the limbic pathways from the hippocampus are connected to prefrontal cortex, anterior cingulate cortex, and thalamus. These pathways are involved in higher cognition and information processing, domains in which schizophrenia patients exhibit severe deficits [12].

A variety of functional MRI (fMRI) studies revealed disturbed connectivity in complex hippoampal, prefrontal and cerebellar-thalamic-prefrontal networks in schizophrenia [31]. In patients and non-psychotic subjects at increased risk dynamic causal modeling in fMRI studies revealed decreased effective connectivity between the posterior hippocampus and prefrontal cortex during working memory tasks [3, 23]. According to these results, postmortem studies revealed a loss of myelin-building oligodendrocytes in prefrontal and hippocampal subregions, leading to impaired nerve cell propagation of information [24, 36]. Furthermore, gene expression of oligodendrocyte-related genes is decreased in schizophrenia. An additional synaptopathy with decreased expression of glutamatergic and gamma-amino-butyric acid (GABA)ergic synaptic proteins and consecutive disturbance of microconnectivity

[7, 25] is completing the complex framework of disconnectivity in schizophrenia.

Neurophysiological investigations of cortical disconnectivity in schizophrenia

Transcranial magnetic stimulation (TMS)

In schizophrenia patients, alterations of intracortical and intercortical connectivities at subsecond timescales were investigated by TMS (see Fig. 1) and these impaired connectivities have been linked to an abnormal cerebral lateralization and a cerebral asymmetry in schizophrenia patients.

The inhibitory connection between both primary motor cortices (M1), which is discussed to be mediated by corpus callosum pathways, was found to be deficient in schizophrenia patients [5]. One further study supported the idea of an altered interhemispheric connection, revealing a selectively impaired facilitatory connectivity between the left dorsal premotor cortex and the right M1 [34]. As a third disrupted interhemispheric pathway, the connection between right cerebellum and left M1 was shown to be deficient in schizophrenia patients [6], indicating a disrupted direct cerebellar-M1 connection or an abnormal
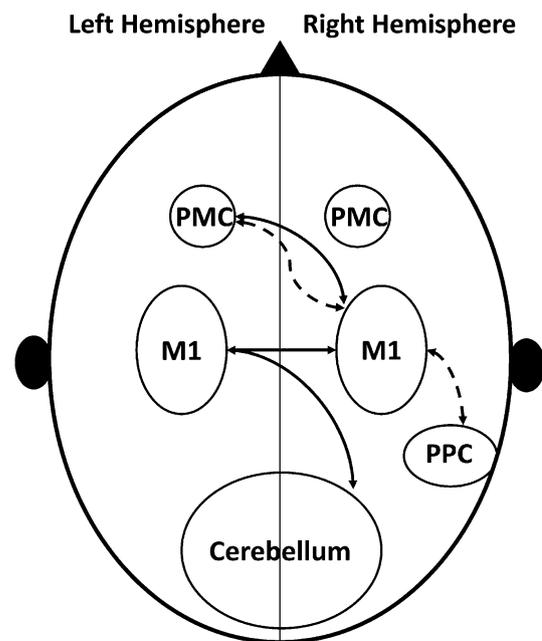
Fig. 1 Schematic presentation of connectivities between different cortical areas evaluated by TMS in schizophrenia patients. The inhibitory connectivity between left premotor areas and the right primary motor cortex is not affected, whereas the facilitatory connectivity between these two areas is reduced. *PMC* Premotor cortex, *M1* Primary motor cortex, *PPC* Posterior parietal cortex, *Dashed line* facilitatory connectivity, *Solid line* inhibitory connectivity

cerebellar inhibitory output. A disturbed intrahemispheric connectivity between the right posterior parietal cortex (PPC) and the right M1 in schizophrenia patients has been reported, too [28]. Finally, a dysfunctional interhemispheric connection between the right premotor and left M1 was discovered with a plasticity inducting repetitive TMS [33].

EEG/MEG

EEG and MEG provide insight into cortical rhythms and neuronal oscillations. In general, synchronous cortical rhythms support the idea of intact functional and anatomical connection between different brain areas [4]. This is of particular importance as disturbed oscillatory activity, alterations in synchronization and dysfunctional intra- and interhemispheric connectivities are an important feature in schizophrenia [40].

Quantitative analysis of resting EEG recordings displayed an increased delta and/or theta activity, a decreased main frequency, a low mean alpha frequency ("hypofrontality") and an increased beta activity in schizophrenia patients [15, 26]. In dependence of the type of measure (steady-state evoked potentials, amplitudes, induced oscillations, and resting state [40]), amplitudes and phases have been found to be abnormal in schizophrenia patients. A common pattern of the different brain oscillations in schizophrenia patients is a reduction in amplitude and altered phase synchronization in all frequency bands (with emphasis on the beta and gamma band activity) at rest, during sensory processing and cognitive tasks [38, 40]. Further evidence is provided by animal studies showing that the synchronization of brain oscillations depends on cortico-cortical connections within and between hemispheres [11, 40]. Therefore, the findings of impaired neural oscillation and the reduced phase synchronization in schizophrenia patients can be considered as a marker for a functional disconnectivity between different brain areas and for dysfunctional cortical networks [40].

Connectivity and neurotransmitter systems

Insights to disturbed connectivity in schizophrenia have been provided by MRI, postmortem, and animal studies. Alterations in GABAergic and n-methyl-D-aspartate receptor (NMDAR)-mediated transmission display a common neurobiological background of connectivity deficits revealed by TMS/EEG/MEG. First, studies on human brain tissues showed lower GABA-related transcripts in four cortical areas in schizophrenia patients [21]. Second, the results of different TMS-studies using specific paradigms to investigate inhibitory intracortical networks point toward a GABAergic dysfunction in the motor system of

this patient group [44]. Third, schizophrenia patients show a reduction in the mRNA expression of the GABA-synthesizing enzyme, GAD67, and a reduction in GABAergic interneurons in several cortical areas [2, 27].

These abnormalities in GABAergic transmission appear to be associated with NMDAR dysfunction and dysfunctional NMDAR, in turn, causes abnormal neuronal plasticity, which is thought to be a crucial pathophysiological process in schizophrenia patients [38]. A theory about abnormal synaptic plasticity from Stephan, Friston and Frith discussed the relationship between dysfunctional NMDAR and disconnectivity in schizophrenia patients [38]. In their theory, the underlying biological and pathophysiological agent of schizophrenia is a dysfunction of NMDAR with a consecutive reduced synaptic and cellular plasticity. This would affect long-range connections in the developing brain, induce abnormalities in different neurotransmitter systems (dopamine, serotonine, acetylcholine, GABA), lead to aberrant corollary discharge and to impaired perceptual interference. This theory and other theories, discussing the glutamate-hypothesis of schizophrenia, are supported by several lines of evidence. A reduced LTP-like focal, spike-timing-dependent-like synaptic plasticity and a reduced LTP-like non-focal, cortical plasticity are recent neurophysiological findings in schizophrenia patients [14, 20]. Taken together, this may indicate dysfunctional NMDARs and a reduced signal-to-noise ratio with consecutive dysfunctional information processing [20]. Additionally, numerous studies display a link between NMDAR dysfunction and affected cortical oscillations and mismatched negativity deficits [40].

In summary, different neurophysiological, imaging, neuropathological and molecular biology methods have revealed a disconnectivity in schizophrenia patients—the underlying pathobiology still needs clarification, but alterations in the GABAergic and glutamatergic, NMDAR-mediated neurotransmissions might be possible candidates.

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