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EDITORIAL

Brain connectivity measures hold promise for informing on the pathobiology of psychosis symptom dimensions

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Schizophrenia spectrum disorders are often considered to be homogeneous syndromes. But while schizophrenia may span multiple symptom dimensions, the behaviors of individuals suffering from schizophrenia spectrum disorders are quite heterogeneous. Currently, we struggle to understand the underlying pathobiology both when considering schizophrenia as a category and when studying specific symptom dimensions. Collectively, the majority of the past neuroimaging studies in schizophrenia demonstrated that no single brain lesion or local dysfunction would be able to explain the complex psychopathology of schizophrenia. Therefore, the field has moved toward studying the interaction of multiple brain areas. This may include the concurrent brain activity in two areas, the dynamics in larger networks, or the organization of network components. Structural and functional magnetic resonance imaging (MRI) allow for testing the connectivity within brains and offer new means of understanding brain-behavior associations. The current issue of this journal provides a number of interesting examples exploring links between connectivity and symptom dimensions in schizophrenia spectrum disorders.

Functional connectivity is assumed when brain regions share the temporal pattern of activation and deactivation of the local blood oxygenation level dependent (BOLD) signal. Researchers are exploring correlations between the temporal signal of two or more brain areas. Typically, these signal fluctuations are measured during the resting state BOLD acquisition. The common interpretation is that two or more distinct brain regions with correlating BOLD resting state fluctuations are synchronized and may share information among each other. Aberrant connectivity profiles at rest, e.g. unexpected correlations, may indicate brain pathology in mental disorders. In this issue, three excellent examples report the associations between functional network alterations and real-life social networks, paranoia, and inhibited catatonia in psychotic disorders.

Zhang et al. explored the association between resting state connectivity in a social brain network derived from meta-analyses and individual real-world social network characteristics in patients with schizophrenia and healthy controls [1]. They found that the left temporal lobe was a hub in the social brain network. Resting-state functional connectivity of this hub was associated with the social network, but the association was lower in patients compared to controls. In contrast, functional connectivity outside this hub was a stronger predictor of social network parameters in schizophrenia. The authors were able to replicate the main associations also in a second independent sample. Thus, the data suggests that the organization of brain areas involved in social cognition also informs on real-life social networks of patients with schizophrenia.

Walther et al. tested resting state connectivity between regions of interest (ROI) in the limbic system (bilateral orbitofrontal cortex, amygdala, hippocampus, and nucleus accumbens) in 49 schizophrenia patients with paranoia, 40 schizophrenia patients without paranoia, and 76 healthy controls [2]. They detected increased resting state functional connectivity between bilateral amygdalae and hippocampi in patients with paranoia compared to patients without paranoia, with healthy controls in an intermediate position between the patient groups. This finding was confirmed by a dimensional analysis associating the severity of expert ratings of paranoia with resting state functional connectivity between bilateral hippocampi and amygdalae. Results indicate that aberrant signaling in the core limbic system is specifically associated with the experience of paranoia in schizophrenia, but do not resemble an alteration in individuals with schizophrenia in general.

Parekh and colleagues reported a rare sample of patients with acute retarded catatonia in whom they detected

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massively increased resting state connectivity within the motor network as compared to healthy controls [3]. At the same time, they found reduced connectivity between primary motor and sensory cortices. Finally, they reported distinct connectivity patters for individuals responding to lorazepam vs. ECT treatment. These findings extend previous reports on increased or less flexible functional connectivity in the sensorimotor system in catatonia [4, 5].

In contrast to functional connectivity parameters, structural connectivity in the white matter is considered to provide more straightforward information on connectivity between brain areas. Diffusion weighted imaging allows for the quantification of the diffusion of water molecules within brain tissue. Densely packed and highly myelinated white matter fibers have distinct diffusion properties compared to fibers with lower myelination or less organization. Researchers may explore white matter properties in whole white matter or in reconstructions of fiber pathways. Finally, network metrics allow for the quantification of multiple network characteristics. Structural brain connectivity may change as a result of pathological processes, such as neurodegeneration or inflammation, but also due to training effects. In schizophrenia, white matter properties have been linked to clinical and demographic variables, such as age, sex, medication, or symptom severity [6]. In the current issue, three studies related to structural connectivity, including post-mortem work and studies linking white matter alterations with cognitive impairment in schizophrenia.

Kolomeets and Uranova investigated oligodendrocytes in post-mortem specimen of schizophrenia pateints and healthy controls [7]. They found a reduced number of oligodendrocyte satellites in the perineuronal space in layer 5 of the anterior prefrontal cortex in schizophrenia. As oligodendrocytes support neuronal metabolism and fiber myelination, these alterations could directly impact brain connectivity.

Wannan et al. applied tractography from the hippocampus to test the association of white matter properties of hippocampal tracts and episodic memory in first episode psychosis, chronic psychosis, as well as younger and older controls [8]. Episodic memory was impaired in first episode and chronic psychosis patients, but only in chronic patients tractography identified altered white matter compared to controls. Finally, poorer episodic memory in chronic patients was linked to increased axial and radial diffusion in hippocampal-thalamic pathways.

Yamada and colleagues investigate the link between white matter properties and cognitive performance in two cohorts [9]. Each cohort included patients with low cognitive performance, patients with high performance, and healthy controls. Consistently in both cohorts, they detected lower mean fractional anisotropy in the whole white matter skeleton in patients with low cognitive performance compared to controls with the strongest effects in the left inferior fronto-occipital fasciculus (IFOF), which was also related to global community functioning.

Further symptom dimensions have been linked to specific alterations in structural connectivity in schizophrenia. For example, subtle sensorimotor abnormalities, i.e. neurological soft signs, have been linked to altered diffusion in white matter motor pathways such as the corticospinal tract, corpus callosum, or superior longitudinal fascicle in patients with schizophrenia [10]. Related work has been done on hallucinations, delusions, or formal thought disorder. Both structural and functional alterations of brain connectivity may contribute to psychopathological phenomena in schizophrenia spectrum disorders. Future studies will need to clarify which alterations resemble vulnerability to develop episodic symptoms or which neural changes might result from altered behavior. Thus, longitudinal measurements and a neurodevelopmental perspective on these networks will be key.

While these examples of structural and functional connectivity alterations in schizophrenia spectrum disorders are just a small selection from the current issue, they highlight the promise of testing network alterations to explore their association with symptom domains in psychosis. Even though, it is unlikely that the one primary brain alteration can be identified in all individuals with schizophrenia, refining the search to symptom dimensions may prove to be informative of the pathobiology of distinct symptoms. Careful phenotyping of symptom dimensions with expert ratings, self-report, and behavioral experiments is as critical to future studies as are standardized neuroimaging procedures to make progress in this field.

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Declarations

Conflict of interest The author reports no conflict of interest with this work.

References

1. Zhang YJ, Li Y, Wang YM, Wang SK, Pu CC, Zhou SZ et al (2021) Hub-connected functional connectivity within social brain network weakens the association with real-life social network in schizophrenia patients. Eur Arch Psychiatry Clin Neurosci. https://doi.org/10.1007/s00406-021-01344-x
2. Walther S, Lefebvre S, Conring F, Gangl N, Nadesalingam N, Alexaki D et al (2021) Limbic links to paranoia: increased resting-state functional connectivity between amygdala, hippocampus and orbitofrontal cortex in schizophrenia patients with paranoia. Eur Arch Psychiatry Clin Neurosci. https://doi.org/10.1007/s00406-021-01337-w
3. Parekh P, Gozi A, Reddi VSK, Saini J, John JP (2021) Resting state functional connectivity and structural abnormalities of the brain in acute retarded catatonia: an exploratory MRI study.

Eur Arch Psychiatry Clin Neurosci. https://doi.org/10.1007/s00406-021-01345-w
4. Walther S, Stegmayer K, Federspiel A, Bohlhalter S, Wiest R, Viher PV (2017) Aberrant hyperconnectivity in the motor system at rest is linked to motor abnormalities in schizophrenia spectrum disorders. Schizophr Bull 43(5):982–992
5. Sambataro F, Hirjak D, Fritze S, Kubera KM, Northoff G, Calhoun VD et al (2021) Intrinsic neural network dynamics in catatonia. Hum Brain Mapp 42(18):6087–6098
6. Seitz-Holland J, Cetin-Karayumak S, Wojcik JD, Lyall A, Levitt J, Shenton ME et al (2021) Elucidating the relationship between white matter structure, demographic, and clinical variables in schizophrenia-a multicenter harmonized diffusion tensor imaging study. Mol Psychiatry 26(9):5357–5370
7. Kolomeets NS, Uranova NA (2021) Reduced number of satellite oligodendrocytes of pyramidal neurons in layer 5 of the prefrontal cortex in schizophrenia. Eur Arch Psychiatry Clin Neurosci. https://doi.org/10.1007/s00406-021-01353-w
8. Wannan CMJ, Bartholomeusz CF, Pantelis C, Di Biase MA, Syeda WT, Chakravarty MM et al (2021) Disruptions in white matter microstructure associated with impaired visual associative memory in schizophrenia-spectrum illness. Eur Arch Psychiatry Clin Neurosci. https://doi.org/10.1007/s00406-021-01333-0
9. Yamada S, Takahashi S, Malchow B, Papazova I, Stocklein S, Ertl-Wagner B et al (2021) Cognitive and functional deficits are associated with white matter abnormalities in two independent cohorts of patients with schizophrenia. Eur Arch Psychiatry Clin Neurosci. https://doi.org/10.1007/s00406-021-01363-8
10. Viher PV, Stegmayer K, Bracht T, Federspiel A, Bohlhalter S, Strik W et al (2022) Neurological soft signs are associated with altered white matter in patients with Schizophrenia. Schizophr Bull 48(1):220–230