*PERSPECTIVE*

# Is schizophrenia a spatiotemporal disorder of the brain's resting state?

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Recently, the brain's resting state activity, i.e., the brain's neural activity in the absence of any specific tasks or stimuli (1), has gained prominence in neuroimaging and in psychiatric research. This resting state activity can be spatially characterized by various neural networks showing close functional connectivity. These include the default-mode network (DMN), mostly consisting of cortical midline structures showing strong low frequency fluctuations (2), the sensorimotor network, the salience network, and the control executive network (CEN) (3). These networks are interrelated in continuously changing constellations (4).

The resting state activity can also be characterized by fluctuations in different frequency bands, ranging from infraslow (0.0001-0.1 Hz) over delta (1-4 Hz), theta (5-8 Hz), alpha (8-12 Hz) and beta (12-30 Hz) to gamma (30-180 Hz). These different frequency bands are coupled with each other (5), constituting a complex temporal structure (6). One can therefore characterize the brain's resting state activity as an integrated spatiotemporal structure that must be understood in a physiological and functional sense, rather than an anatomical and structural one (7,8).

There have been numerous investigations of resting state activity and functional connectivity in schizophrenia (e.g., 9,10). Resting state functional connectivity within the cortical midline structures/DMN tends to increase, while functional connectivity of the CEN, including the lateral prefrontal cortex, is rather decreased in schizophrenia (9). This increased functional connectivity in midline regions appears to be compatible with the observation of stronger low frequency fluctuations in schizophrenia, particularly in the anterior midline regions (10).

How are these changes in the resting state's spatial structure related to the symptoms in schizophrenia? Investigations in healthy subjects associated the negative relationship, or anticorrelation, between the DMN and the CEN with the balance between internal (self-related) and external (environment-related) mental contents in awareness (11-13). If the resting state activity and functional connectivity in medial regions/DMN is stronger, the focus will be primarily on internal mental contents that are more related to the own self, the own thoughts, and the body (12). In contrast, stronger resting state activity and functional connectivity in lateral regions/CEN leads to increased external mental contents in awareness (12).

Most importantly, this predominance of external mental contents in awareness takes place at the expense of the internal mental contents, with a reciprocal balance between them: either the load of internal mental contents is high and that of external mental contents is low or, conversely, the latter predominate while the former recede into the background (11,12). Such reciprocal balance between internal and external mental contents is mediated neuronally by the anticorrelation between midline regions/DMN and lateral regions/CEN.

Using the psychedelic drug psilocybin to mimic psychosis in healthy subjects, Carhart-Harris et al (14) observed a decreased anticorrelation between DMN and CEN. This was also reported by other investigations in patients with schizophrenia (15).

The anticorrelation between DMN and CEN makes possible a clear distinction between internal and external mental content by balancing them reciprocally. Decrease in anticorrelation, or its conversion into positive correlation between DMN and CEN, resolves that distinction: external mental contents are now no longer reduced when internal mental contents are strong. This makes possible confusion between internal and external mental contents. For instance, external (or internal) mental contents may interfere with, and penetrate into, the ongoing processing of internal (or external) mental contents. This is typically observed in symptoms such as thought insertion, thought withdrawal and passivity symptoms in schizophrenia. One may want to describe the confusion between internal and external mental contents as "self-environment blurring", which may represent a "basic spatial disturbance" underlying passivity symptoms and ego disorder in schizophrenia.

Confusion between internal and external contents with "self-environment blurring" may also underlie auditory hallucinations. Several studies demonstrated abnormally high resting state activity and functional connectivity in the auditory cortex during auditory hallucinations (16). Why, though, during auditory hallucinations are the voices experienced as external rather than internal? This may be related to the DMN and CEN and their relation with the auditory cortex. More specifically, the DMN seems to be less connected in the resting state to the auditory cortex which, in contrast, is rather strongly connected to CEN (15). Such disengagement of DMN functional connectivity from auditory cortex and the latter's association with CEN may account for the assignment of an external origin to the hallucinated voices rather than relating them back to an internal origin (17). Auditory hallucinations and their localization in the environment – rather than in the own

self – may therefore be yet another instance of internal-external confusion and "self-environment blurring" which, put in cognitive terms, is often referred to as deficit in self-monitoring or self-recognition (18).

In addition to internal-external confusion, temporal features, as investigated in EEG, may play a central role in generating auditory hallucinations. Angelopoulos et al (19) reported an increase in phase synchrony in the alpha band of the auditory cortex before and during the onset of auditory hallucinations. Moreover, increased phase-phase coupling between theta and gamma in fronto-temporal areas and the temporal electrode T7, indicating the auditory cortex, was observed during the experience of auditory hallucinations (20). This suggests that the abnormal coupling of auditory cortical resting state activity to other regions/networks such as CEN may be temporally mediated by abnormally increased phase synchrony.

In conclusion, recent neuroimaging results highlighted the brain's resting state activity and its abnormalities in psychiatric disorders such as schizophrenia. However, the exact meaning of the resting state abnormalities for psychiatric symptoms remains unclear. Based on recent findings, I here suggest directly linking abnormalities of the resting state's spatiotemporal structure to psychopathological symptoms such as ego disturbances and auditory hallucinations in schizophrenia.

Future studies may aim to target and investigate directly the spatiotemporal structure of the various schizophrenic symptoms. This may lead to the development of novel forms of interventions aiming to "normalize" the brain's resting state and the spatiotemporal structure of its neural activity.

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