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Spatiotemporal Psychopathology – A Novel Approach to Brain and Symptoms

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ABSTRACT

How can we characterize psychopathological symptoms and connect them to the brain? Current psychopathological symptoms only focus on either the symptoms themselves or predominantly on the brain. This leaves open their intimate connection. A novel approach, Spatiotemporal Psychopathology, proposes that the brain inner spatiotemporal organisation of its neural activity provides the spatiotemporal organization of the psychopathological symptoms. Specifically, the brains' neuronal topography and dynamic is manifest in a more or less analogous spatiotemporal organisation on the mental level, i.e., mental topography and dynamic. This is strongly supported by various examples including major depressive disorder, bipolar disorder, schizophrenia, and autism. We therefore conclude that Spatiotemporal Psychopathology provides a promising approach to intimately connect brain and symptoms.

Keywords: Brain, depression, psychopathological symptoms, schizophrenia, spatiotemporal psychopathology

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INTRODUCTION

Linking Symptoms to the Brain

One key challenge in current psychiatry concerns our understanding of the psychopathological symptoms, that is, how they can be characterized and connected to abnormalities in the brain. Psychopathology concerns the empirical and theoretical framework in which symptoms, behavior, and experiences in psychiatric patients can be described, categorized, and classified (1–5). Different branches of psychopathology have been developed including descriptive psychopathology, structural psychopathology, and phenomenological psychopathology (6–9).

These forms of psychopathology focus on the symptoms themselves understanding and ideally also explaining them with regard to the person and its context. Despite their differences, descriptive, structural, and phenomenological approaches share their primarily psychological framework: psychopathological symptoms are explained primarily in psychological-phenomenological terms. The focus is here on first- and second-person approaches in order to grasp subjects' experience and the meaning of the psychopathological symptoms in a wider social and cultural context (10).

The rapid developments of neuroscience and biological psychiatry make it necessary to link psychopathological symptoms and thus psychopathology in general to the brain's neural mechanisms. However, the primarily first– and/or second-person approach of descriptive, structural, and phenomenology psychopathology seemingly conflicts with the objective third-person investigation of the brain. In order to adjust psychopathology to neuroscience, one requires a third-person (rather than first- or second-person) approach. This is provided by Cognitive Psychopathology and its affective sibling Affective Psychopathology (11,12).

Highlights

- **Mechanisms of the connection of brain and symptoms remain yet unclear.**
- **Spatial and temporal features provide the link between brain and symptoms.**
- **The brain's topography and dynamic resurface in time-space experience of symptoms.**

Cognitive and/or Affective Psychopathology view the psychopathological symptoms as primarily disturbances of the brain's various cognitive and affective functions. For instance, the various symptoms of Major depressive disorder (MDD) are conceived in terms cognitive emotion regulation which is related to decreased top-down modulation of the amygdala by the prefrontal cortex (13). While Affective Psychopathology conceives MDD primarily as an emotional disorder, that is, dysfunction of the "seeking" system as originating in subcortical nuclei (12).

Despite all progress, we are nevertheless still lacking direct link of brain and symptoms. We currently do no know the exact neuronal mechanisms by means of which the brain yields the various psychopathological symptoms. Specifically, we are still missing the link of first– and second-person symptoms, i.e., their experience and meaning, to the third-person based observation of the brain's neuronal mechanisms. One way to bridge the gap of brain and symptoms is to search for what they share, that is, their "common currency" as only that can provide their intimate connection (14).

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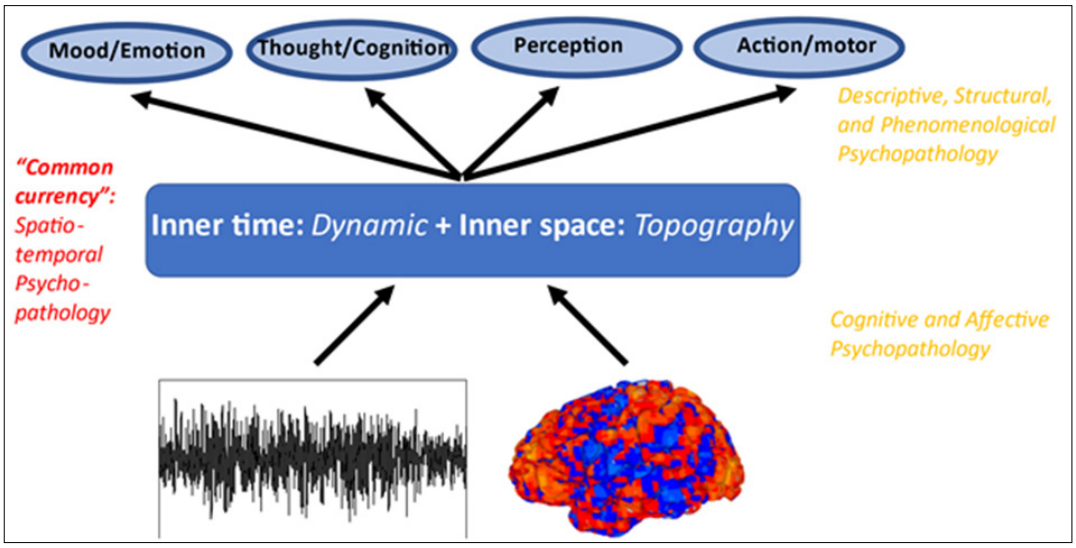


Figure 1. Spatiotemporal Psychopatology –Connecting brain and symptoms through topography and dynamic as their "common currency.

Time-Space as "Common Currency" of Brain and Symptoms

What do neuronal and mental features share? Despite their differences, neuronal and mental features share their basic spatial and temporal organisation or structure (14,15). The brain's spontaneous activity constructs its own "inner time and space" (as distinguished from the world's "outer time and space") in its neural activity; that, in turn, surfaces in the temporal and spatial structure of the psychopathological symptoms including their first-person experience (16).

Speed may provide one prototypical example of a "common currency" between brain and symptoms. Depressed patients experience abnormal slowness of their inner time which, in turn, is manifest in the abnormal slowness of their mood, social behavior, psychomotor activity and cognition (6). Decreased speed in inner time perception and the various symptoms is related to decreased speed on the neuronal level, that is, neural activity shows decreased variability as index of neuronal speed. Abnormally slow speed is thus shared by both brain and symptoms in depression providing their "common currency" (17–19).

Accordingly, in order to link psychopathological symptoms to the brain, we may need to characterize them primarily in spatial and temporal terms. This requires what we recently introduced as "Spatiotemporal Psychopathology" (SPP) (17–20). The main claim of SPP is that certain spatial and temporal configurations are shared as "common currency" by both the brain's neural activity and the psychopathological symptoms. Psychopathological symptoms are then no longer conceived as cognitive or affective disturbances but primarily as spatiotemporal disorders of the brain's inner time and space (and how these align to the world's outer time and space).

SPP assumes that changes in the brain's inner spatiotemporal configuration provide an abnormal spatiotemporal envelop or framing for cognitive, sensory, motor, and affective functions. Such abnormal spatiotemporal envelop or frame is by itself manifest in the subject's perception or experience of time and space as thematized in Phenomenological Psychopathology (1–6). Phenomenological Psychopathology may thus provide an important methodological link to intimately connect the brain's time-space to the spatiotemporal organisation of symptoms.

How can we characterize the spatial and temporal configurations of brain and symptoms? Spatial configuration refers to the organisation between different regions and networks in the brain; this can be described as the brain's topography. SPP now proposes that the brain's neuronal topography is manifest in the spatial organisation of psychopathological symptoms, that is, the way they are coupled with each other ('symptom coupling') amounting to a 'mental topography' (21). Analogously so on the temporal side. The brain's different timescales of its neural activity are organized in a certain way which is manifest in an analogous way on the psychological side in the symptoms – neuronal dynamic surfaces in mental dynamic (Figure 1).

FROM NEURONAL TO MENTAL TOPOGRAPHY – SPATIAL ORGANISATION OF PSYCHOPATHOLOGICAL SYMPTOMS

The Brain's Inner Space and its Global Topography

The brain exhibits a particular organisation and hierarchy of its own inner space, an "inner neuronal space". Such inner neuronal space is manifest in a particular neuronal topography that distinguishes the brain's inner space from the outer space of the world (22,23). While there are extensive studies about how the neural correlates of our perception and cognition of the world's outer space, the brain's inner space, that is, its "operational space" has just come recently to our attention (24).

How can we measure the brain's global activity and thus its inner space? One way to measure ongoing brain activity is the global signal (GS) in fMRI (25–27). However, when speaking of GS, fMRI researchers are first confronted with a controversy as to whether to remove GS or not from the signal (28,29). Many studies suggest to regress the global signal from rest and task data in fMRI (30–32) as GS has been associated with mere noise stemming from extra-neuronal sources like respiration (33,34). Recent evidence, as described below, points out that GS is not mere non-neuronal noise and thus mere artifact but carries important physiological and possibly cognitive function (27,29,35–37). Hence, GS seem to be physiological and reflect 'real' neuronal activity that, as we postulate, may mediate the ongoing activity's role as neuronal baseline.

Several studies combined GS in fMRI with electrophysiological measurements in mainly monkeys and humans (38–41). One key electrophysiological feature of GS is that it is related to the bandpower of different frequency ranges in different ways. For instance, infraslow frequency ranges (IFS) (<0.1 Hz) show a much higher relationship, i.e., correlation with GS than faster frequencies like those in the slower (0.1–1 Hz), and faster ranges (1–100 Hz) (38,39).

Together, these studies document that GS is not mere non-neuronal noise, i.e., an artifact but is based on 'real' neuronal activity. Specifically, these results show that GS is strongly driven by the long cycle durations of the very slow, i.e., infraslow frequencies (<0.1 Hz) and less so by the faster frequencies. The differential contributions of slow and fast frequencies to GS seems to be a function of both frequency range and cortical distance. Several studies showed that delta/theta (1–8 Hz) and faster frequencies (40–80 Hz) contribute strongly to the extension of neural activity on the cortical level, i.e., GS (38–41).

In contrast, the faster alpha/beta range (10–30 Hz) is not related to such global extension but remains rather local as in visual cortex and thalamus. Accordingly, the slower the frequency range, the more and stronger its contributions to the global extension of neural activity across longer cortical distances as measured by GS (38–41).

Do changes in the brain's global neuronal topography shape the organisation of our experience and cognition in abnormal ways in psychiatric disorders? Building on the assumption of "common currency" (14), SPP assumes that topographic changes on the neuronal level, i.e., neuronal topography, resurface on the cognitive and thus level in a more or less corresponding way, i.e., mental topography. Providing support for that is the main goal of the spatial dimension of Spatiotemporal Psychopathology; this will be shown in the following.

Abnormal GS and its Topography in Schizophrenia

Schizophrenia is characterized by changes in both GS and its topography. Yang, et al. (2014, 2017) first observe significantly higher levels of GS across the whole brain in two schizophrenia samples. In addition to the level of GS, in a later study from the same group, topographical differences are also observed in schizophrenia (42,43). Yang, et al. (2017) report significant GS representation decreases in sensorimotor networks in schizophrenia while it is increased in higher-order association networks (43). Further, lower-order sensorimotor and higher-order association networks' GS anti-correlate in healthy subjects which is highly diminished in schizophrenia. In another study, Wang et al. (2019) demonstrate that this topography can be subdivided into different states whose dynamic alternations in sub-states were correlated with clinical scales.

However, findings are not fully consistent in schizophrenia. Argyelan, et al (2014, 2015) (44,45) reported decreased (rather than increased) global functional connectivity (FC) in unmedicated patients with schizophrenia which also correlates with their decreased processing speed in cognitive tasks (see Hahamy, et al. (2014) for similar findings of GS reduction in schizophrenia) (46). The inconsistences may relate to different approaches in measuring GS topography, as Yang, et al. (2017) used beta value in GS regression while the other studies employed global brain connectivity or different weights of non-neuronal noise in GS (43).

Together, these findings demonstrate that schizophrenia exhibits abnormalities in both GS and its topography in lower-order sensory and higher-order cognitive regions. Abnormal GS topography, in turn, may contribute to the various perceptual and cognitive behavioral abnormalities like the confusion of internally– and externally-oriented cognition as it is typical for schizophrenic symptoms like delusion, thought disorder, passivity phenomena, auditory hallucination, and ego-disturbances (47,48).

Abnormal GS Topography in Other Psychiatric Disorders

Unlike elevated GS level in schizophrenia, findings in bipolar disorder (BD) show normal levels of GS (49,50). However, GS topography is abnormal in these patients. Zhang, et al. (2019) show increased GS representation in motor cortex in mania which, most likely, is related to their increased motor activity, i.e., psychomotor agitation (49). While in bipolar depression the hippocampus exhibits increased GS as possibly related to the increased autobiography memory recall in these patients (49). Hence, abnormal shifts in GS topography may be related to corresponding shifts or misbalances in behavior and cognition as in motor activity and memory recall (Figure. 2).

One may assume that these subjects' resting state activity in hippocampus (depressive episode) and motor cortex (manic episode) may display elevated GS-based activity levels in rest that are "normally" only observed in task states (like during motor or autobiographical memory recall tasks, see Zhang, et al. (2020);, Zhang, et al. (2019 for such suggestion) (27,49). However, the assumption of such "virtual" task-like states being already present during the resting state needs to be investigated in future studies probing real tasks; if the hypothesis is correct, one would expect decreased task-related activity and smaller or no rest-task differences (46).

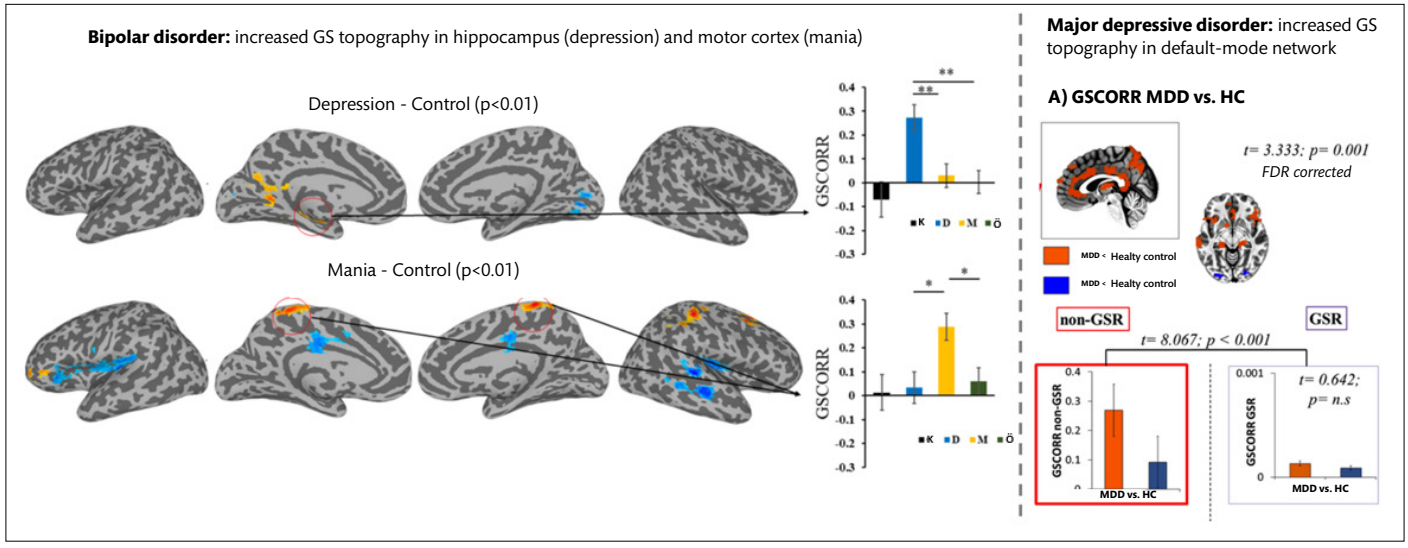


Figure 2. Altered global signal (GS) topography in different psychiatric disorders
The GS topography is significantly altered in the different phases of bipolar disorder, with increased GSCORR in hippocampus (and parahippocampus/fusiform gyrus) in bipolar depression and motor cortex in bipolar mania (49). In major depressive disorder, the GS topography is increased in default-mode regions that shows abnormally strong global functional connectivity with all other regions, i.e., non-DMN in the rest of the brain (53). C: Control group; D: Depression; E: Euthymic; GS: Global signal; GSCORR: Global signal correlation; GSR: Global signal regression; HC: Healthy control; M: Mania; MDD: Major depressive disorder.

Alterations in GS topography can also be observed in other psychiatric conditions such as autism and attention deficit hyperactivity disorder (50,51). Yet another condition is major depressive disorder (MDD). Clinically, MDD is characterized by increased internally-oriented cognition like mind wandering, i.e., rumination, and self-referential thought which are typically associated with increased regional/network activity in default-mode network (DMN). Various fMRI findings observe abnormal GS correlation to the regions in DMN regions like medial prefrontal cortex and hippocampus, which correlates with depressive symptoms and predicts treatment response (52–56).

Most recently, Scalabrini, et al. (2020) demonstrate that abnormal within-DMN FC is related to alterations in GS topography (53). Specifically, the FC of non-DMN networks to the DMN is significantly higher in MDD than in healthy subjects – the DMN thus seems to "enslave" the non-DMN networks. Moreover, the degree of DMN-non-DMN FC, i.e., the abnormal GS topography, could predict clinical diagnosis to a high degree, i.e., 90%, as revealed in vector machine learning. Together, these findings suggest abnormal global-to-local shift of GS topography towards DMN where GS is represented in increased degrees at the expense of its representation in non-DMN (Figure. 2).

Following the neuronal shift of GS towards the DMN, the behavior in MDD may also shift from non-DMN related externally-oriented cognition to abnormally strong representation of internally-oriented cognition – this is exactly what can be observed in symptoms like increased mind wandering, i.e., rumination, and self-referential thought, i.e., increased self-focus (7,18,57). We therefore hypothesize that abnormal GS topography with its abnormally increased shift from non-DMN to DMN may be closely related to the abnormal shift towards internally-oriented cognition, i.e., increased self-focus, mind-wandering, and autobiographical memory retrieval, at the expense of externally-oriented cognition, i.e., decreased environment-focus with decreased perception (Figure. 2) (7,18).

FROM NEURONAL TO MENTAL DYNAMIC – TEMPORAL ORGANISATION OF PSYCHOPATHOLOGICAL SYMPTOMS

Inner Time of the Brain – Neuronal Dynamic

How about the brain's inner time? The brain's spontaneous neural activity can be characterized by different frequencies ranging from infraslow (0.01–0.1 Hz), over slow (0.1–1 Hz), fast (1–40 Hz) to ultrafast (40–180 Hz) (58). Power is strongest in the infraslow range and decreases across the slow, fast and ultrafast ranges following a power law distribution (59,60). Together, the different frequencies and their distinct degrees of power constitute a complex temporal structure in the brain's spontaneous activity which, in large parts, can be featured by the balance between infraslow, slow, and faster frequencies.

The relationship between these frequencies is maintained across different temporal scales and can therefore be characterized by what is described as "scale-free dynamics" (61,62). Roughly, scale-free activity describes the fractal (i.e., self-similar) organisation and thus temporal nestedness in the relationship between power and the different frequency ranges: the longer and more powerful slower frequencies nest and contain the shorter and less powerful faster frequencies – this amounts to long-range temporal correlation (LRTC) which operates across different time scales or frequencies (59–63).

The LRTC makes it possible to assess the degree to which past neuronal patterns exert their influence on future dynamics, thus accounting for LRTC (61,63). That amounts to a form of memory that is here defined not by specific contents that are encoded, stored, and recalled or retrieved. Instead, memory refers here to the structure, the temporal structure of the neural activity across distinct time points. One could thus speak of temporal memory or dynamic memory, i.e., process– and structure-based memory, as distinct from the more content-based cognitive memory in the traditional sense (64,65). Accordingly, LRTC and henceforth scale-free activity provide not only temporal stability through their correlation of different timescales, i.e., temporal continuity, but also temporal memory, i.e., temporal stability, through connecting past, future, and present timepoint.

Yet another feature of the brain's inner time are its different timescales. The brain's neural activity in the resting state constitutes temporal windows of various durations including long and short – these timescales are called "intrinsic neural timescales" (INT) (66,67). The temporal windows of the INT are based on the degree to which neural activity auto-correlates with itself over time as it can be measured by the autocorrelation window (ACW). Various studies showed a hierarchical topography of INT with shorter time windows in the sensory unimodal regions, the periphery, while longer time windows can be observed in the associative transmodal regions like prefrontal cortex, the core (68–70).

Why and how is the brain's inner time, its LRTC and INT, are important for cognition? Recent studies shows that both LRTC and INT are key in mediating our consciousness and self (60,71–76). Since both consciousness and self are also altered in various psychiatric disorders, the brain's inner time with its LRTC and INT may be key in understanding psychopathological symptoms. Specifically, building on the "common currency" assumption, SPP assumes that changes in the brain's neuronal dynamic are manifest in more or less analogous changes in dynamic of the psychopathological symptoms, i.e., mental dynamic (14,77). Providing support for that is the main goal of the temporal dimension of Spatiotemporal Psychopathology.

Intrinsic Neural Time Scales in Autism

Are intrinsic neural timescales relevant for behavior and cognition? Evidence for that comes from their changes in psychiatric disorders. A recent resting state fMRI study applied the ACW in subjects with autism (78). They observed significantly shorter ACW in primary sensory regions (visual, sensorimotor, auditory) in adult autism spectrum disorder (ASD) compared to healthy subjects; these changes correlated negatively with the severity of autism. In contrast, ACW in right caudate was significantly longer in ASD which also correlated with the degree of repetitive restrictive behavior in ASD subjects.

They then investigated fMRI resting state ACW an adolescent children ASD dataset where they obtained similar ACW changes in the same regions including analogous correlation results. This means that there is a developmental component to the intrinsic timescales. That was complemented by investigating the neuro-anatomical basis through calculating the local grey matter volume. Significant positive correlation of local grey matter volume with the duration of ACW in the same region was observed which also hold for the regions altered in ASD. Finally, they calculated mediation analysis showing the grey matter volume in the above-mentioned regions were mediated in their impact on autistic symptoms by the duration of the ACW (78).

The relevance of intrinsic timescales in autism is further supported by another fMRI resting state study in ASD (79). They calculated the Power-Law Exponent (PLE) (and spectral entropy) and observed that ASD showed increased PLE with stronger power in slow frequencies in specifically regions of the salience network (insula, supragenual anterior cingulate cortex, thalamus). Moreover, they demonstrated that such increased PLE in salience network was not observed in schizophrenia. Moreover, this was specific for PLE whereas other measures like regional homogeneity

(REHO) and neural variability did not show any changes in these regions in ASD. These results hold the promise that intrinsic neural timescales may serve as marker for differential diagnosis of ASD, schizophrenia, and other psychiatric disorders.

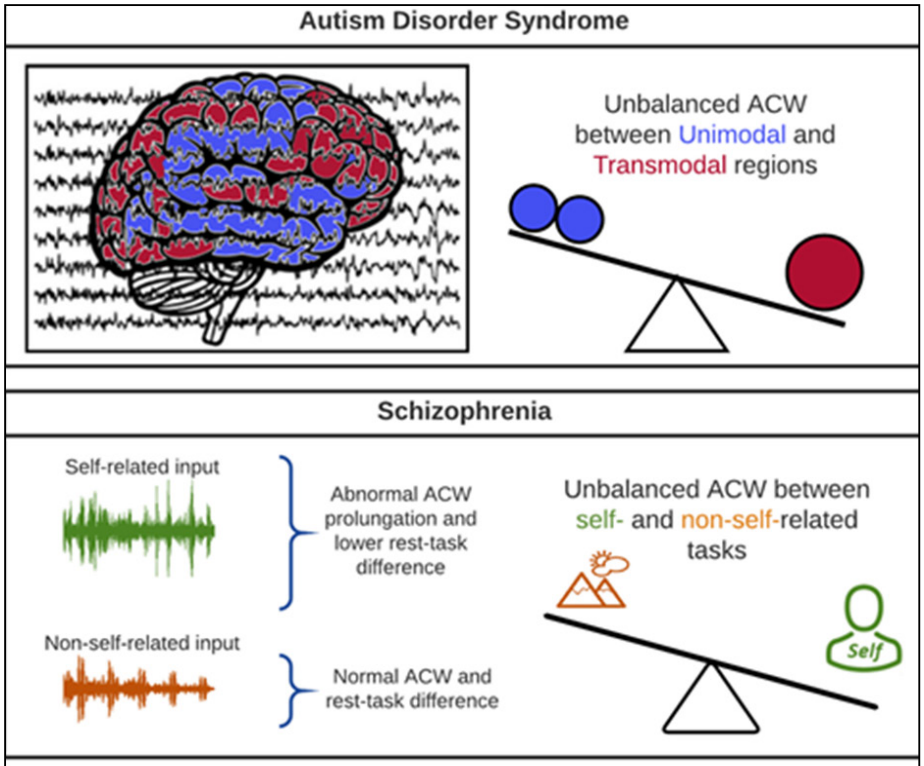
Intrinsic Neural Time Scales in Schizophrenia

One recent study in schizophrenia including mostly post-acute first-episode subjects showed abnormally long ACW (and high PLE) in several electrodes during a task state involving self-specificity (i.e., enfacement task) (46). They also demonstrated that the degree of change in ACW from rest to task was significantly lower in schizophrenia subjects, that is, unlike in healthy subjects, they barely shortened their ACW during the task. Abnormal prolongation of ACW was further confirmed in a larger EEG sample of 100 patients with schizophrenia which, interestingly went along with decreased phase coherence (during an auditory oddball paradigm).

Is the abnormal prolongation of ACW related to psychopathological symptoms? Applying moderation model, Northoff et al. (2021) showed that the degree of ACW mediated the relationship between self-disturbance and negative symptoms in participants with schizophrenia (46). As in the autism study by Watanabe and colleagues (2019), these data support the assumption that changes in intrinsic neural timescales may be related to psychopathological symptoms and, more generally, be relevant for behavior and cognition of schizophrenia (78).

This is further supported in a recent fMRI study on psychosis in schizophrenia. Wengler et al. (2020) show that the progressive hierarchical prolongation of INT from peripheral to more central regions in the sensory input streams (auditory, visual, somatosensory) is not present anymore in schizophrenia: these subjects no longer show longer INT in higher-order transmodal regions compared to lower-order sensory regions (80).

Importantly, the balance of the two extreme ends (unimodal, transmodal) of the sensory input streams was reversed in opposite ways in hallucination and delusion thus showing some topographic-dynamic specificity for particular symptoms (80). The assumption of changes in the hierarchical progression of INT in fMRI is further evidenced in another study who also found INT changes in somatosensory and visual input regions of schizophrenia which, importantly, also correlated with symptom severity (81).



Psychiatric Disorder	Rest	Task
Autism Spectrum Disorder	↓ ACW - Primary sensory regions ↑ ACW - Right caudate ↑ PLE - Salience network	---
Schizophrenia	↔ PLE - Salience network	↓ Rest-task change: poor shortening of ACW during self-related task ↑ ACW/PLE - self-related task ↔ ACW - no change in non-self task

Figure 3. Unbalanced ACW in unimodal vs. transmodal regions and self-related vs. non-self-related tasks. The different lengths of ACW observed in subjects with autism and schizophrenia compared to healthy subjects suggest that changes in the intrinsic neural timescales may be associates to the psychopathological symptoms of these disorders, in terms of cognitive and behavioral performances.

Together, these findings strongly support changes in the INT of schizophrenia including their relationship to psychopathological symptoms like self-disturbances, delusions, hallucinations, and global symptom severity. This holds the promise of INT (and other measures of temporal dynamic) being key in serving as symptom-specific markers as well as for differential diagnosis of for instance autism, schizophrenia and depression (Figure. 3) (79,82).

CONCLUSION

One of the key issues in current psychiatry is that we still lack proper understanding of the psychopathological symptoms and how they are connected to the brain's neuronal changes. Various forms of psychopathology including those focusing on the experience of the symptoms themselves and the ones more linking them to the brain's cognitive functions have been proposed. This leaves open the connection of brain and symptoms, though.

Spatiotemporal Psychopathology provides a novel approach in that it aims to bridge the gap of brain and symptoms. Specifically, Spatiotemporal Psychopathology proposes that brain and symptoms share an underlying spatial and temporal organisation as their "common currency" (14,15). This shifts the focus to the brain's inner time-space, that is, its neuronal dynamic and topography, and how these surface in the spatial and temporal organization of the psychopathological symptoms, i.e., neuronal and mental topography.

We here demonstrate several examples of such spatiotemporal approach in various psychiatric disorders including depression, bipolar disorder, schizophrenia and autism. These show that, despite being in its initial stages, Spatiotemporal Psychopathology provides a promising approach for linking brain and symptoms through space-time, i.e., topography and dynamic. This is not only relevant for a deeper and better understanding of psychopathological symptoms but also for their clinical differential diagnosis and ultimately for therapeutic intervention.

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