



# How do resting state changes in depression translate into psychopathological symptoms? From ‘Spatiotemporal correspondence’ to ‘Spatiotemporal Psychopathology’

Georg Northoff<sup>a,b,c,d,e</sup>

## Purpose of review

To review the recent findings in resting-state activity in major depressive disorder (MDD) and link them to psychopathological symptoms.

## Recent findings

MDD shows changes in resting state functional connectivity (rsFC) mainly within the default-mode network with a focus on especially the perigenual anterior cingulate cortex. rsFC in perigenual anterior cingulate cortex is abnormally high in MDD and decreased in the lateral prefrontal cortex with the central executive network (CEN). rsFC in other networks like the salience network, including the insula, amygdala, and supragenual anterior cingulate cortex and the sensorimotor network is also affected in MDD.

## Summary

Resting-state activity in MDD shows abnormal topographical and spatiotemporal pattern. The spatiotemporal alterations in resting state may translate into corresponding spatiotemporal changes underlying the sensorimotor, affective, and cognitive functions, and thus, the various symptoms. Such spatiotemporal correspondence between resting state changes and psychopathological symptoms may make necessary the development of what I describe as ‘Spatiotemporal Psychopathology’.

## Keywords

bipolar disorder, major depressive disorder, resting state, spatiotemporal psychopathology

## INTRODUCTION

Psychiatric disorders are complex disturbances showing a wide variety of symptoms that cover most brain functions, including sensorimotor, affective, cognitive, and social functions. For instance, patients with major depressive disorder (MDD) suffer from cognitive changes as manifest in ruminations, affective changes that predominate here with anhedonia, sensorimotor abnormalities are manifest in psychomotor agitation or retardation, and social dysfunctions can be often observed as related to social withdrawal and isolation.

Neuroimaging using techniques like functional MRI (fMRI) and electroencephalography (EEG) has focused on extrinsic activity that concerns the brain’s response to sensorimotor, cognitive, affective, or social stimuli or tasks [1], that is, stimulus-induced or task-evoked activity. For all the progress in investigating the brain’s extrinsic activity and its various functions, diagnostic or therapeutic markers

still remain nevertheless, elusive though. In its search for these specific markers, recent neuroimaging in psychiatry has shifted to the brain’s intrinsic activity, its so-called resting-state activity.

Roughly, the brain’s intrinsic activity or resting-state activity describes the brain’s neural activity in the absence of any specific tasks or stimuli [2,3]. The

<sup>a</sup>Institute of Mental Health Research, University of Ottawa, Ottawa, Canada, <sup>b</sup>Center for Cognition and Brain Disorders, Hangzhou Normal University, Hangzhou, China, <sup>c</sup>Center for Brain and Consciousness, Department of Radiology and Psychiatry, Shengho Hospital, <sup>d</sup>College for Humanities and Medicine, Taieph Medical University (TMU), Taieph, Taiwan and <sup>e</sup>ITAB, University of Chieti, Chieti, Italy

Correspondence to Georg Northoff, MD, PhD, FRCP Royal. Ottawa Healthcare Group, University of Ottawa Institute of Mental Health Research, 1145 Carling Avenue, Room 6467, Ottawa, ON K1Z 7K4, Canada. Tel: +613 722 6521 Ext. 6801; fax: +613 798-2982; e-mail: georg.northoff@theroyal.ca; Website: www.georgnorthoff.com

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## KEY POINTS

- Patients with MDD show spatial abnormalities in their resting state in medial and lateral frontal regions.
- Patients with MDD show temporal dysbalance with relative shift toward lower frequencies (1–8 Hz).
- The resting state's spatiotemporal abnormalities may manifest in and correspond to the spatiotemporal features underlying the various psychopathological symptoms entailing 'spatiotemporal correspondence'.
- Spatiotemporal correspondence between resting state and psychopathological symptoms may ultimately lead to the development of 'Spatiotemporal Psychopathology'.

brain's intrinsic activity can spatially be characterized by various neural networks consisting of regions showing close 'functional connectivity' yielding a particular spatial structure (see below). The same applies to the temporal domain, where fluctuations in different frequency ranges are coupled with each other, providing a certain temporal structure [3,4]. Neuroimaging reports a variety of changes in both functional connectivity and neural synchrony (see below) in MDD with their exact meaning for the diverse psychopathological symptoms remaining unclear though. I conclude that the various psychopathological symptoms in cognitive, affective, sensorimotor, and social domains may result from abnormal spatiotemporal structuring as related to the underlying resting state. We may consecutively need to develop what I describe as 'spatiotemporal psychopathology' [5<sup>•</sup>,6].

### Resting state-operational measures and spatiotemporal features

One should be aware that the concept of the brain's intrinsic or resting-state activity is a rather heterogeneous one and raises several methodological (see here) questions [3,7–10]. Apart from resting-state activity, other terms like baseline, spontaneous activity or intrinsic activity are also used to describe the internally generated activity in the brain [3,7,8]. Even more important, the exact relationship between resting-state activity and stimulus-induced or task-evoked activity remains unclear with some authors assuming mere additive interaction [11], whereas others presume nonlinear interaction [12,13].

Depending on the measure, resting-state activity can be characterized in metabolic-energetic, neural/neurovascular, electrophysiological/magnetic, and

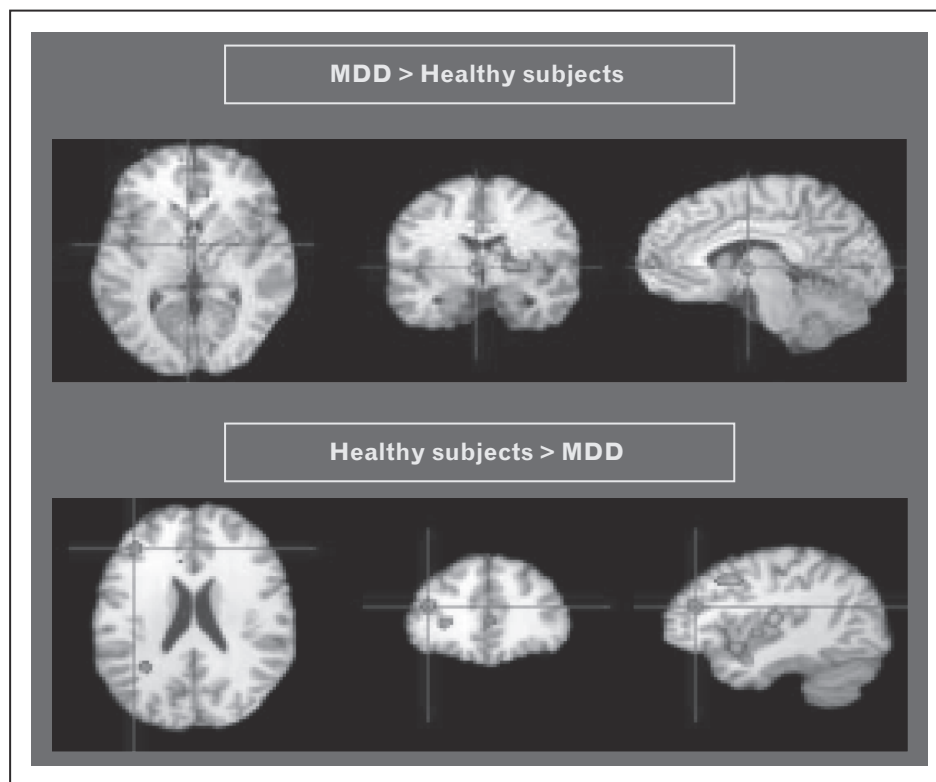
biochemical (and also psychological) terms. Resting-state activity can be measured in different ways: metabolic investigations using PET focus on measuring quantitatively the brain's energetic metabolism indicating the resting state's utilization and distribution of for instance glucose [14<sup>••</sup>]. In contrast, fMRI as relying on the blood oxygen level desaturation effects as a neurovascular (rather than metabolic) signal targets different resting state's neural networks as based on statistical, that is, correlative relationships between different regions' voxel signifying functional connectivity [15–17] (which may also depend on some methodological specifics such as global signal regression; [18,19]. Resting-state activity can also concern electrophysiological or magnetic activity as measured with EEG or magnetoencephalography [7,8] that targets neural activity changes in different frequency ranges and thus the temporal features of the resting state.

### Spatial resting state abnormalities in major depressive disorder

How about the spatial structure of the resting-state activity in MDD? [20] conducted a meta-analysis of all imaging studies in human MDD that focused on resting-state activity. This yielded hyperactive regions like perigenual anterior cingulate cortex (PACC), ventromedial prefrontal cortex (VMPFC), thalamic regions like the dorsomedial thalamus (DMT) and the pulvinar, pallidum/putamen and midbrain regions like the ventral tegmental area, substantia nigra, the tectum and the periaqueductal gray (PAG). In contrast, resting-state activity was hypoactive, and thus reduced in the dorsolateral prefrontal cortex (DLPFC), the posterior cingulate cortex and adjacent precuneus/cuneus [21,22]. The PACC and anterior midline resting state hyperactivity seems to be somehow specific for depression since in schizophrenia there is rather hypoactivity [22,23] (Fig. 1).

These results are well in accord with other meta-analyses [24–27]. Also, [26] and [28,29] emphasized the role of the hippocampus, parahippocampus, and the amygdala where resting-state hyperactivity was also evident in MDD. Interestingly, the very same regions and the PACC also show structural abnormalities with reduced grey matter volume in imaging studies and reduced cell counts markers of cellular function in postmortem studies [26,28,29].

Involvement of these regions in MDD is further corroborated by the investigation of resting-state activity in animal models of MDD. Reviewing evidence for resting-state hyperactivity in various animal models, yielded diverse participating brain



**FIGURE 1.** The figure shows resting-state activity patterns in major depressive disorder, when compared with healthy study participants. Major depressive disorder shows higher resting-state activity in anterior midline regions like the ventromedial prefrontal cortex (and also subcortical regions), whereas lateral prefrontal and other lateral regions show decreased resting-state activity.

regions – the anterior cingulate cortex, the central and basolateral nuclei of the amygdala, the bed nucleus of the stria terminalis, the dorsal raphe, the habenula, the hippocampus, the hypothalamus, the nucleus accumbens, the PAG, the DMT, the nucleus of the solitary tract, and the piriform and prelimbic cortex [20]. In contrast, evidence of hypoactive resting-state activity in animal models remains sparse with no clear results [20].

How do these regional changes translate onto the network level? As illustrated above, anterior and posterior midline regions like especially PACC and VMPFC are core regions of the default-mode network (DMN), whereas the DLPFC is part of the CEN. A recent meta-analysis of resting state functional connectivity observed the following abnormal changes in DMN and CEN in MDD [30<sup>\*\*\*</sup>]. The DMN shows functional hyperconnectivity among its regions and especially between anterior and posterior midline regions. In contrast to the regions within the DMN, regions within the CEN show functional hypoconnectivity and also less connected to parietal regions implicated in attention toward the external environment. This suggests spatial dysbalance between the two networks with an abnormal spatial shift toward the DMN and away

from the CEN with the former also enslaving the latter (as suggested by functional hyperconnectivity between DMN and CEN [30<sup>\*\*\*</sup>]; see also [31] for reciprocal modulation between DMN and CEN in healthy study participants, which may explain the findings in MDD).

In sum, the data provide evidence for opposite resting state changes in medial and lateral regions: the anterior midline regions show abnormally elevated resting state activity, whereas the lateral regions like the DLPFC show decrease in resting state activity. The observed reciprocal modulation between DMN and CEN as reported in healthy study participants [31] is well compatible with the observation in MDD, where increased functional connectivity in PACC–VMPFC, and thus, DMN is accompanied by decreased functional connectivity in lateral prefrontal cortex and the CEN [3,23,32,33<sup>\*\*\*</sup>]. One can thus speak of abnormal reciprocal modulation between DMN and CEN with their spatial balance tilting abnormally toward the former at the expense of the latter.

### Temporal resting state abnormalities in major depressive disorder

The temporal structure of the resting-state activity can be measured using EEG. EEG is predominantly

used to measure event-related potentials in response to specific stimuli thus targeting stimulus-induced or task-evoked activity. Additionally, EEG can also measure the power in different frequency oscillations including delta (1–4 Hz), theta (5–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (30–180 Hz) in resting state as during eyes open (EO) and eyes closed (EC). Resting state investigations in MDD showed consistently power increase in the lower frequency ranges like delta and especially theta [34,35,36,37] (in preparation). In contrast, power in higher frequencies like gamma does not seem to be really altered in MDD. Together, this suggests (tentatively) that the relative balance in power shifts toward low-frequency oscillations that relatively predominate over higher ones.

The abnormal temporal structure with increased theta (and delta) may also impact the spatial structure of the resting state. A combined EEG-FDG-PET study observed that resting state theta power was high in PACC/subgenual anterior cingulate (as measured with current source density in EEG) and correlated well with glucose metabolism in that same region (as measured with FDG-PET) [38]. This suggests that the increase in theta in MDD seems to be directly related to the increase in resting-state activity in PACC–VMPFC as described above. Hence, the resting state's spatial dysbalance toward the anterior DMN, that is, PACC–VMPFC, may be closely related to temporal dysbalance between lower and higher frequency oscillations.

In addition to the low frequencies, that is, delta and theta, an intermediate frequency like alpha seem to be consistently elevated in MDD (see [34,36,37,39] for reviews). Moreover, when shifting from EC to EO, alpha power shows a typical decrease, the alpha blockade. Interestingly, this alpha decrease or blockade during the shift from EC to EO is significantly lower in MDD. Alpha power has been associated with inhibition of processing and attending external stimuli, whereas its decrease is related to disinhibition as for instance during the shift from EC to EO [40]. Increase in alpha power as in MDD thus suggests increased inhibition, whereas the decreased alpha blockade may be related to the decreased capacity to disinhibit the ongoing resting-state activity. This suggests that external stimuli (as for instance during EO) can no longer properly disinhibit the ongoing resting state's alpha power any more thus showing decreased resting state reactivity; that in turn may lead to the decreased (external) stimulus processing resulting subsequently in decreased attention toward external stimuli, that is, the decreased environment focus [5].

One can also investigate the functional connectivity between different areas in EEG using measures

of coherence or synchronization. Fingelkurts *et al.* [41] and Leuchter *et al.* [42] observed increased coherence between frontopolar electrodes and posterior parietal and temporal electrodes in theta and alpha bands (but also in delta and beta bands) in MDD [43]; demonstrated that stronger coherence, for example, functional connectivity strength in delta and theta in frontopolar electrodes predicted subsequent nonresponse to antidepressant treatment [44]; and measured functional connectivity in EEG by the degree of synchronization between phase onsets, that is, lagged phased synchronization. This revealed increased alpha phase-lagged synchronization between subgenual/pregenual anterior cingulate cortex and medial prefrontal cortex (VMPFC, DMPC) and DLPFC in unmedicated MDD patients before treatment [44]. Interestingly, increased alpha coherence also predicted subsequent treatment response which went along with shift of phase-lagged synchronization to a higher frequency namely beta.

Taken together, these data suggest the increased fronto-cingulate coherence or phase-lagged synchronization in delta, theta, and alpha may be related to the analogous observations of increased anterior midline and medial-lateral functional connectivity in fMRI. We have to be careful though. Although EEG measured frequencies from 1 Hz upwards, fMRI taps into even lower frequencies at a range between 0.001 and 0.1 Hz, that is, infra-slow frequencies. The occurrence of abnormal functional connectivity (or coherence) in both fMRI and EEG suggests that both infraslow (as they are called) (fMRI: 0.001–0.1 Hz) and slow (EEG: 1–12 Hz) frequency fluctuations seem to be abnormally strong powered in resting state in MDD. In contrast, data do not suggest major abnormalities in higher frequencies like gamma (30–180 Hz).

## CONCLUSION

### From 'Spatiotemporal correspondence' to 'Spatiotemporal Psychopathology'

The findings clearly show spatial and temporal resting state abnormalities in MDD. How though can we relate these spatiotemporal abnormalities to the complex psychopathological symptoms that cover cognitive, affective, sensorimotor, and social functions? The spatial balance between PACC/DMN and DLPFC/CEN may for instance mediate the balance between internal, that is, self-related and external, that is, environmental-related mental contents. If now their resting state balance is abnormally tilted toward the PACC/DMN, one may expect internal mental contents, that is, self-related ones to

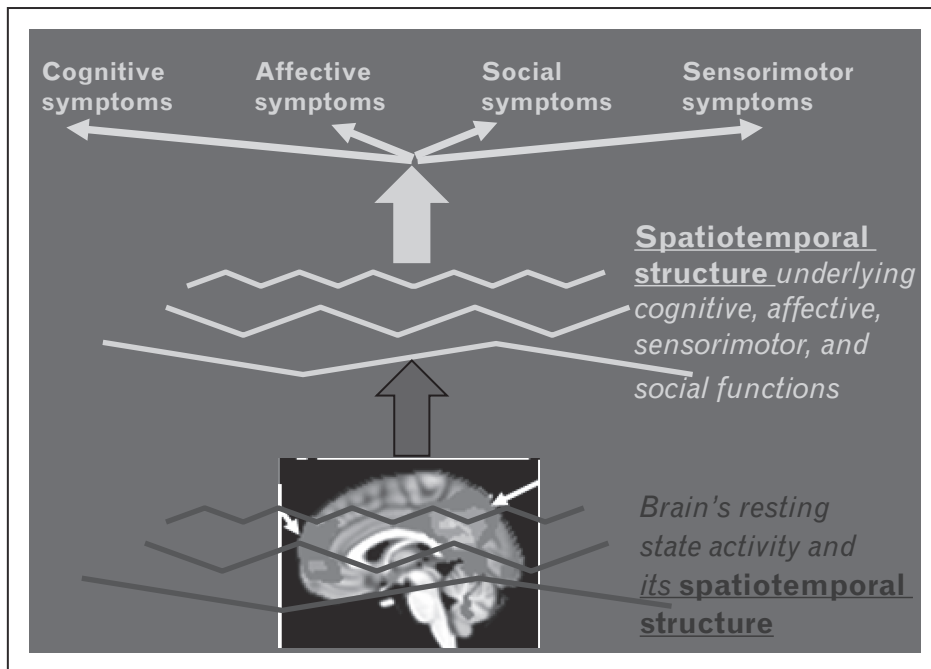
predominate over external, that is, environmental-related ones. Such spatial retreat to and focus on the own self with its internal mental contents occurs at the expense of external environmentally-oriented contents and their respective social and psychomotor functions; this shift may be manifest in symptoms like social withdrawal and psychomotor retardation. Moreover, because of their predominant processing of internal mental contents, cognitive functions like attention, working memory, episodic memory, etc. are blocked and subsequently impaired, when it comes to the processing of external mental contents from the environment leading to various neuropsychological deficits [see [5<sup>\*</sup>] for details; bipolar disorder (unpublished observations)].

How about the resting state's temporal dysbalance with the abnormal shift toward lower frequencies like delta and theta (and possibly even infraslow frequencies between 0.001 and 0.1 Hz as measured in fMRI)? Lower frequencies show longer phase cycles, whereas the latter are much shorter in higher frequencies like in beta and gamma range. The abnormal predominance of slow frequencies may literally slow the brain with decreased change as related to the at least relative decrease in higher frequencies. Such slowing of the brain's resting-state activity may in turn affect subsequent stimulus-induced or task-evoked activity as related to cognitive, affective, sensorimotor, and social functions

and their respective psychopathological symptoms: cognitive functions are slowed leading to various cognitive impairments, affective functions, and emotions do not change so that hopelessness with regard to the future predominates leading to sadness and anhedonia, sensorimotor functions are slowed as manifest in psychomotor retardation, and social functions are slowed as visible in social withdrawal.

One may consequently be inclined to assume what I describe as 'spatiotemporal correspondence': the spatial and temporal structure of the resting state may be transferred (in yet unclear ways), and therefore, correspond to the spatial and temporal structure underlying cognitive, affective, social, and sensorimotor functions. If now the resting state's spatiotemporal structure becomes abnormal, the spatiotemporal structure underlying the cognitive, affective, sensorimotor, and social functions will change too leading to the respective psychopathological symptoms. One can consequently assume spatiotemporal correspondence in the spatial and temporal structure between resting state and psychopathological symptoms.

What exactly do I mean by 'spatiotemporal correspondence'? One may want to contest that the resting state's integrated spatiotemporal nature makes the assumption that its abnormalities are spatiotemporal almost trivially true. Resting state abnormalities are by their very nature, that is, by default spatiotemporal. This is indeed banal or



**FIGURE 2.** The figure shows the supposed spatiotemporal correspondence between the resting state's spatiotemporal features and the spatiotemporal structure underlying the various psychopathological symptoms in affective, cognitive, sensorimotor, and social functions.



trivially true. However, the central point I want to make here is not about the resting state itself and its spatiotemporal nature but rather about how its spatiotemporal features translate into psychopathological symptoms: the abnormal spatiotemporal nature of the brain's resting state is supposed to directly translate into corresponding spatiotemporal abnormalities that underlie and account for psychopathological symptoms (Fig. 2).

For instance the temporal changes in the resting state as the shift to the longer cycle durations in the slow frequencies may be directly one-to-one manifest in corresponding temporal changes, that is, delays in cognitive, affective, social, and sensorimotor functions. Moreover, the exact temporal delay as manifest psychomotor slowing and retardation may be directly related to corresponding temporal slowing and delays in the frequency fluctuations in the psychomotor networks, including regions like the premotor and motor cortex. If such direct spatiotemporal correspondence with the resting state can be demonstrated for the various kinds of psychopathological symptoms in MDD and other disorders like schizophrenia ([5<sup>\*</sup>]) one may indeed speak of what I recently described as 'Spatiotemporal Psychopathology' ([6,45<sup>\*\*</sup>]).

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## Conflicts of interest

There are no conflicts of interest.

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The study introduces for the first time the concept of 'spatiotemporal psychopathology' and compares it with both past and present forms of psychopathology.