11 Why Do We Need Psychopathology? From the Brain's Resting State to "Spatiotemporal Psychopathology" of Depression

Georg Northoff

> Neither the "brainless" psychiatry of the middle of the 20th century, nor the "mindless" variety of the past 30 years should be taken to represent the most we can achieve. The future should yield a synthesis. (Panksepp 2004, p 17)

11.1 Introduction

Neuroscience has made enormous progress in the last 20–30 years on all levels ranging from the genetic over the molecular to the regional and network level of neural activity. This has also affected psychiatry as in Biological Psychiatry. Various psychiatric disorders including schizophrenia, major depressive disorder (MDD), and bipolar disorder (BP), as well as others like addiction, personality disorders, etc. show molecular, genetic, regional, and network abnormalities in the brain. However, despite all progress in Biological Psychiatry, we still fall short in explaining the exact neuronal mechanisms of the various psychopathological symptoms. Specifically, Biological Psychiatry cannot yet explain how the brain's neuronal changes transform into the mind's alterations, the psychopathological symptoms.

Traditionally, the explanation and understanding of psychopathological symptoms have been the focus of psychopathology. Put in a nutshell, psychopathology concerns the empirical and theoretical framework in which symptoms, behavior, and experiences in psychiatric patients can be described, categorized, and classified (Parnas et al. 2008, 2013; Stanghellini 2009a, b; Stanghellini and Broome 2014). Different empirical and theoretical frameworks have been suggested in past and present approaches to psychopathology. However, how the different approaches to psychopathology (see below for details) are linked to the brain and its various neuronal mechanisms remains unclear.

Taken all together, we are facing a divide between Biological Psychiatry and Psychopathology. The advocates of Biological Psychiatry tend to claim that all we need is the brain: the more we understand the brain and its abnormal changes in psychiatric disorders, the better we will understand and explain the psychopathological symptoms. This makes psychopathology as separate scientific discipline (Stanghellini and Broome 2014) meaning- and senseless and thus superfluous. Conversely advocates of psychopathology resist such interpretation. There is "more" to psychopathological symptoms than just the brain, and this "more"

G. Northoff
Mind, Brain Imaging and Neuroethics Research Unit, Institute of Mental Health Research, University of Ottawa, Ottawa, Canada

Royal Ottawa Mental Health Centre, Ottawa, Canada
e-mail: Georg.Northoff@theroyal.ca

Y.-K. Kim (ed.), *Understanding Depression* , https://doi.org/10.1007/978-981-10-6580-4_11

consists in the central role of experience or consciousness, i.e., the mind (Parnas et al. 2008, 2013; Stanghellini 2009a, b; Stanghellini and Broome 2014). Taken in this view, Biological Psychiatry remains as "mindless" as Psychopathology is "brainless," to pick up our initial quote.

How can we resolve the divide between brain and mind/symptoms and thus Biological Psychiatry and Psychopathology? The aim in this paper is to show that a novel approach, "Spatiotemporal Psychopathology," can bridge this divide by providing a "common currency" between brain and symptoms—that "common currency" is supposed to consist in spatiotemporal features that transform abnormal neuronal activity in psychopathological symptoms.

11.2 Spatiotemporal Psychopathology: Determination and Distinction

11.2.1 Psychological Approaches to Psychopathology

Roughly, one may want to divide between psychological and experiential approaches to psychopathology. Psychological approaches focus on specific psychological functions like cognitive or affective-cognitive as in cognitive psychopathology (David and Halligan 2000; Halligan and David 2001) and affective psychopathology (Panksepp 2004). With the development of neuroimaging, these approaches are now able to link the objectified changes in cognitive and affective functions onto the brain. However, such "mapping" of cognitive into neural functions leaves open how and why abnormal changes in the brain's neural activity are transformed into psychopathological symptoms.

How can more strongly link cognitive and affective and cognitive functions to the brain and its neuronal mechanisms? We would need to unravel a yet unclear "common currency" that allows to transform neuronal into psychological activity. To be clear, I am not raising the question which regions or networks in the brain are related to cognitive functions. Such "cognitive-neural mapping" has been well established in cognitive neuroscience that showed how cognitive functions like executive functions, attention, memory, etc. are related to specific regions or networks in the brain (Gazzaniga 2010). This and the respective changes in those regions and networks have been well researched intensely over the last 10–20 years. Instead, I am raising the question why and how the brain's neuronal activity in those regions and networks transforms into cognitive (and affective functions) rather than remaining merely neuronal (and non-cognitive).

What is needed is a "common currency" between neural and cognitive functions—due to such yet unclear "common currency" neural activity translates into cognitive function basically by default. And it is this transformation or translation that seems to be altered in psychiatric disorders that can indeed be characterized by numerous cognitive deficits (see, for instance, Barch et al. 2016 in schizophrenia). I postulate that the spatial and temporal features of the brain's spontaneous activity provide such "common currency"—cognitive symptoms are spatiotemporal symptoms for which reason I speak of "Spatiotemporal Psychopathology."

11.2.2 "Common Currency" Between Brain and Cognition

We are confronted with a divide between the brain on the one hand and cognition on the other. Biological Psychiatry focuses on the brain while leaving out the mind and its experience. While psychological approaches to psychopathology focus on cognitive functions and the relation of their contents to the brain. Neither has yet provided a full-fledged explanation and understanding of psychopathological symptoms though. We are thus confronted with a divide between brain and cognition.

Psychological approaches to psychopathology focus on contents, i.e., cognitive, affective, sensorimotor, and social contents and their related functions. The cognitive, affective, sensorimotor, and social contents are then "mapped" upon the

brain and its various regions and networks—this is where psychological approaches to psychopathology converge with Biological Psychiatry. This neglects one central dimension of the contents though. The contents are organized and structured in a particular way, and this organization is mainly spatial and temporal. Spatiotemporal Psychopathology as suggested here focuses on the temporal and spatial organization of the contents rather than the nature of the contents themselves, i.e., cognitive, affective, sensorimotor, or social.

Spatiotemporal Psychopathology aims to unravel the spatiotemporal organization and structure within which the various kinds of contents are embedded hence the name "Spatiotemporal Psychopathology." Alterations in cognition in psychiatric disorders are consequently not related to specific contents, i.e., cognitive, affective, etc. Instead, abnormal cognition is related and traced to abnormal spatial and temporal organization within which the contents are embedded.

Let us give an empirical example. Duncan et al. (2015) recently demonstrated that early childhood traumatic experience is manifest in adulthood in the spatiotemporal patterns of the brain's spontaneous activity (as indexed by entropy) which, in turn, impacts subsequent stimulus-induced activity in relation to aversive stimuli. The early childhood traumata were thus encoded in terms of spatiotemporal features, i.e., entropy, rather than in terms of specific contents and cognitions. Sure, the very same spatiotemporal pattern impacts the contents and their subsequent cognition—however, it is clear that the latter has a spatiotemporal basis in the spatiotemporal features of the brain's spontaneous activity. Hence early childhood trauma is primarily a matter of spatiotemporal organization of the contents, i.e., life events, rather than being directly related one to one to the life event and its content itself.

Taken together, the spatiotemporal organization of the brain's spontaneous activity may provide the "currency" that translates directly into the cognitive level with the cognition of contents. Spatial and temporal features as manifest in both the brain's spontaneous activity and our cognition of contents may consequently provide the "common currency" between brain and cognition. Changes in cognition as in psychiatric disorders may then be traced to alterations in the resting state's spatial and temporal features. This would link the psychological approaches to psychopathology even more tightly to the brain while, at the same time, providing a new view on the brain and especially its resting state, a spatiotemporal rather than cognitive view (Northoff 2014a).

11.2.3 Experiential Approaches to Psychopathology

In contrast to psychological approaches to psychopathology, experiential approaches focus on the subject's experience, i.e., subjective experience, of self, world, and body rather than on objectified cognitive and affective functions. The hallmark experiential approach is Phenomenological Psychopathology which takes the subject's experience of self, body, and world and thus the structure of its consciousness as explanatory framework for psychopathological symptoms (Jaspers 1963; Fuchs 2007, 2013; Northoff 2015b; Parnas et al. 2008, 2013; Stanghellini 2009a, b; Stanghellini and Broome 2014).

Siblings of Phenomenological Psychopathology include existential psychopathological that focuses on the existence as the deeper layer underlying experience and the hermeneutical psychopathology that emphasizes the meaning of symptoms in a wider biographical and environmental context (Stanghellini 2009a, b). Despite the difference in focus or emphasis, the overall explanatory framework in all three approaches consists in experience or consciousness for which I reason I subsume under the "experiential approaches" to psychopathology.

Phenomenological Psychiatry takes experience or consciousness itself as starting point and focuses on exploring first-person experiences in detail (Parnas et al. 2008, 2012; Stanghellini 2009a, b). Specifically, the focus is on the first-person experience of time and space as well as body, self, and world. The brain, in contrast, nowhere surfaces in experience in particular, and

phenomenology in general, since it cannot be accessed in experience in first-person perspective but only in observation as in third-person perspective. The brain is thus excluded in experience of the own self, body, and world including time and space in particular and phenomenology in general. Such exclusion of the brain in experience or consciousness occurs by default, e.g., on methodological grounds, since the brain cannot be accessed in experience in first-person perspective. Importantly, this leaves the link to the brain open and renders the experiential approaches to psychopathology ultimately as "brainless" (as picking up our initial quote).

11.2.4 "Common Currency" Between Brain and Experience

How can we close the gap between experience and the brain? Closing this gap is central for psychiatry since we need to understand the processes that transform abnormal neuronal into phenomenal states which psychiatric patients experience in first-person perspective. How can we apprehend these transformative processes, e.g., neuronal-phenomenal transformation? For that we may want to search for a shared overlap or "common currency" between neuronal and phenomenal states that drives the transformation of the former into the latter.

The shared overlap or common currency between neuronal and phenomenal states, e.g., brain and experience, may consist in spatiotemporal features. On the side of the brain, it is the spontaneous activity (rather than its stimulus-induced or task-evoked activity) that may be central in providing or constituting such spatiotemporal structure (see below for details). The brain's spontaneous activity shows certain spatiotemporal features, a particular spatial and temporal structure in its neural activity that surfaces in and is transformed into phenomenal state, e.g., experience (see Northoff 2014a for many examples). One would consequently expect a common, similar, or analogous spatiotemporal structure between the brain's spontaneous activity and the phenomenal features of experience.

Such common, similar, or analogous spatiotemporal structure between brain and experience amounts to what I describe as "spatiotemporal correspondence." The concept of spatiotemporal correspondence means that the brain's spontaneous activity and the phenomenal features of experience show corresponding or analogous spatial and temporal features: the spatial and temporal configuration or structure of the neural activity in the brain's spontaneous activity surface in the spatial and temporal features within which the contents of experience (like specific objects or events including body, self, and world) are integrated and thus structured and organized.

For instance, a recent study of ours demonstrated that private self-consciousness is directly related to the temporal patterns of spontaneous or resting state activity across different frequency ranges (as indexed by what is described as "power law") (Huang et al. 2016). This suggests that mental features like self may be rooted in spatiotemporal features of the brain's spontaneous activity. The self as mental feature may then be characterized in spatiotemporal terms, that is, by specific spatiotemporal schemata or structure rather than by cognition of particular contents (see Fig. 11.1).

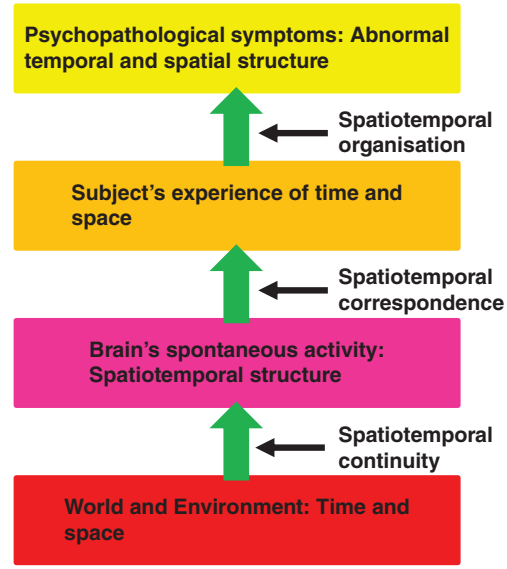

Fig.11.1 Different levels in Spatiotemporal Psychopathology

Unlike Biological Psychiatry that focuses on the brain itself independent of its respective ecological context, Phenomenological Psychiatry emphasizes the integration of experience including the subject of experience within the ecological context of the world. There is continuity between experience and world with such continuity often assumed to be mediated by the body, e.g., experience of the body as lived body (see, for instance, Northoff and Stanghellini 2016). Such continuity between subject and world is deemed central for making experience including the first-person perspective itself first and foremost possible.

11.3 Spatiotemporal Psychopathology: Depression and Bipolar Disorder

11.3.1 Spatiotemporal Psychopathology: Bipolar Disorder and Neuronal Variability

How about spatiotemporal changes in the resting state in bipolar disorder (BP)? Several resting state investigations observed changes in functional connectivity in the default mode network in bipolar disorder though the phases, i.e., depressed, euthymic, and manic, are rarely specified (see Martino et al. 2016a). Going beyond functional connectivity, we investigated neuronal variability in different resting state network in manic, euthymic, and depressed phases of BP as well as healthy subjects. Neuronal variability is measured by the root means square of the amplitude; in that it reflects the change in the amplitude over time and the degree to which these changes vary over time. Taken in this sense, neuronal variability can be considered a measure of the temporal structure and, more specifically, the temporal dynamics of the ongoing spontaneous activity.

We focused on neuronal variability (SD) in the main neural networks, default mode network (DMN), central executive network (CEN), salience network (SN), and sensorimotor network (SMN) (Martino et al. 2016b). Depressed BP patients showed significantly decreased SD in the sensorimotor network, while their SD was significantly increased in the DMN. The other neural networks like SN and CEN did not show any SD changes. We then calculated the ratio or balance between DMN SD and SMN SD; this was tilted significantly toward the DMN SD at the expense of the SMN SD.

What does this mean? Neuronal variability may be linked to the initiation of internally directed cognition in DMN and movements/actions in SMN. The more often the neuronal variability change surpasses a certain threshold, the more often the respective regions internally, i.e., by itself independent of external stimuli, initiate either cognition or action. Let us be more specifically regionally. The DMN has been associated with internally directed cognition as in spontaneous cognition and mind wandering (Kristoff et al. 2016; Smallwood and Schooler 2015). If now neuronal variability is abnormally high in the DMN, there is a higher likelihood that spontaneous thoughts will be initiated. This is exactly what one can observe in depressed BP where the patients suffer from increased spontaneous thought which are described as rumination.

How about the SMN? In that case, neuronal variability may be related to the spontaneous or internal initiation of movements and actions. If now neuronal variability in SMN is decreased, one would expect decreased internal initiation of movements and actions. This, again, is exactly what can be observed in depressed BP where patients often suffer from psychomotor retardation. Most interestingly, it seems that the balance between DMN SD and SMN SD is central since the balance correlated significantly positively with depressive symptoms (as measured with Hamilton depression scale): the more the SD balance was shifted toward the DMN at the expense of the SMN, the more and stronger depressive symptoms.

The reverse could be observed in the manic phase. Here SD was significantly lower in the DMN and abnormally high in the SMN; the balance between DMN SD and SMN SD is consequently tilted toward the SMN at the

expense of the DMN. This is symptomatically manifest in increased internal initiation of movement/action as it is reflected in the well-known psychomotor agitation in mania. In contrast, internally directed cognition like spontaneous thought are no longer initiated internally as much—this is reflected in the fact that many manic patients say "that they do not think much or not at all" in the manic episode.

11.3.2 Spatiotemporal Psychopathology: From Neuronal Variability to Cognition and Experience

What do these findings tell us about the nature of psychopathological symptoms? There is still internal initiation of movements as related to SMN and internally directed cognition, i.e., spontaneous thought as based on DMN. However, the neuronal mechanism potentially underlying such internal initiation, i.e., neuronal variability, is expressed to an abnormal degree. It is either too high or too low which leads to either increased or decreased internal initiation of the respective function. That very same neuronal mechanism is temporal, i.e., SD, and spatial, i.e., in different networks like DMN and SMN, and can therefore be considered "spatiotemporal mechanism" as I say (see Fig. 11.2).

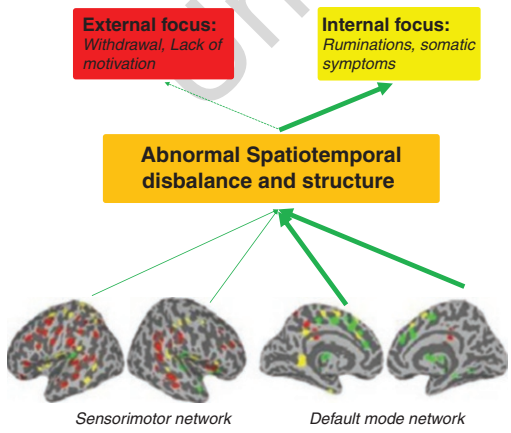

Fig. 11.2 Network disbalance and abnormal spatiotemporal structure in depression

Let me be more precise. The function, i.e., internal initiation of movements/action and internally directed cognition, is still intact by itself—the bipolar patients are still able to internally initiate them. This distinguishes psychiatric patients from neurological patients. In the latter, the region itself is lesioned which makes impossible the internal initiation of, for instance, movement and action as in Parkinson's disease. However, the function of internal initiation of movement/action and internally directed cognition is expressed in an abnormally high or low way due to some spatial and temporal abnormalities in the brain's spontaneous activity, i.e., SD in SMN and DMN. The resulting abnormalities in movement/action and internally directed cognition, i.e., the psychopathological symptoms, are thus based on and can be traced to spatiotemporal changes in the brain's spontaneous activity. Rather than being primarily motor, as in Parkinson's disease, the psychomotor changes in mania and depression are thus spatiotemporal at their very basis.

The same holds analogously for internally guided cognition. Unlike in neurological lesion patients, the bipolar patients can still initiate internally directed cognition like spontaneous thought. However, that very same internal initiation is temporally disorganized by the abnormal high neuronal variability in DMN in depression and the low SD in DMN in mania. The cognitive symptoms like rumination (or decreased thought) are consequently not primarily cognitive but rather spatiotemporal as they are related to spatiotemporal changes in the brain's spontaneous activity.

Taken together, the example of BP nicely demonstrates that cognitive and motor symptoms in both depression and mania are not related to primary dysfunction in either cognitive or motor functions. Instead, the basic function, i.e., cognitive or motor, is preserved by itself but abnormally organized in spatial and temporal terms. Therefore, the symptoms are spatiotemporal rather than cognitive and motor. What is described as cognitive in Cognitive Psychopathology is based on and can be traced spatiotemporal abnormalities in the brain's spontaneous activity and thus Spatiotemporal Psychopathology.

The same holds for experience and Phenomenological Psychopathology. Depressed patients often experience their "inner time," i.e., the time of their own self, as extremely slow which, when taken as reference, lets them perceive the "outer time," i.e., the time in the environment, as extremely fast (Fuchs 2014; Northoff et al. 2017). We measured neuronal variability in the neural network underlying "inner time," i.e., the somatosensory network (SS), and the one related to "outer time," i.e., primary sensory regions like visual cortex (VS). This yielded decreased SD in the SS and increased SD.

How are these findings related to the experience or perception of time? Neuronal variability indicates change in neural activity, and the more change there is, the faster the time. Decreased SD in SS thus indicates slower "inner time," while increased SD in VC reflects faster "outer time"—this corresponds exactly to the experience of time depressed patients report (Northoff et al. 2017 for details). The opposite SD pattern with increased SD in SS and decreased SD in VC was observed in manic patients—this corresponds well to their experience of faster "inner time" and slower "outer time."

Taken together, these findings indicate how a temporal measure like neuronal variability is translated into experience or perception, i.e., the experience of the speed of time. Hence, experience of the speed of time may be traced to and be based on a corresponding neuronal measure that indicates the speed of the brain's time, i.e., neuronal variability. Hence, the change in the brain's time speed, i.e., its neuronal time as indexed by neuronal variability, is transformed into corresponding experience or perception, i.e., the experience of the speed of time. Experience of time and experience in general is thus spatiotemporal by itself and thereby based on the spatiotemporal features of the brain's spontaneous activity. Experiential approaches like Phenomenological Psychopathology are thus ultimately based on and can be traced to spatiotemporal features and hence Spatiotemporal Psychopathology.

Conclusion

How can we bridge the divide between brain and cognition and hence between Biological Psychiatry and Cognitive Psychopathology? I demonstrated how cognitive changes like rumination in depression and decreased cognition in mania are related to abnormal expression of spatial and temporal mechanisms of the brain's spontaneous activity. Hence, I postulate that what is described as abnormal cognition in Cognitive Psychopathology is based on and can be traced to abnormal spatial and temporal organization of cognitive functions—this entails what I describe as "Spatiotemporal Psychopathology." Accordingly, I postulate that the spontaneous activity's spatial and temporal features provide the bridge between brain and cognition. Therefore, Spatiotemporal Psychopathology provides the bridge between Biological Psychiatry on the one hand and Cognitive Psychopathology on the other.

How about the divide between brain and experience and hence between Biological Psychiatry and Phenomenological Psychopathology? I showed how the abnormal experience of time in depression and mania may be based on abnormal temporal features like neuronal variability in the brain's spontaneous activity. Experience is thus based on spatiotemporal features—the spatiotemporal features of the brain's spontaneous activity transform into experience which thereby can be characterized as spatiotemporal. Hence, the spontaneous activity's spatiotemporal structure allows linking brain and experience and can therefore bridge the divide between Biological Psychiatry and Phenomenological Psychopathology.

The initial question and title in this paper is: Why do we need psychopathology? We need psychopathology to bridge the gap between brain and cognition as well as the one between brain and experience. This does not only provide common link between biological, cognitive, and experiential forms of psychopathology but also a novel, i.e., spatiotemporal, understanding of both brain and symptoms. I postulate that Spatiotemporal Psychopathology as sketched here provides exactly that form of psychopathology that allows us to understand the brain and how its

neural activity transforms into cognition and experience and subsequently the kind of symptoms we observe in our patients.

References

Alcaro A, Panksepp J, Witczak J, Hayes DJ, Northoff G. Is subcortical-cortical midline activity in depression mediated by glutamate and GABA? A cross-species translational approach. Neurosci Biobehav Rev. 2010;34(4):592–605.

Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med. 2013;11:126. https://doi.org/10.1186/1741-7015-11-126.

David AS, Halligan PW. Cognitive neuropsychiatry: potential for progress. J Neuropsychiatry Clin Neurosci. 2000;12(4):506.

Doege K, Jansen M, Mallikarjun P, Liddle EB, Liddle PF. How much does phase resetting contribute to event-related EEG abnormalities in schizophrenia? Neurosci Lett. 2010a;481(1):1–5.

Doege K, Kumar M, Bates AT, Das D, Boks MPM, Liddle PF. Time and frequency domain event-related electrical activity associated with response control in schizophrenia. Clin Neurophysiol. 2010b;121(10):1760–71.

Duncan NW, Hayes DJ, Wiebking C, Brice T, Pietruska K, Chen D, Northoff G. Negative childhood experiences alter a prefrontal-insular-motor cortical network in healthy adults: a multimodal rsfMRI-fMRI-MRS-dMRI study. Hum Brain Mapp. 2015;36(11):4622–37.

Fuchs T. The temporal structure of intentionality and its disturbance in schizophrenia. Psychopathology. 2007;40(4):229–35.

Fuchs T. Temporality and psychopathology. Phenomenol Cogn Sci. 2013;12(1):75–104.

Halligan PW, David AS. Cognitive neuropsychiatry: towards a scientific psychopathology. Nat Rev Neurosci. 2001;2(3):209–15.

Hamm JP, Bobilev AM, Hayrynen LK, Hudgens-Haney ME, Oliver WT, Parker DA, Clementz BA. Stimulus train duration but not attention moderates γ-band entrainment abnormalities in schizophrenia. Schizophr Res. 2015;165(1):97–102.

Hamm JP, Gilmore CS, Picchetti NA, Sponheim SR, Clementz BA. Abnormalities of neuronal oscillations and temporal integration to low- and high-frequency auditory stimulation in schizophrenia. Biol Psychiatry. 2011;69(10):989–96. https://doi.org/10.1016/j.biopsych.2010.11.021.

Hasler G, Northoff G. Discovering imaging endophenotypes for major depression. Mol Psychiatry. 2011;16(6):604–19.

Huang Z, Obara N, Davis HH, Pokorny J, Northoff G. The temporal structure of resting-state brain activity in the medial prefrontal cortex predicts self-consciousness. Neuropsychologia. 2016;82:161–70.

Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA Psychiat. 2015;72(6):603–11.

Kuhn S, Gallinat J. Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis. Schizophr Bull. 2013;39(2):358–65.

Lakatos P, Schroeder CE, Leitman DI, Javitt DC. Predictive suppression of cortical excitability and its deficit in schizophrenia. J Neurosci. 2013;33(28):11692–702.

Logothetis NK, Murayama Y, Augath M, Steffen T, Werner J, Oeltermann A. How not to study spontaneous activity. NeuroImage. 2009;45(4):1080–9. https://doi.org/10.1016/j.neuroimage.2009.01.010.

Northoff G. Unlocking the brain: volume 1: Coding, vol. 1. Oxford: Oxford University Press; 2014a.

Northoff G. Unlocking the brain. Volume II: consciousness. Oxford: Oxford University Press; 2014b.

Northoff G. Spatiotemporal psychopathology I: is depression a spatiotemporal disorder of the brain's resting state? J Affect Disord. 2015a;190:854–66.

Northoff G. Spatiotemporal psychopathology II: how does a psychopathology of the brain's resting state look like? J Affect Disord. 2015b;190:867–79.

Northoff G. Is schizophrenia a spatiotemporal disorder of the brain's resting state? World Psychiatry. 2015c;14(1):34–5.

Northoff G. Resting state activity and the "stream of consciousness" in schizophrenia-neurophenomenal hypotheses. Schizophr Bull. 2015d;41:280–90. https://doi.org/10.1093/schbul/sbu116.

Northoff G, Stanghellini G. How to link brain and experience? spatiotemporal psychopathology of the lived body. Front Hum Neurosci. 2016;10:172.

Northoff G, Synille E. Depression and GABA-A cross-level translational hypothesis. Mol Psychiatry. 2014;19:966–77.

Panksepp J. Textbook of biological psychiatry. Hoboken: Wiley; 2004.

Parnas J, Sass LA, Zahavi D. Recent developments in philosophy of psychopathology. Curr Opin Psychiatry. 2008;21(6):578–84.

Parnas J, Sass LA, Zahavi D. Rediscovering psychopathology: the epistemology and phenomenology of the psychiatric object. Schizophr Bull. 2012;39(2):270–7.

Parnas J, Sass LA, Zahavi D. Rediscovering psychopathology: the epistemology and phenomenology of the psychiatric object. Schizophr Bull. 2013;39(2):270–7. https://doi.org/10.1093/schbul/sbs153.

Schroeder CE, Lakatos P. Low-frequency neuronal oscillations as instruments of sensory selection. Trends Neurosci. 2009a;32(1):9–18. https://doi.org/10.1016/j.tins.2008.09.012.

Schroeder CE, Lakatos P. The gamma oscillation: master or slave? Brain Topogr. 2009b;22(1):24–6. https://doi.org/10.1007/s10548-009-0080-y.

Schroeder CE, Lakatos P, Kajikawa Y, Partan S, Puce A. Neuronal oscillations and visual amplification of

speech. Trends Cogn Sci. 2008;12(3):106–13. https://doi.org/10.1016/j.tics.2008.01.002.

Schroeder CE, Wilson DA, Radman T, Scharfman H, Lakatos P. Dynamics of active sensing and perceptual selection. Curr Opin Neurobiol. 2010;20(2):172–6. https://doi.org/10.1016/j.conb.2010.02.010.

Stanghellini G. A hermeneutic framework for psychopathology. Psychopathology. 2009a;43(5):319–26.

Stanghellini G. The meanings of psychopathology. Curr Opin Psychiatry. 2009b;22(6):559–64.

Stanghellini G, Broome MR. Psychopathology as the basic science of psychiatry. Br J Psychiatry. 2014;205(3):169–70.

Zhu X, Wang X, Xiao J, Liao J, Zhong M, Wang W, Yao S. Evidence of a dissociation pattern in resting-state default mode network connectivity in first-episode, treatment-naive major depression patients. Biol Psychiatry. 2012;71(7):611–7.

Author Queries

Chapter No.: 11 0003330794

Queries	Details Required	Author's Response
AU1	Please check the presentation of the author's affiliation, and correct if necessary.	
AU2	Please check the placement of block quote and correct if necessary.	
AU3	Please check the hierarchy of the section headings and correct if necessary.	
AU4	Please check if edit to sentence starting "Psychological approaches focus..." is okay.	
AU5	Refs. "Gazzaniga (2010), Barch et al. (2016), Jaspers (1963), Martino et al. (2016a), Martino et al. (2016b), Kristoff et al. (2016), Smallwood and Schooler (2015), Fuchs (2014), Northoff et al. (2017)" are cited in the text but not provided in the reference list. Please provide them in the reference list or delete these citations from the text.	
AU6	Please check if inserted closing parenthesis is okay.	
AU7	Refs. "Alcaro et al. (2010a), Cuthbert and Insel (2013), Doege et al. (2010a, b), Hamm et al. (2011, 2015), Hasler and Northoff (2011), Kaiser et al. (2015), Kuhn and Gallinat (2013), Lakatos et al. (2013), Logothetis et al. (2009), Northoff (2015a, b, c, d), Northoff and Synille (2014), Schroeder and Lakatos (2009a, b), Schroeder et al. (2008, 2010), Zhu et al. (2012)" are not cited in the text. Please provide the citation or delete them from the list.	