Progress in Neuropsychopharmacology & Biological Psychiatry 80 (2018) 81–90

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

The brain's spontaneous activity and its psychopathological symptoms – "Spatiotemporal binding and integration"

Georg Northoff[1]

Mind, Brain Imaging and Neuroethics, University of Ottawa, Institute of Mental Health Research, Canada

ARTICLE INFO

Keywords:
Spontaneous activity
Spatiotemporal structure
Depression
Schizophrenia
Spatiotemporal psychopathology

ABSTRACT

Neuroimaging provided much insight into the neural activity of the brain and its alterations in psychiatric disorders. However, despite extensive research, the exact neuronal mechanisms leading to the various psychopathological symptoms remain unclear, yet. In addition to task-evoked activity during affective, cognitive, or other challenges, the brain's spontaneous or resting state activity has come increasingly into the focus. Basically all psychiatric disorders show abnormal resting state activity with the relation to psychopathological symptoms remaining unclear though. I here suggest to conceive the brain's spontaneous activity in spatiotemporal terms that is, by various mechanisms that are based on its spatial, i.e., functional connectivity, and temporal, i.e., fluctuations in different frequencies, features. I here point out two such spatiotemporal mechanisms, i.e., "spatiotemporal binding and integration". Alterations in the resting state's spatial and temporal features lead to abnormal "spatiotemporal binding and integration" which results in abnormal contents in cognition as in the various psychopathological symptoms. This, together with concrete empirical evidence, is demonstrated in depression and schizophrenia. I therefore conclude that we need to develop a spatiotemporal approach to psychopathology, "spatiotemporal psychopathology:" as I call it.

1. Introduction

Neuroimaging has provided a novel method to investigate the biological mechanisms of altered brain activity in psychiatric disorders. In addition to task-evoked paradigm as related to cognitive, affective, social, or sensorimotor challenges, the investigation of the brain's resting state activity has gained considerable traction in psychiatric. Put in a nutshell, the brain's resting state activity is the neural activity we measure in the absence of any specific stimuli or tasks (Logothetis et al., 2009; Northoff, 2014a,b). The idea is that the measurement of resting state activity taps into the brain's intrinsically generated neural activity, its spontaneous activity. While the brain's spontaneous activity shows an elaborate spatiotemporal structure (Northoff, 2014a; Cabral et al., 2014; Raichle, 2015a,b), its exact role and function for especially psychopathological symptoms remains unclear so far.

Due to its unclear role and functions, the brain's resting state activity has been under critical scrutiny (Weinberger and Radulescu, 2016; Power et al., 2014). This shall not detract though from the features of the spontaneous activity itself, its elaborate spatiotemporal structure and its changes and abnormalities in psychiatric disorders. I here describe the spatiotemporal features of the brain's spontaneous activity in more detail and point out their role in binding and integrating different stimuli and contents in spatiotemporal terms – I therefore speak of "spatiotemporal binding and integration". Based on various findings, I suggest abnormal "spatiotemporal binding and integration" in the resting state in depression and schizophrenia which, in turn, leads to psychopathological symptoms like ruminations and hallucinations.

I postulate that the two features as introduced here, "spatiotemporal binding and integration", are hallmark features of what can be described as "Spatiotemporal Psychopathology" (Northoff, 2015a,b,c,d). The concept of "Spatiotemporal Psychopathology" refers to the fact that psychopathological symptoms are conceived primarily in spatiotemporal terms rather than in cognitive (as in Cognitive Psychopathology), phenomenological (as in Phenomenological Psychopathology), affective (as in Affective Psychopathology), or neuronal terms (as in Biological Psychiatry).

Cognitive Psychopathology, for instance, conceives psychopathological symptoms as consequence of cognitive dysfunction; the perceived contents are processed in an abnormal cognitive way leading to distortions as manifest in the symptoms (David and Halligan, 2000). Spatiotemporal Psychopathology, in contrast, searches for the spatial and temporal organisation of cognitive functions and their respective contents: psychopathological symptoms result from abnormal spatial

E-mail address: Georg.northoff@theroyal.ca.
[1] www.georgnorthoff.com

http://dx.doi.org/10.1016/j.pnpbp.2017.03.019
Received 7 March 2017; Accepted 27 March 2017
Available online 28 March 2017
0278-5846/

and temporal organisation of cognitive functions and their contents rather than from the latter themselves.

How about experience as emphasized in Phenomenological Psychopathology (Parnas et al., 2013)? Phenomenological Psychopathology focuses on subjective experience of for instance time and space as well as of self, body, and world as central dimensions of symptoms. Spatiotemporal Psychopathology agrees with that but extends that claim to the neuronal level of spontaneous activity with its organisation and construction of the brain's time and space: the latter supposedly provides the neuronal basis for our experience of time and space and the subsequent shaping of self, body, and world (Northoff, 2014a). Finally, unlike Biological Psychiatry that approaches the brain is mainly neuronal terms of various functions (like sensory, motor, cognitive, etc.), Spatiotemporal Psychopathology views the brain in predominantly spatial and temporal terms: what are the temporal and spatial mechanisms, as based on the brain's spontaneous activity, that give rise and organize its various functions including affective functions as focused on in Affective Psychopathology (Panksepp, 2004).

The aim of this contribution is to demonstrate how changes in the resting state's spatiotemporal structure translate into psychopathological symptoms. In a first part I will describe "spatiotemporal binding and integration" in the brain's "normal" spontaneous activity; this is followed by showing their alterations in depression (second part) and schizophrenia (third part).

2. Part I: Spontaneous brain activity: Spatiotemporal features and "spatiotemporal binding and integration"

2.1. The brain's spontaneous activity – Spatial and temporal features

The brain's intrinsic activity (or spontaneous activity) can spatially be characterized by various neural networks that consist of regions showing close functional connectivity with each other. There is for instance the core default-mode network (DMN) that includes mainly the cortical midline structures (Northoff et al., 2006, Andrews-Hanna et al., 2016), which show strong low frequency fluctuations (Northoff, 2014a; Raichle, 2009, 2001). Other neural networks include the sensorimotor network, the salience network, the ventral and dorsal attention network, the cingulum-operculum network, and the central executive network (CEN) (see Menon (2011) for a review). These neural networks are related to each other in continuously dynamically changing constellations (de Pasquale et al., 2010, 2012), resulting in what may be described as spatial structure that, through its functional nature, supercedes the anatomical structure.

In addition to such spatial structure on the functional level, the spontaneous activity can also be characterized by fluctuations in its neural activity 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). Most importantly, these different frequency bands are coupled with each other, with for instance the phase of lower frequency bands being coupled to the phase or power of higher ones (Buzsaki, 2006; Buzsaki et al., 2013; Northoff, 2014a). This amounts to a complex temporal structure in the brain's intrinsic activity that, as shown most recently, is related in some yet unclear ways to the spatial structure and its various neural networks (e.g., Ganzetti and Mantini, 2013; Northoff, 2014a) (Fig. 1).

To be more specific, spontaneous BOLD fluctuations as observed in fMRI are found in lower frequency ranges including the delta band (1–4 Hz), up- and down-states (0.8 Hz) and infra-slow fluctuations (ISFs) (0.001–0.1 Hz) (Logothetis, 2008, Zhigalov et al., 2015). The slow frequency fluctuations observed in fMRI have been assumed to correspond to what is measured as slow cortical potentials (SCPs) in EEG (He and Raichle, 2009; Khader et al., 2008). These SCPs are not easy to obtain in EEG because they are subject to artifacts caused by sweating, movements, and electrode drift; their measurement therefore

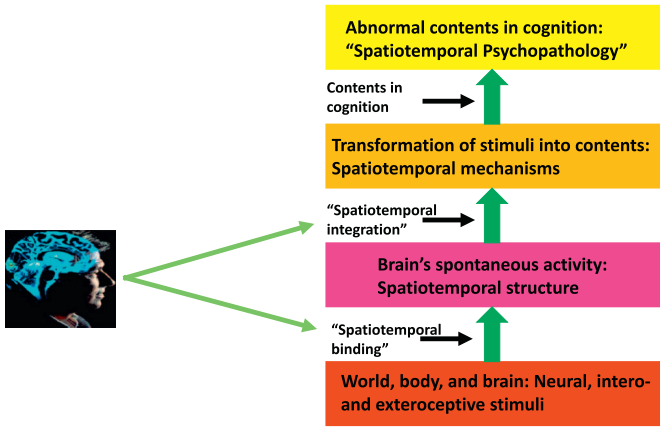

Fig. 1. The brain's spontaneous activity and "Spatiotemporal Psychopathology".The figure shows in the bottom that the various stimuli from world, body, and brain, i.e., neural and intero- and exteroceptive, are bind together based on their spatiotemporal features; i.e., "spatiotemporal binding". The resulting contents are integrated, i.e., "spatiotemporal integration". Abnormalities in the spatiotemporal features of the brain's spontaneous activity lead then to abnormal "spatiotemporal binding and integration" which, in turn, results abnormal contents in cognition and thus the various psychopathological symptoms (upper part).

requires a more direct approach by so-called direct current (DC) recording. There is some evidence that what is measured as SCP in EEG corresponds, or is even identical, to the low frequency fluctuations obtained in fMRI (He and Raichle, 2009; Khader et al., 2008).

In addition to such low frequency fluctuations, there are also higher frequency fluctuations in the brain's resting state activity. These cover 1 Hz and higher frequency ranges, thus including delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (> 30 Hz) (Mantini et al., 2007; Sadaghiani et al., 2010). This raises the question of how low and high frequencies are related to each other in the brain's resting state (Canolty and Knight, 2010; Fell and Axmacher, 2011; Fries, 2009; Sauseng and Klimesch, 2008). For instance, Vanhatalo et al. (2004) conducted an EEG study in healthy and epileptic subjects during sleep using DC-EEG to record low frequency oscillations. All subjects showed infraslow oscillations (0.02–0.2 Hz) cross all electrodes—and thus the whole brain—without any specific, visually obvious spatial distribution evident.

Most interestingly, Vanhatalo et al. (2004) observed phase-locking or phase-synchronization between the phase of slow (0.02–0.2 Hz) oscillations and the amplitudes of the faster (1–10 Hz) oscillations: the amplitudes of the higher frequency oscillations (1–10 Hz) were highest during the negative phases or deflection (e.g., during periods in the fluctuating cycle of the low frequency oscillation that show higher degrees of excitability for subsequent stimuli when compared to positive periods in the cycle) of the slow oscillations (0.02–0.2 Hz) (see Fig. 2).

Such phase-locking of high frequency oscillations' power to the

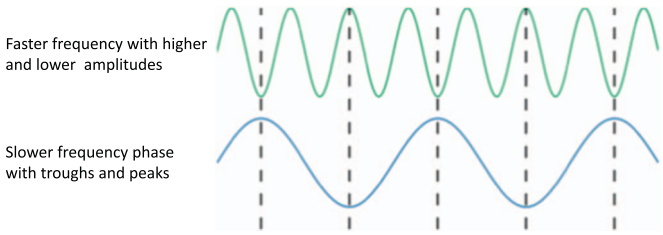

Fig. 2. Cross-frequency coupling.The figure illustrates in a schematic way how the phase (as featured by peaks and troughs) of the slower frequency (blue at bottom) couples to the level of amplitude of the faster frequency (green at top). The figures shows that the peaks of the slower frequency are always related to low levels in the amplitude of the faster frequency as indicated by the dotted vertical lines. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

phases of lower ones is described as *phase-power coupling*, with phase-phase and power-power coupling also being possible (Canolty and Knight, 2010; Sauseng and Klimesch, 2008). Generally, such cross-frequency coupling (CFC) seems to occur in the direction from low to high frequency fluctuations as well as from phase to amplitude/power (Buzsaki, 2006; Buzsaki et al., 2013) – the phase of the lower frequency entrains the amplitude of the higher frequency. Such low-high frequency entrainment may be central in integrating and embedding the stimuli (and their respective contents) into the ongoing temporal structure of the brain's intrinsic activity.

2.2. The brain's spontaneous activity – Different stimuli and their baselines

How can we better describe the brain's spontaneous activity? I here understand the concept of the brain's spontaneous activity in a purely neuronal sense as distinguished from a cognitive sense (as it is often presupposed in the context of spontaneous thought). Often the brain's spontaneous activity is considered to be devoid of the processing of specific stimuli or tasks, for instance the absence of a particular visual picture during task-evoked activity. In that case, the concept of spontaneous activity is more or less equated with the one the "resting state" that is defined by the absence of specific external stimuli (Logothetis et al., 2009; Northoff, 2014a). However, it is important to note that the absence of specific stimuli or tasks does not imply the complete or total absence of any kind of stimuli (or tasks). Even in the resting state, there are still plenty of stimuli that are processed.

When closing the eyes as during the resting state, there is the continuous interoceptive input or stimuli from the body that need to be processed. There is for instance continuous input from the heart (heartbeat) and lungs (respiration). One would therefore expect that neural activity in the resting state is related to the interoceptive activity in the body. This possibility is supported by a study that demonstrated that resting state functional connectivity in the resting state is directly related to (i.e., correlates with) heart variability (Chang et al., 2013), and by a recent meta-analysis of functional neuroimaging studies of spontaneous thought showing that the insula – the key interoceptive cortex – is consistently recruited (Fox et al., 2015). The close link between interoceptive stimuli from the body and the brain's spontaneous activity is further supported by recent studies from the group around Tallon-Baudry that show how the heartbeat and the gastral dynamics (as related to slower frequencies) are directly related and coupled to neural activity in the brain's spontaneous activity (Richter et al., 2017; Park and Tallon-Baudry, 2014; Babo-Rebelo et al., 2016).

Due to the strong of the body's interoceptive stimuli, Marx et al. (2004) therefore characterize the resting state as obtained during eyes closed as an "interoceptive state" where neural activity is strongly determined by and reflects the predominant processing of interoceptive stimuli from the body by the brain. Correspondingly, Barry et al., (2007) speak of an "arousal baseline" referring to an unspecific level or state of arousal as triggered mainly by the body's interoceptive input.

What happens if subjects open their eyes? In that case additional exteroceptive input, e.g. visual input, is added to the ongoing exteroceptive input stemming from gustatory, olfactory, auditory and tactile input (that is already ongoing in the interoceptive state). The balance between the continuous interoceptive and exteroceptive input may thus shift towards the latter when opening the eyes. The primarily interoceptive state and its "arousal baseline" is then transformed into a primarily "exteroceptive state" and a corresponding "activation baseline" (Barry et al., 2007).

In addition to the continuous interoceptive and exteroceptive input from body and environment, there is also input from the brain itself and its intrinsic activity. The thalamus, for instance, generates its own activity pattern with oscillations which may be imputed into other regions. Analogously to interoceptive and exteroceptive input one may want to speak here of "neural input" with a "neural state" and a corresponding "neural baseline" (Northoff, 2014a). These different baselines, i.e., activation, arousal, and neural baseline, may be prevalent throughout the whole brain and thus in all regions and networks.

Different brain regions and networks may show different balances between the three different states though. For instance, subcortical regions in the brain stem receive strong interoceptive inputs from the body such that the interoceptive state and its arousal baseline may predominate here in the resting state. On the other hand, sensory regions and their respective sensory networks receive rather strong exteroceptive input so that the exteroceptive state and the activation baseline may predominate here. Finally, the 'neural state' and its neural baseline may predominate in regions like the cortical midline structures that neither receive direct stimulus input (either intero- or exteroceptive) nor send out stimulus output (like the motor cortex and the executive control network) (Northoff, 2014a).

Taken together, these short deliberations show that the brain's spontaneous activity is far from a true 'resting' state in the literal sense of the term. There are many different stimuli being processed, intero- and exteroceptive and neural, which leads to different balances between intero- and exteroceptive and neural states (and their respective baselines) across different regions and networks in the brain. This raises the question of how the integration of these different stimuli ultimately results in the brain's spontaneous activity (or resting state if taken in an operational way). How are the different continuous inputs, intero- and exteroceptive and neural, linked or bound together such that they constitute what we observe as spontaneous (or resting state) activity? I suggest in the following section that "spatiotemporal integration" and, more specifically "spatiotemporal binding" may be central for that.

2.3. "Spatiotemporal binding" – Transforming stimuli into contents

What is spatiotemporal binding? The concept of binding has been used often in the context of consciousness where it describes the linkage, e.g., binding between different stimuli into one content by means of which the latter is supposed to become conscious (Crick and Koch, 2003). This has been called the "binding hypothesis" of consciousness (Crick and Koch, 2003; Rhodes, 2006). For instance, stimuli are supposed to be bound together by 40 Hz (i.e., gamma band) oscillations in the visual cortex that allow the stimuli to be synchronized, amounting to "binding by synchronization" (Mudrik et al., 2014). However, the association of such binding of different stimuli into contents with conscious awareness has been contested. Studies have demonstrated that the linkage or binding between different stimuli, for instance during multisensory integration, can occur in the absence of consciousness (Mudrik et al., 2014; Revonsuo, 2006; Zmigrod and Hommel, 2011).

Independent of the association with consciousness, one can conceive binding nevertheless as a central mechanism to link different stimuli. I suggest that such binding occurs in the brain's spontaneous activity: the different continuous intero- and exteroceptive and neural inputs are temporally and spatially linked and thus bound together in that they result in contents which later resurface as the contents of thought. Such binding between the different contents occurs, I propose, on the grounds of the spatiotemporal features of the brain. Let us detail the mechanisms of such "spatiotemporal binding" as I call it (while I will distinguish it from other forms of binding in the next section).

Each region in the brain shows certain specific spatial and temporal features in its spontaneous activity. Spatially, brain regions may show a certain functional connectivity pattern with other regions. For instance, cortical midline structures, the core part of the DMN, have shown a rather high (if not the highest) degree of functional connectivity within the brain's spontaneous activity (when compared to other regions and networks) (de Pasquale et al., 2012; Hagmann et al., 2008; Honey et al., 2009).

In contrast, sensory regions show a much lower degree of functional connectivity. Temporally, each region (and network) seems to have its

own range of time windows within which it can bind or integrate different stimuli into one pattern of neural activity. These intrinsic time windows may surface in what has been described as "temporal receptive windows" (Hasson et al., 2015; Honey et al., 2009; Murray et al., 2014) that have been shown to be rather short in sensory cortex (60–80 ms) whereas they seem to be rather long in other areas, especially the cortical midline structures (up to 250–300 ms).

What do these spatial and temporal features imply for the binding of intero- and exteroceptive and neural inputs in the brain's spontaneous activity? They suggest that different regions may bind different inputs in different ways depending on their respective spatial and temporal profile. For instance, the sensory cortices with their low degrees of functional connectivity and short intrinsic time windows may not be able to bind as many and or as wide a range of stimuli including their different points in time and space together as the cortical midline structures with their high degree of functional connectivity and long intrinsic time windows. There may consequently be different spatio-temporally-based "neural binding patterns" for integrating different stimuli across the brain's different regions and networks.

How are these different neural binding patterns related to thoughts and their contents? I propose that the contents of thought result from and are constituted or generated on the basis of the binding between different stimuli including their different points in time and space. By binding different stimuli and their different points in time and space together, a certain unity (an "objectual unity" as philosophers would call it; cf. Bayne and Chalmers, 2003) is constituted which may correspond to what we describe as the content (or object) of thought.

Contents may then be distinguished on the basis of their neural binding pattern and its spatiotemporal features. Different contents (or objects) of thought may consequently be assumed to correspond to different neural binding pattern and different spatiotemporal features. Depending on the predominant content, one may want to distinguish between somatically-guided, perceptually-guided, and self-generated thoughts.

If, for instance, interoceptive input prevails over exteroceptive input in the brain's spontaneous activity, the contents of our spontaneous thought may more likely concern one's body rather than referring to the environment. Such somatically-guided thoughts may for instance predominate in psychiatric patients with anxiety, panic, or depression, who can be abnormally preoccupied with their body (or parts of it, such as the heart), resulting in various somatic symptoms. In that case one would expect that the balance of spontaneous activity shifts towards the subcortical or interoceptively-involved regions like the insula and the somatosensory cortex which is indeed the case (de Greck et al., 2012; Andrews-Hanna et al., 2016).

If, in contrast, exteroceptive input predominates, the spontaneous activity balance may shift more towards the sensory cortices, resulting in the predominance of external thoughts contents, e.g., 'externally-guided cognition' (Dixon et al., 2014) or alternatively, 'perceptually-guided thought' (Smallwood and Schooler, 2015). Finally, the neural input from the brain's spontaneous activity itself and especially that from the cortical midline structures may predominate in the brain's spontaneous activity. In that case one would expect internally-guided cognition (Dixon et al., 2014) with thought contents strongly related to the self, amounting more or less to self-generated thoughts (Smallwood and Schooler, 2015) (see Fig. 3).

How are the three different kinds of content related to each other? Since intero-, exteroceptive, and neural stimuli are all integrated and bound together within the brain's spontaneous activity, there are no exclusively somatically- or perceptually-guided thoughts, nor solely self-generated thoughts or, as one may want to say, internally- and externally-directed cognition. Instead, the contents of our thoughts including both internally- and externally-directed cognition are supra-modal and domain-independent and can therefore be traced to the balance between interoceptive, exteroceptive, and neural stimuli. Rather than considering each type of stimulus independent of the others, it is rather a matter of their balance and the degree to which one predominates over the others. The hypothesis of such a balance is consistent with recent findings of decoupling from sensory processing, including sensory cortex, during self-generated thought (Andrews-Hanna et al., 2014; Baird et al., 2014; Gorgolewski et al., 2014).

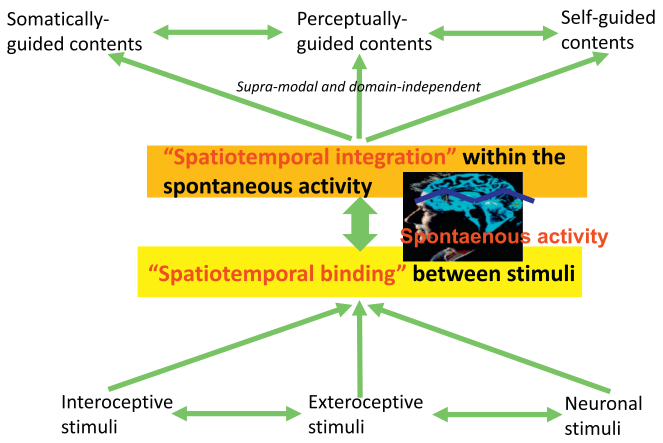

Fig. 3. "Spatiotemporal binding and integration".The figure illustrates that different stimuli, intero- and exteroceptive and neuronal, are bind together and integrated within the spontaneous activity and its spatiotemporal structure. This provides the basis for the balance between self-generated, perceptually- and somatically-guided contents as they surface in thoughts.

2.4. "Spatiotemporal integration" – Basic and fundamental form of integration

I have suggested that "spatiotemporal integration" and, more specifically "spatiotemporal binding" is central in constituting the contents of our thoughts as in both internally- and externally-directed cognition. What exactly do I mean by integration? One can describe different forms of integration such as multisensory integration, perceptual integration, semantic integration, cognitive integration, and formal mathematical integration (see Mudrik et al. (2014) for an excellent overview). These forms of integration implicate sensory and perceptual functions like multisensory integration and perceptual integration, as well as cognitive functions such as semantic and cognitive integration, or even higher-order cognitive functions as required in mathematical integration.

Those more complex forms of integration must be distinguished from the kind of integration proposed here. The integration between different stimuli in spontaneous brain activity does not yet implicate any specific active recruitment of sensorimotor, perceptual, cognitive, or higher-order cognitive functions. Instead, the integration by the spontaneous activity occurs in an automatic way, by default, due to the nature of the spontaneous activity's spatiotemporal structure. The intero- and exteroceptive and neural stimuli constituting the different baselines are by default (i.e., automatically) integrated within the brain's spontaneous activity. No recruitment of sensory, perceptual, motor, cognitive, or higher-order cognitive functions is required.

Instead, the different stimuli and their spatial and temporal features are integrated by and within the spatiotemporal features of the brain's spontaneous activity so that one may want to speak of "spatiotemporal integration". Such spatiotemporal integration features a most basic and fundamental level of integration that is inherent in the spontaneous activity and its spatiotemporal structure prior to and independent of any subsequent sensorimotor, affective, cognitive, and social function including their respective forms of integration, i.e., multisensory, cognitive, etc. Accordingly, taken together, spatiotemporal integration can be characterized by (i) its automatic nature occurring by default because of the spontaneous activity's spatiotemporal structure; and (ii) prior to and independent of the recruitment of specific sensorimotor,

affective, cognitive, and social function.

One may want to argue that such spatiotemporal integration is trivially true. Any integration between different stimuli occurs at one particular or discrete point in time and space within the brain, for instance at a particular region or cell population as well as in a specific frequency range. This is not contested here. Taken in this sense the characterization of integration as spatiotemporal is indeed trivially true. However, that is not the sense that I mean by the concepts of space and time as the core of spatiotemporal integration. Rather than referring to discrete points, here the concepts of space and time refer to a distribution of different points across space and time entailing a stochastic or statistically-based and ultimately neural rather than mental meaning of time and space.

Let us illustrate such stochastic meaning of space and time by the example of multisensory integration (Stein et al., 2009; Ferri et al., 2015). Multisensory integration is assumed to rely on different principles including spatial and temporal coincidence between the cross-modal stimuli: if the two cross-modal stimuli coincide at the same point in space, as for instance in a particular cell population or region, their likelihood of being integrated is much higher than when they do not spatially coincide (Stein et al. 2009 as well as Chapter 10 in Northoff, 2014a for details). The same holds analogously for temporal coincidence: if the two stimuli temporally coincide and do thus occur stochastically at the same point in time, they can be much better integrated with each other than when occurring at different points in time. This makes it clear that multisensory stimuli are integrated with each other on stochastically-based spatial and temporal grounds.

I now assume the same in an analogous way to hold for the integration of the ongoing intero- and exteroceptive and neural stimuli with each other into the brain's spontaneous activity. The more the temporal and spatial features of interoceptive stimuli coincide with the spatial and temporal features of the brain's spontaneous activities, the better the former will be integrated within the latter. The same holds, obviously, for the integration of exteroceptive and neural stimuli into the spontaneous activity which also occurs on purely spatial and temporal grounds.

Instead of the single stimulus itself and its specific points in time and space, the spontaneous activity encodes the relation, e.g., difference, of the former's points in time and space to its own points in time and space, i.e., its own spatial and temporal features. The resulting neural activity is thus based on the stochastically-based spatiotemporal difference between stimulus and spontaneous activity – this presupposes difference-based coding (as distinguished from stimulus-based coding) (Northoff, 2014a). I now postulate that such stochastically-based spatiotemporal encoding strategy, i.e., difference-based coding, allows for the kind of spatiotemporal integration and binding that transforms simple stimuli into contents.

Such encoding strategy, i.e., difference-based coding (Northoff, 2014a), is based on the spatiotemporal features of stimuli – this distinguishes it from other strategies that are rather based on the nature of the stimuli themselves like their origin as in body, environment, or brain or, alternatively, on associated sensorimotor, cognitive, affective, or social function as in more complex forms of integration; see above). Therefore, the concept of 'spatiotemporal' as presupposed in spatiotemporal integration cannot be considered trivially true but rather substantial in that it describes a most basic and fundamental form of integration.

I postulate that spatiotemporal integration in this most basic and fundamental sense, e.g., prior to and independent of other more complex forms of integration, is central for integrating and binding and thus transforming stimuli into contents as essential ingredient of both internally- and externally-directed cognition as with a certain balance between self-, somatically-, and perceptually-guided contents. The non-trivial nature of the spatiotemporal features of spatiotemporal integration will become even more clear when considering psychopathological symptoms. Conceived in this way, psychopathological symptoms can be traced to abnormal spatiotemporal binding and integration in the resting state – these symptoms are neither primarily cognitive, sensorimotor, affective, nor social but spatiotemporal. That shall be illustrated in the next part.

3. Part II: "Spatiotemporal Psychopathology": Abnormal "spatiotemporal integration" in depression

3.1. Abnormal "Spatiotemporal integration" – Dysbalance between medial and lateral cortical regions in in resting state activity in depression

How are the resting state's spatiotemporal binding and integration related to psychopathological symptoms? I start with an example from depression, i.e., major depressive disorder (MDD). In a recent meta-analysis Alcaro et al. (2010a,b) looked at the brain's resting state activity that is, the neural activity that can be observed in different regions and networks during the absence of specific stimuli or tasks (Logothetis et al., 2009). This yielded hyperactive regions in medial prefrontal cortex like perigenual anterior cingulate cortex (PACC) and ventromedial prefrontal cortex (VMPFC) (as well as subcortical midline regions as thalamic regions like the dorsomedial thalamus and the pulvinar, pallidum/putamen and midbrain regions like ventral tegmental area (VTA), Substantia nigra (SN), the Tectum and the periaqueductal gray (PAG).

In contrast, resting-state activity was hypoactive in lateral prefrontal cortex regions being reduced in the dorsolateral prefrontal cortex (DLPFC) (and other regions like the posterior cingulate cortex (PCC) and adjacent precuneus/cuneus (Alcaro et al., 2010a,b) (see also Kühn and Gallinat (2013) for similar results). Especially the medial prefrontal resting state hyperactivity changes in PACC and VMPFC seems to be somehow specific for depression since in schizophrenia there is rather hypoactivity (see Kuhn & Gallinat, 2013; Zhu et al., 2012).

The medial prefrontal regions like PACC and VMPFC are core regions of the default-mode network (DMN) while lateral prefrontal regions like DLPFC a part of the central executive network (CEN). A recent meta-analysis of resting state functional connectivity observed the following abnormal changes in these networks that seem to be (more or less) specific to MDD as distinguished from other psychiatric disorders (Kaiser et al., 2015). 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 towards the external environment.

This suggests spatial dysbalance between the two networks with an abnormal spatial shift towards the DMN and away from the CEN with the former also enslaving the latter (as suggested by abnormally negative functional hyperconnectivity between DMN and CEN (Kaiser et al., 2015)). These findings are specific to MDD as in BD such a pattern cannot be observed (Martino et al., 2016) while in schizophrenia functional connectivity between DMN and CEN is positive (rather than abnormally negative as in MDD) (Carthart-Harris et al., 2013; Northoff and Duncan, 2016).

In sum, the data provide evidence for abnormal resting state hyperactivity in medial prefrontal regions as part of the DMN in MDD while there is resting state hypoactivity in lateral prefrontal regions as part of the CEN. This suggests opposite that is, reciprocal modulation between medial and lateral prefrontal cortex with resting state activity being abnormally increased in the former and decreased in the latter. Abnormal opposite or reciprocal modulation between medial and lateral prefrontal cortical resting state activity in MDD is further supported by analogous functional connectivity: increased functional connectivity in PACC-VMPFC and thus within DMN is accompanied by decreased functional connectivity in lateral prefrontal cortex and the CEN (Hasler and Northoff, 2011; Northoff, 2014a; Northoff and Synille, 2014; Zhu et al., 2012). One can thus speak of abnormal reciprocal

modulation between medial/DMN and lateral/CEN prefrontal cortex with their spatial balance tilting abnormally towards the former at the expense of the latter.

3.2. Abnormal "Spatiotemporal integration" – Dysbalance between self-/somatically-guided and perceptually-guided contents in depression

How now is the abnormal spatial balance between medial and lateral prefrontal cortex related to the psychopathological symptoms in MDD? This spatial imbalance on the level of the brain's spontaneous activity is well reflected on the psychopathological level: MDD patients' experiences are characterized by an increased focus on the own self- and somatically-guided contents as consisting in either thoughts, as in ruminations with increased self-focus, or/and the body leading to the various unspecific somatic symptoms, e.g., increased body-focus (Northoff et al., 2011; Northoff, 2015a). Internally-directed cognition with somatically- or/and self-guided contents is abnormally strong: increased self-guided contents are manifest in increased self-focus and ruminations while increased somatically-guided contents are manifest in the various somatic and vegetative symptoms in MDD.

In contrast, these patients' experience is no longer focused on the external environment at all which psychopathologically is manifest in social withdrawal and lack of motivation (Northoff et al., 2004; Northoff, 2015a). Perceptually-guided contents as related to contents from the external environment, i.e., exteroceptive stimuli, are thus vanishing which is manifest symptomatically in lack of motivation and withdrawal from the external environment, i.e., "decreased environment-focus". The perceptually-guided contents are no longer properly integrated spatiotemporally with the somatically- and self-generated contents which results in their dysbalance in depression: self- and body-focus predominate over the environment-focus which results in rumination and somatic symptoms combined with lack of motivation and social withdrawal (see Fig. 4).

Yet another example of abnormal spatiotemporal integration can be found in bipolar depression (BD). A recent study (Mantini et al., 2007) investigated neuronal variability in resting state activity in BD. Neuronal variability describes the fluctuations in the amplitude of the resting state activity over time. They now looked for changes in neuronal variability in different resting state networks including the DMN and the sensorimotor network (SMN). They observed that in the depressed phase bipolar patients show increased neuronal variability in the DMN while it was decreased in SMN. Interestingly, bipolar patients in the manic phase showed the opposite pattern with increased variability in SMN and decreased variability in DMN (Mantini et al., 2007).

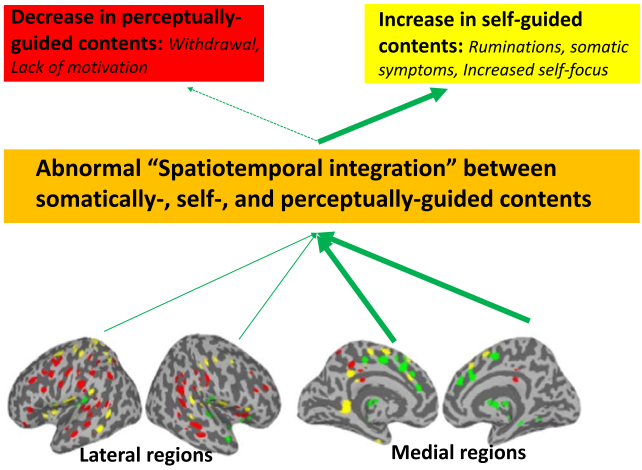

Fig. 4. Abnormal "spatiotemporal integration" between medial and lateral regions in depression.The figure shows in the bottom the dysbalanced between medial (hyperactivity) and lateral (hypoactivity) prefrontal cortical resting state activity in depression (as demonstrated in both animal models and human depression). While the medial regions process mainly the contents of internally-directed cognition with self-guided contents, the lateral regions rather process the contents of externally-directed cognition with perceptually-guided contents. Dysbalance between medial and lateral prefrontal cortical regions consequently results in abnormal dysbalanced and integration between internally- and externally-directed contents in our cognition and thus between self- and perceptually-guided contents. Depressive patients show increased self-guided contents with rumination etc. (upper right) while perceptually-guided contents are decreased as manifest in withdrawal from the environment (upper left).

Interestingly, the balance or ratio in neuronal variability between DMN and SMN correlated with psychopathological symptoms: the more the neuronal balance was tilted towards the DMN, the more depressive symptoms (as measured with the Hamilton depression scale). If, in contrast, the more it was tilted towards the SMN, the more manic symptoms (as measured with Young Mania rating scale) (Mantini et al., 2007). This fits well with the symptoms. Increased internally-directed cognition with increased self-focus and rumination as self-generated contents are initiated increasingly due to increased neuronal variability in DMN. While movements are no longer as much initiated as related to decreased neuronal variability in SMN – this results symptomatically in psychomotor retardation as cardinal symptom in depression. Mania, in contrast, showed the opposite pattern with specifically increased neuronal variability in SMN being related to increased movements with psychomotor agitation.

Taken together, the various kinds of psychopathological symptoms may be based on abnormal spatiotemporal integration between neural, interoceptive, and exteroceptive stimuli in the resting state. That leads to the kind of dysbalanced between somatically-, self-, and perceptually-guided contents with the respective psychopathological symptoms we observe in depression. While plenty of resting state studies have been conducted in depression, the impact of the different kinds of stimuli, i.e., neural, interoceptive, and exteroceptive, including their interaction remains to be investigated within the resting state itself.

One would expect abnormal "spatiotemporal binding" and consequently altered "spatiotemporal integration" in the resting state itself. For instance, depressed patients with predominantly somatic symptoms may show increased spatiotemporal binding of specifically interoceptive stimuli to others, i.e., neural and exteroceptive, – this results in the predominance of somatically-guided contents and the subsequent somatic symptoms. While patients with strong ruminations and increased self-focus may rather show abnormal binding of neural to intero- and exteroeptive stimuli in their resting state – this results in the predominance of self-guided contents over somatic- and perceptually-guided contents. The specific neuronal mechanisms of such abnormal "spatiotemporal binding and integration" remain to be investigated though.

The opposite pattern with decreased self-focus and concomitantly increased environment-focus can be observed in mania as part of bipolar disorder. They show predominance of perceptually-guided contents over self- and somatically-guided contents (Mantini et al., 2007). One may consequently expect increased integration and binding of the resting state's neural stimuli to exteroceptive stimuli dominating over their binding to interoceptive and other neural stimuli. That remains to be tested in the future though.

4. Part III: "Spatiotemporal Psychopathology": Abnormal "spatiotemporal binding" in schizophrenia

4.1. Abnormal "Spatiotemporal binding" – Reduced entrainment to auditory stimuli in schizophrenia

Schizophrenia can be characterized by various abnormalities in both spatial and temporal features of resting state activity (Northoff and Stanghellini, 2016 for a recent review). However, the exact relationship to psychopathological symptoms like auditory hallucinations remains unclear so far. I here discuss one particular study which sheds some light on that.

Lakatos et al. (2013) recently conducted an EEG study in schizophrenic patients whom they presented a stream of auditory stimuli (i.e. tones) with regular, i.e., rhythmic interstimulus intervals (1500 ms). They presented the stream of auditory stimuli with some deviant stimuli (20%) that were distinguished in their frequency. Subjects had to either passively listen (passive task), detect the easily detectable deviant stimuli (easy task), or detect the more difficult (variation by frequency) detectable stimuli (difficult task).

They observed that the phase coherence (i.e., the intertrial coherence/ITC) in different frequency ranges like delta (1–4 Hz that mediates basic processes of the brain's attunement to its respective environmental context; Northoff, 2014c) (in central electrodes that can be traced back to neural activity in auditory cortex) increased from the passive over the easy to the difficult condition with the latter showing the highest degree of ITC at stimulus onset in the delta range. This though was only the case in healthy subjects whereas such task-related increase in delta ITC was not observed in schizophrenic patients. These patients were thus not able to properly align, shift, their auditory cortical phase onsets in the delta range (that corresponded to the stimulation frequency with the ITI of the presented tones) to the onset of the tones and thus to properly adapt their neural activity to the task. This suggests decreased phase alignment or entrainment to external auditory stimuli.

Interestingly, in the intertrial interval (1500 ms) task-dependent amplitude in the delta range could be observed with the highest amplitude in the difficult task. This again was observed only in the healthy subjects whereas schizophrenic subjects did not show such delta amplitude in the ITI. In contrast to the phase, i.e., ITC, power in delta did not increase during any of the conditions in either healthy or schizophrenic patients. There though was a power increase in other frequency ranges that is, theta (5–7 Hz as related to memory processes) and beta (12–30 Hz as related to sensorimotor processing)/gamma (30–40 Hz as related to sensory processing) range from passive over easy to difficult tasks in healthy subjects.

Schizophrenic patients showed abnormally strong 7 Hz increase while the beta/gamma power was decreased during especially the difficult condition. Finally, reduced delta ITC correlated with both the behavioral measure, e.g., the detection rate of the deviant tones, and the electrophysiological index, the P300 (in response to deviant tones), in schizophrenic subjects. Importantly, reduced delta ITC also predicted the severity of psychopathological symptoms (as measured with BPRS) and especially the positive symptoms (that include hallucinations, delusions, and excitement).

Abnormal, i.e., reduced entrainment of phase onsets to external stimuli have also been observed in other studies in schizophrenia as for instance in response to 40 Hz auditory stimuli (Hamm et al., 2011, 2015). Other studies also observed major abnormalities in phase resetting in delta (1–4 Hz) and theta (5–8 Hz) ranges in schizophrenia (Doege et al., 2010) during an auditory oddball task, which, even more interesting, predicted the degree of positive symptoms in schizophrenia, e.g., disorganization (see also J. P. Hamm et al. (2011)). Unfortunately, there are not yet clear findings about cross-frequency coupling between reduced delta phase reset and the phase/power (or amplitude) of higher frequencies in the beta or gamma range. Based on the findings described here, one would predict that decreased delta phase reset is closely linked to reduced cross-frequency coupling to beta and gamma as it is supported indirectly by the findings (and the impact of delta phase ITC on ERP like P300) (see above).

4.2. Abnormal "Spatiotemporal binding" – Decreased "temporal binding" between exteroceptive and neural stimuli in schizophrenia

Taken together, these findings suggest that schizophrenic patients remain unable to properly link their internal auditory cortical neural activity, as indexed by phase onsets in delta, to a stream of external auditory stimuli. Lakatos et al. (2013) speak of deficits in active predictive sensing by phase resetting that does not allow schizophrenic patients to increase their cortical excitability at stimulus onset for the subsequent processing of external stimuli. This suits well with the theory of predictive coding (Friston, 2010) that considers the prediction or anticipation of future stimuli or inputs as central: stimulus-induced activity is supposed to result from the comparison between predicted and actual input which yields the prediction error. The prediction error may be particularly high in schizophrenia during auditory hallucination (see Corlett and Fletcher, 2015) as it is related to abnormally increased resting state activity in auditory cortex (Qin and Northoff, 2011; Alderson-Day et al., 2016). However, the findings by Lakatos suggest that the primary deficit in schizophrenia may lie even deeper than on the level of predictive coding (see also Northoff, 2014a, Chapters 7–9), that is, in the way how the brain can entrain or align its spontaneous activity to the temporal structure of external stimuli in the environment.

Given the evidence described above, one may assume severe deficits in phase entrainment (or alignment) to external stimuli, i.e., internal-external alignment in schizophrenia. More generally put, phase resetting allows for internal-external stimulus' (or, more generally, rest/brain-environment) alignment and thus for what Schroeder and Lakatos (Schroeder and Lakatos, 2009a,b; Schroeder et al., 2008, 2010) describe as 'rhythmic mode' of brain function. The rhythmic mode of brain function can be characterized by good phase alignment of the brain's low frequency fluctuations (like delta) to the statistical frequency distributions of the external stimuli; this entails also that the high frequencies (like beta and gamma) show decreased power. In contrast, the brain may also operate in a 'continuous mode' where the low frequencies are no longer phase-aligned to the external stimuli while the higher frequencies are now decoupled (i.e., low cross-frequency coupling) from the lower ones and show stronger power than in the rhythmic mode (Schroeder & Lakatos, 2009a,b; Northoff, 2014b).

Given the findings in auditory cortex with decreased delta ITC, increased resting state gamma, decreased task-evoked gamma (see above) and, to some degree, also decreased cross-frequency coupling, one would assume the auditory cortex in schizophrenia to operate in a continuous rather than rhythmic mode in relation to its respective environmental context. These temporal alterations mean that the schizophrenic patients' auditory cortical resting state activity can no longer align and adapt itself to its respective auditory environment, i.e., external stimuli and remains quasi 'decoupled' or 'dissociated' from the external environment. Specifically, the resting state's neural stimuli can no longer be bind to the continuous exteroceptive input with the latter therefore being decupled from the former. There is decreased "spatiotemporal binding" between neural and exteroceptive stimuli in the resting state.

One may consequently want to speak of "sensory decoupling" that describes the reduced entrainment or phase alignment to external sensory stimuli. Instead, as indicated by Lakatos et al. (2013), auditory cortical activity may rather align or entrain itself to internal stimuli or events (like thoughts). Instead of suppressing internal activity during entrainment to external stimuli, auditory cortical activity may rather phase align and entrain itself to internal stimuli of the ongoing resting state, i.e., neural and interoceptive, while, at the same time, suppressing its spatiotemporal binding and alignment to external, i.e., exteroceptive, stimuli (see Fig. 5).

Specifically, periods of high cortical excitability as provided by the long phase durations of delta oscillations, may now be shifted or reset in orientation on the temporal timing of internal, i.e., neural and interoceptive, stimuli (like self-generated thoughts) rather than external, i.e., exteroceptive, stimuli (like tones), e.g., reversed entrainment or phase alignment. That though is a hypothesis at this point which needs to be investigated in the future. Such "reversed entrainment or phase alignment" to internal (rather than external) stimuli entails that there is spatiotemporal discontinuity (rather than spatiotemporal

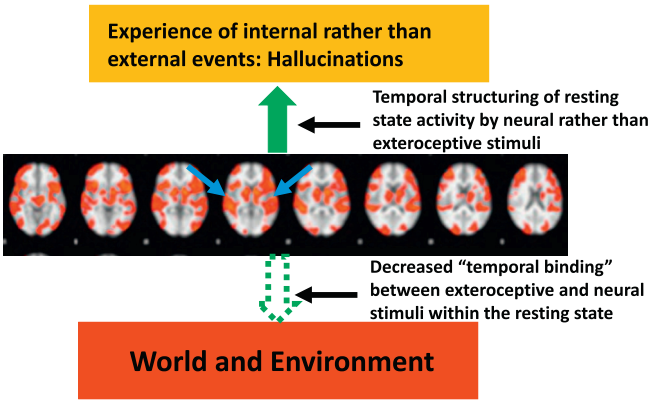

Fig. 5. Abnormal "spatiotemporal binding" between neural and exteroceptive stimuli in schizophrenia.The figure shows in the lower half the decreased entrainment of the auditory cortical resting state (little blue arrows) to exteroceptive stimuli from the environment. This, in turn, leads to predominance of neural stimuli in the resting state and subsequently to auditory hallucination (upper half of the figure). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

continuity) between world/environment and brain in the spontaneous activity. This is phenomenally reflected in the decoupling of experience from the ecological context, e.g., the world and results psychopathologically in auditory hallucinations (and probably delusions).

Rather than focusing on outward contents originating within the world, experience turns inwards to internal contents as like delusions and hallucinations. The abnormal temporal structure of the brain's spontaneous activity that is, its phase onsets including their temporal detachment from the temporal structure of the tones' onsets, surfaces in experience in the shift from external tones to internal contents like hallucinations. The abnormal temporal structure of the brain's spontaneous activity with its lacking phase shift during the tones thus translates into hallucinations as abnormal contents in experience. Rather than originating in the cognitive contents of cognitive function, hallucinations may then be traced to the abnormal temporal structure of the brain's spontaneous activity and its decreased "spatiotemporal binding" between neural/interoceptive and exteroceptive stimuli.

5. Conclusion

In sum, I consider "Spatiotemporal Psychopathology" an approach that can bridge the gap between the resting state's spatiotemporal structure and the psychopathological symptoms with their often rather bizarre contents. Though other neuronal, i.e., spatiotemporal mechanisms may be revealed in the future, "spatiotemporal binding and integration", as described here, may be core mechanisms that may be altered in different ways in different disorders. This opens the door for a dimensional rather than categorical approach to psychopathology (Cuthbert and Insel, 2013): "spatiotemporal binding and integration" as most basic spatiotemporal mechanisms may show changes in different degrees leading to partially overlapping symptoms in different disorders.

In a nutshell, "Spatiotemporal Psychopathology" provides a novel approach to both the brain's resting state and psychopathology that may finally allow us to bridge the gap between brain and symptoms. Future work including both empirical and conceptual is required though to more develop "Spatiotemporal Psychopathology" and, even more important, to put it into clinical practice and therapy. Different subjects may, for instance, slightly distinct balances between self-, perceptually-, and somatically-guided contents in their perception and cognition; these may then be treated in an individual way by modulating the respective individual subjects' spatiotemporal pattern in the brain.

Acknowledgments

I thank Wendy Carter for sorting the references. Financial contributions to GN are acknowledged from the Canada Research Chair program (CRC), the Canadian Institute of Health Research (CIHR), the Michael Smith Foundation, and the National Science Foundation of China.

References

Alcaro, A., Panksepp, J., Witczak, J., Hayes, D.J., Northoff, G., 2010a. Is subcortical-cortical midline activity in depression mediated by glutamate and GABA? A cross-species translational approach. Neurosci. Biobehav. Rev. 34 (4), 592–605.
Alcaro, A., Panksepp, J., Witczak, J., Hayes, D.J., Northoff, G., 2010b. Is subcortical–cortical midline activity in depression mediated by glutamate and GABA? A cross-species translational approach. Neurosci. Biobehav. Rev. 34 (4), 592–605.
Alderson-Day, B., Diederen, K., Fernyhough, C., Ford, J.M., Horga, G., Margulies, D.S., McCarthy-Jones, S., Northoff, G., Shine, J.M., Turner, J., van de Ven, V., van Lutterveld, R., Waters, F., Jardri, R., 2016. Auditory Hallucinations and the Brain's Resting-State Networks: Findings and Methodological Observations. Schizophr. Bull. 42 (5), 1110–1123. http://dx.doi.org/10.1093/schbul/sbw078. (Epub 2016 Jun 8).
Andrews-Hanna, J.R., Smallwood, J., Spreng, R.N., 2014. The default network and self-generated thought: component processes, dynamic control, and clinical relevance. Ann. N. Y. Acad. Sci. 1316 (1), 29–52.
Andrews-Hanna, J.R., Irving, Z., Fox, K., Spreng, N., Christoff, C., 2016. In: Fox, K.C.R., Christoff, K. (Eds.), The Oxford Handbook of Spontaenous Thought: Mind-wandering, Creativity, Dreaming, and Clinical Conditions. Oxford University Press, New York.
Babo-Rebelo, M., Richter, C.G., Tallon-Baudry, C., 2016. Neural Responses to Heartbeats in the Default Network Encode the Self in Spontaneous Thoughts. J. Neurosci. 36 (30), 7829–7840. http://dx.doi.org/10.1523/JNEUROSCI.0262-16.2016.
Baird, B., Smallwood, J., Lutz, A., Schooler, J.W., 2014. The decoupled mind: mind-wandering disrupts cortical phase-locking to perceptual events. J. Cogn. Neurosci. 26 (11), 2596–2607.
Barry, R.J., Clarke, A.R., Johnstone, S.J., Magee, C.A., Rushby, J.A., 2007. EEG differences between eyes-closed and eyes-open resting conditions. Clin. Neurophysiol. 118 (12), 2765–2773.
Bayne, T., Chalmers, D., 2003. What is the unity of consciousness? In: Cleeremans, A. (Ed.), The Unity of Consciousness. Oxford University Press, Oxford, England, pp. 23–58.
Buzsaki, G., 2006. Rhythms of the Brain. Oxford University Press.
Buzsaki, G., Logothetis, N., Singer, W., 2013. Scaling brain size, keeping timing: evolutionary preservation of brain rhythms. Neuron 80 (3), 751–764. http://dx.doi.org/10.1016/j.neuron.2013.10.002.
Cabral, J., Kringelbach, M.L., Deco, G., 2014. Exploring the network dynamics underlying brain activity during rest. Prog. Neurobiol. 114, 102–131. http://dx.doi.org/10.1016/j.pneurobio.2013.12.005. Epub 2013 Dec 31. Review.
Canolty, R.T., Knight, R.T., 2010. The functional role of cross-frequency coupling. Trends Cogn. Sci. 14 (11), 506–515.
Carhart-Harris, R.L., Leech, R., Erritzoe, D., Williams, T.M., Stone, J.M., Evans, J., Sharp, D.J., Feilding, A., Wise, R.G., Nutt, D.J., 2013. Functional connectivity measures after psilocybin inform a novel hypothesis of early psychosis. Schizophr. Bull. 39 (6), 1343–1351. http://dx.doi.org/10.1093/schbul/sbs117. (Epub 2012 Oct 8).
Chang, C., Metzger, C.D., Glover, G.H., Duyn, J.H., Heinze, H.J., Walter, M., 2013. Association between heart rate variability and fluctuations in resting-state functional connectivity. NeuroImage 68, 93–104. http://dx.doi.org/10.1016/j.neuroimage.2012.11.038.
Corlett, P.R., Fletcher, P.C., 2015. Delusions and prediction error: clarifying the roles of behavioural and brain responses. Cogn. Neuropsychiatry 20 (2), 95–105. http://dx.doi.org/10.1080/13546805.2014.990625. (Epub 2015 Jan 3).
Crick, F., Koch, C., 2003. A framework for consciousness. Nat. Neurosci. 6 (2), 119–126. http://dx.doi.org/10.1038/nn0203-119.
Cuthbert, B.N., Insel, T.R., 2013. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med. 11, 126. http://dx.doi.org/10.1186/1741-7015-11-126.
David, A.S., Halligan, P.W., 2000. Cognitive neuropsychiatry: potential for progress. J. Neuropsychiatr. Clin. Neurosci. 12 (4), 506.
de Greck, M., Scheidt, L., Bölter, A.F., Frommer, J., Ulrich, C., Stockum, E., Enzi, B., Tempelmann, C., Hoffmann, T., Han, S., Northoff, G., 2012. Altered brain activity during emotional empathy in somatoform disorder. Hum. Brain Mapp. 33 (11), 2666–2685. http://dx.doi.org/10.1002/hbm.21392. (Epub 2011 Oct 13).
Dixon, M.L., Fox, K.C.R., Christoff, K., 2014. A framework for understanding the relationship between externally and internally directed cognition. Neuropsychologia 62, 321–330. http://dx.doi.org/10.1016/j.neuropsychologia.2014.05.024.
Doege, K., Jansen, M., Mallikarjun, P., Liddle, E.B., Liddle, P.F., 2010. How much does phase resetting contribute to event-related EEG abnormalities in schizophrenia? Neurosci. Lett. 481 (1), 1–5. http://dx.doi.org/10.1016/j.neulet.2010.06.008. (Epub 2010 Jun 16).
Fell, J., Axmacher, N., 2011. The role of phase synchronization in memory processes. Nat. Rev. Neurosci. 12 (2), 105–118.
Ferri, F., Costantini, M., Huang, Z., Perrucci, M.G., Ferretti, A., Romani, G.L., Northoff, G., 2015. Intertrial Variability in the Premotor Cortex Accounts for Individual Differences in Peripersonal Space. J. Neurosci. 35 (50), 16328–16339. http://dx.doi.org/10.1523/JNEUROSCI.1696-15.2015.
Fox, K.C.R., Spreng, R.N., Ellamil, M., Andrews-Hanna, J.R., Christoff, K., 2015. The wandering brain: Meta-analysis of functional neuroimaging studies of mind-

wandering and related spontaneous thought processes. NeuroImage 111, 611–621. http://dx.doi.org/10.1016/j.neuroimage.2015.02.039.
Fries, P., 2009. Neuronal gamma-band synchronization as a fundamental process in cortical computation. Annu. Rev. Neurosci. 32, 209–224.
Friston, K., 2010. The free-energy principle: a unified brain theory? Nat. Rev. Neurosci. 11 (2), 127–138. http://dx.doi.org/10.1038/nrn2787. (Epub 2010 Jan 13. Review).
Ganzetti, M., Mantini, D., 2013. Functional connectivity and oscillatory neuronal activity in the resting human brain. Neuroscience 240, 297–309. http://dx.doi.org/10.1016/j.neuroscience.2013.02.032.
Gorgolewski, K.J., Lurie, D., Urchs, S., Kipping, J.A., Craddock, R.C., Milham, M.P., ... Smallwood, J., 2014. A correspondence between individual differences in the brain's intrinsic functional architecture and the content and form of self-generated thoughts. PLoS One 9 (5), e97176.
Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C.J., Wedeen, V.J., Sporns, O., 2008. Mapping the structural core of human cerebral cortex. PLoS Biol. 6 (7), e159http://dx.doi.org/10.1371/journal.pbio.0060159.
Hamm, J.P., Gilmore, C.S., Picchetti, N.A., Sponheim, S.R., Clementz, B.A., 2011. Abnormalities of neuronal oscillations and temporal integration to low- and high-frequency auditory stimulation in schizophrenia. Biol. Psychiatry 69 (10), 989–996. http://dx.doi.org/10.1016/j.biopsych.2010.11.021. (Epub 2011 Jan 8).
Hamm, J.P., Bobilev, A.M., Hayrynen, L.K., Hudgens-Haney, M.E., Oliver, W.T., Parker, D.A., McDowell, J.E., Buckley, P.A., Clementz, B.A., 2015. Stimulus train duration but not attention moderates γ-band entrainment abnormalities in schizophrenia. Schizophr. Res. 165 (1), 97–102. http://dx.doi.org/10.1016/j.schres.2015.02.016. (Epub 2015 Apr 11).
Hasler, G., Northoff, G., 2011. Discovering imaging endophenotypes for major depression. Mol. Psychiatry 16 (6), 604–619. http://dx.doi.org/10.1038/mp.2011.23. (Review).
Hasson, U., Chen, J., Honey, C.J., 2015. Hierarchical process memory: memory as an integral component of information processing. Trends Cogn. Sci. 19 (6), 304–313.
He, B.J., Raichle, M.E., 2009. The fMRI signal, slow cortical potential and consciousness. Trends Cogn. Sci. 13 (7), 302–309.
Honey, C., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J.-P., Meuli, R., Hagmann, P., 2009. Predicting human resting-state functional connectivity from structural connectivity. Proc. Natl. Acad. Sci. 106 (6), 2035–2040.
Kaiser, R.H., Andrews-Hanna, J.R., Wager, T.D., Pizzagalli, D.A., 2015. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA Psychiatry 72 (6), 603–611. http://dx.doi.org/10.1001/jamapsychiatry.2015.0071.
Khader, P., Schicke, T., Röder, B., Rösler, F., 2008. On the relationship between slow cortical potentials and BOLD signal changes in humans. Int. J. Psychophysiol. 67 (3), 252–261.
Kühn, S., Gallinat, J., 2013. Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis. Schizophr. Bull. 39 (2), 358–365. http://dx.doi.org/10.1093/schbul/sbr151. (Epub 2011 Nov 10).
Lakatos, P., Schroeder, C.E., Leitman, D.I., Javitt, D.C., 2013. Predictive suppression of cortical excitability and its deficit in schizophrenia. J. Neurosci. 33 (28), 11692–11702.
Logothetis, N.K., 2008. What we can do and what we cannot do with fMRI. Nature 453 (7197), 869–878. http://dx.doi.org/10.1038/nature06976. (Review).
Logothetis, N.K., Murayama, Y., Augath, M., Steffen, T., Werner, J., Oeltermann, A., 2009. How not to study spontaneous activity. NeuroImage 45 (4), 1080–1089. http://dx.doi.org/10.1016/j.neuroimage.2009.01.010.
Mantini, D., Perrucci, M.G., Del Gratta, C., Romani, G.L., Corbetta, M., 2007. Electrophysiological signatures of resting state networks in the human brain. Proc. Natl. Acad. Sci. U. S. A. 104 (32), 13170–13175. http://dx.doi.org/10.1073/pnas.0700668104.
Martino, M., Magioncalda, P., Huang, Z., Conio, B., Piaggio, N., Duncan, N.W., Rocchi, G., Escelsior, A., Marozzi, V., Wolff, A., Inglese, M., Amore, M., Northoff, G., 2016. Contrasting variability patterns in the default mode and sensorimotor networks balance in bipolar depression and mania. Proc. Natl. Acad. Sci. U. S. A. 113 (17), 4824–4829. http://dx.doi.org/10.1073/pnas.1517558113. (Epub 2016 Apr 11) PMID: 27071087.
Marx, E., Deutschländer, A., Stephan, T., Dieterich, M., Wiesmann, M., Brandt, T., 2004. Eyes open and eyes closed as rest conditions: impact on brain activation patterns. NeuroImage 21 (4), 1818–1824.
Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn. Sci. 15 (10), 483–506. http://dx.doi.org/10.1016/j.tics.2011.08.003.
Mudrik, L., Faivre, N., Koch, C., 2014. Information integration without awareness. Trends Cogn. Sci. 18 (9), 488–496.
Murray, J.D., Bernacchia, A., Freedman, D.J., Romo, R., Wallis, J.D., Cai, X., Padoa-Schioppa, C., Pasternak, T., Seo, H., Lee, D., Wang, X.J., 2014. A hierarchy of intrinsic timescales across primate cortex. Nat. Neurosci. 17 (12), 1661–1663. http://dx.doi.org/10.1038/nn.3862. (Epub 2014 Nov 10).
Northoff, G., 2014a. Unlocking the Brain: Volume 1: Coding. Vol. 1 Oxford University Press.
Northoff, G., 2014b. Unlocking the Brain. Volume II: Consciousness. Oxford University Press, Oxford.
Northoff, G., 2014c. How is our self altered in psychiatric disorders? A neurophenomenal approach to psychopathological symptoms. Psychopathology 47 (6), 365–376. http://dx.doi.org/10.1159/000363351. (Epub 2014 Oct 3).
Northoff, G., 2015a. Resting state activity and the "stream of consciousness" in schizophrenia–neurophenomenal hypotheses. Schizophr. Bull. 41 (1), 280–290. http://dx.doi.org/10.1093/schbul/sbu116. (Epub 2014 Aug 23).
Northoff, G., 2015b. Spatiotemporal psychopathology II: How does a psychopathology of the brain's resting state look like? J. Affect. Disord.
Northoff, G., 2015c. Is schizophrenia a spatiotemporal disorder of the brain's resting state? World Psychiatry. 14 (1), 34–35. http://dx.doi.org/10.1002/wps.20177. (No abstract available).
Northoff, G., 2015d. Resting state activity and the "stream of consciousness" in schizophrenia-neurophenomenal hypotheses. Schizophr. Bull. http://dx.doi.org/10.1093/schbul/sbu116.
Northoff, G., Duncan, N.W., 2016. How do abnormalities in the brain's spontaneous activity translate into symptoms in schizophrenia? From an overview of resting state activity findings to a proposed spatiotemporal psychopathology. Prog. Neurobiol. 145-146, 26–45. http://dx.doi.org/10.1016/j.pneurobio.2016.08.003. (Epub 2016 Aug 12. Review).
Northoff, G., Stanghellini, G., 2016. How to link brain and experience? Spatiotemporal psychopathology of the lived body. Front. Hum. Neurosci. 10, 172.
Northoff, G., Sibille, E., 2014. Why are cortical GABA neurons relevant to internal focus in depression? A cross-level model linking cellular, biochemical and neural network findings. Mol. Psychiatry 19 (9), 966–977. http://dx.doi.org/10.1038/mp.2014.68. (Epub 2014 Jul 22).
Northoff, G., Heinzel, A., Bermpohl, F., Niese, R., Pfennig, A., Pascual-Leone, A., Schlaug, G., 2004. Reciprocal modulation and attenuation in the prefrontal cortex: an fMRI study on emotional-cognitive interaction. Hum. Brain Mapp. 21 (3), 202–212. http://dx.doi.org/10.1002/hbm.20002.
Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., Panksepp, J., 2006. Self-referential processing in our brain – a meta-analysis of imaging studies on the self. NeuroImage 31 (1), 440–457.
Northoff, G., Wiebking, C., Feinberg, T., Panksepp, J., 2011. The 'resting-state hypothesis' of major depressive disorder-a translational subcortical-cortical framework for a system disorder. Neurosci. Biobehav. Rev. 35 (9), 1929–1945. http://dx.doi.org/10.1016/j.neubiorev.2010.12.007. (Epub 2010 Dec 28. Review).
Panksepp, J., 2004. Textbook of Biological Psychiatry. Wiley Online Library.
Park, H.D., Tallon-Baudry, C., 2014. The neural subjective frame: from bodily signals to perceptual consciousness. Philos. Trans. R. Soc. Lond. B Biol. Sci. 369 (1641), 20130208. http://dx.doi.org/10.1098/rstb.2013.0208. (Print 2014 May 5).
Parnas, J., Sass, L.A., Zahavi, D., 2013. Rediscovering psychopathology: the epistemology and phenomenology of the psychiatric object. Schizophr. Bull. 39 (2), 270–277. http://dx.doi.org/10.1093/schbul/sbs153. (Epub 2012 Dec 23).
de Pasquale, F., Della Penna, S., Snyder, A.Z., Lewis, C., Mantini, D., Marzetti, L., ... Romani, G.L., 2010. Temporal dynamics of spontaneous MEG activity in brain networks. Proc. Natl. Acad. Sci. 107 (13), 6040–6045.
de Pasquale, F., Della Penna, S., Snyder, A.Z., Marzetti, L., Pizzella, V., Romani, G.L., Corbetta, M., 2012. A cortical core for dynamic integration of functional networks in the resting human brain. Neuron 74 (4), 753–764.
Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. NeuroImage 84, 320–341. http://dx.doi.org/10.1016/j.neuroimage.2013.08.048. (Epub 2013 Aug 29).
Qin, P., Northoff, G., 2011. How is our self related to midline regions and the default-mode network? NeuroImage 57 (3), 1221–1233. http://dx.doi.org/10.1016/j.neuroimage.2011.05.028. (Epub 2011 May 15. Review).
Raichle, M.E., 2009. A brief history of human brain mapping. Trends Neurosci. 32 (2), 118–126.
Raichle, M.E., 2015a. The restless brain: how intrinsic activity organizes brain function. Phil. Trans. R. Soc. Lond. B Biol. Sci. 370 (1668), 20140172.
Raichle, M.E., 2015b. The Brain's default mode network. Annu. Rev. Neurosci. 38 (1).
Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc. Natl. Acad. Sci. U. S. A 98 (2), 676–682.
Revonsuo, A., 2006. Inner Presence: Consciousness as a Biological Phenomenon. MIT Press.
Rhodes, P., 2006. The properties and implications of NMDA spikes in neocortical pyramidal cells. J. Neurosci. 26, 6704–6715.
Richter, C.G., Babo-Rebelo, M., Schwartz, D., Tallon-Baudry, C., 2017. Phase-amplitude coupling at the organism level: The amplitude of spontaneous alpha rhythm fluctuations varies with the phase of the infra-slow gastric basal rhythm. NeuroImage 146, 951–958. http://dx.doi.org/10.1016/j.neuroimage.2016.08.043. (Epub 2016 Aug 21).
Sadaghiani, S., Hesselmann, G., Friston, K.J., Kleinschmidt, A., 2010. The relation of ongoing brain activity, evoked neural responses, and cognition. Front. Syst. Neurosci. 4.
Sauseng, P., Klimesch, W., 2008. What does phase information of oscillatory brain activity tell us about cognitive processes? Neurosci. Biobehav. Rev. 32 (5), 1001–1013.
Schroeder, C.E., Lakatos, P., 2009a. Low-frequency neuronal oscillations as instruments of sensory selection. Trends Neurosci. 32 (1), 9–18. http://dx.doi.org/10.1016/j.tins.2008.09.012. (Epub 2008 Nov 13).
Schroeder, C.E., Lakatos, P., 2009b. The gamma oscillation: master or slave? Brain Topogr. 22 (1), 24–26. http://dx.doi.org/10.1007/s10548-009-0080-y. (Epub 2009 Feb 10).
Schroeder, C.E., Lakatos, P., Kajikawa, Y., Partan, S., Puce, A., 2008. Neuronal oscillations and visual amplification of speech. Trends Cogn. Sci. 12 (3), 106–113. http://dx.doi.org/10.1016/j.tics.2008.01.002. (Epub 2008 Feb 15. Review).
Schroeder, C.E., Wilson, D.A., Radman, T., Scharfman, H., Lakatos, P., 2010. Dynamics of Active Sensing and perceptual selection. Curr. Opin. Neurobiol. 20 (2), 172–176. http://dx.doi.org/10.1016/j.conb.2010.02.010. (Epub 2010 Mar 20. Review).
Smallwood, J., Schooler, J.W., 2015. The science of mind wandering: empirically navigating the stream of consciousness. Annu. Rev. Psychol. 66, 487–518.
Stein, B.E., Stanford, T.R., Ramachandran, R., Perrault Jr, T.J., Rowland, B.A., 2009. Challenges in quantifying multisensory integration: alternative criteria, models, and inverse effectiveness. Exp. Brain Res. 198 (2-3), 113–126. http://dx.doi.org/10.

1007/s00221-009-1880-8. (Epub 2009 Jun 24. Review).
Vanhatalo, S., Palva, J.M., Holmes, M., Miller, J., Voipio, J., Kaila, K., 2004. Infraslow oscillations modulate excitability and interictal epileptic activity in the human cortex during sleep. Proc. Natl. Acad. Sci. U. S. A. 101 (14), 5053–5057.
Weinberger, D.R., Radulescu, E., 2016. Finding the Elusive Psychiatric "Lesion" With 21st-Century Neuroanatomy: A Note of Caution. Am. J. Psychiatry 173 (1), 27–33. http://dx.doi.org/10.1176/appi.ajp.2015.15060753. (Epub 2015 Aug 28. Review).
Zhigalov, A., Arnulfo, G., Nobili, L., Palva, S., Palva, J.M., 2015. Relationship of fast- and slow-timescale neuronal dynamics in human MEG and SEEG. J. Neurosci. 35 (13), 5385–5396. http://dx.doi.org/10.1523/JNEUROSCI.4880-14.2015.
Zhu, X., Wang, X., Xiao, J., Liao, J., Zhong, M., Wang, W., Yao, S., 2012. Evidence of a dissociation pattern in resting-state default mode network connectivity in first-episode, treatment-naive major depression patients. Biol. Psychiatry 71 (7), 611–617.
Zmigrod, S., Hommel, B., 2011. The relationship between feature binding and consciousness: Evidence from asynchronous multi-modal stimuli. Conscious. Cogn. 20 (3), 586–593.