Journal of Affective Disorders ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Spatiotemporal psychopathology I: No rest for the brain's resting state activity in depression? Spatiotemporal psychopathology of depressive symptoms

Georg Northoff[a,b,c,d,e,*]

[a] University of Ottawa Institute of Mental Health Research, Ottawa, ON, Canada
[b] Center for Cognition and Brain Disorders, Hangzhou Normal University, Hangzhou, China
[c] Center for Brain and Consciousness, Taipeh Medical University (TMU), Taipeh, Taiwan
[d] College for Humanities and Medicine, Taipeh Medical University (TMU), Taipeh, Taiwan
[e] ITAB, University of Chieti, Chieti, Italy

ARTICLE INFO

Article history:
Received 7 January 2015
Received in revised form
21 April 2015
Accepted 22 April 2015

Keywords:
Major depressive disorder
Resting state
fMRI

ABSTRACT

Despite intense neurobiological investigation in psychiatric disorders like major depressive disorder (MDD), the basic disturbance that underlies the psychopathological symptoms of MDD remains, nevertheless, unclear. Neuroimaging has focused mainly on the brain's extrinsic activity, specifically task-evoked or stimulus-induced activity, as related to the various sensorimotor, affective, cognitive, and social functions. Recently, the focus has shifted to the brain's intrinsic activity, otherwise known as its resting state activity. While various abnormalities have been observed during this activity, their meaning and significance for depression, along with its various psychopathological symptoms, are yet to be defined. Based on findings in healthy brain resting state activity and its particular spatial and temporal structure – defined in a functional and physiological sense rather than anatomical and structural – I claim that the various depressive symptoms are spatiotemporal disturbances of the resting state activity and its spatiotemporal structure. This is supported by recent findings that link ruminations and increased self-focus in depression to abnormal spatial organization of resting state activity. Analogously, affective and cognitive symptoms like anhedonia, suicidal ideation, and thought disorder can be traced to an increased focus on the past, increased past-focus as basic temporal disturbance o the resting state. Based on these findings, I conclude that the various depressive symptoms must be conceived as spatiotemporal disturbances of the brain's resting state's activity and its spatiotemporal structure. Importantly, this entails a new form of psychopathology, "Spatiotemporal Psychopathology" that directly links the brain and psyche, therefore having major diagnostic and therapeutic implications for clinical practice.

© 2015 Elsevier B.V. All rights reserved.

Contents

* Corresponding author at: Mind, Brain Imaging and Neuroethics, Canada Research Chair, EJLB-Michael Smith Chair for Neuroscience and Mental Health, Royal Ottawa Healthcare Group, University of Ottawa Institute of Mental Health Research, 1145 Carling Avenue, Room 6467, Ottawa, ON, Canada K1Z 7K4.
Tel.: +1 613 722- 6521 Ext. 680101; fax: 1 613 798 2982.
E-mail address: georg.northoff@theroyal.ca
URL: http://www.georgnorthoff.com

http://dx.doi.org/10.1016/j.jad.2015.05.007
0165-0327/© 2015 Elsevier B.V. All rights reserved.

Please cite this article as: Northoff, G., Spatiotemporal psychopathology I: No rest for the brain's resting state activity in depression? Spatiotemporal psychopathology of.... Journal of Affective Disorders (2015), http://dx.doi.org/10.1016/j.jad.2015.05.007

ARTICLE IN PRESS

1. Introduction

Major depressive disorder (MDD) is a complex disturbance showing a wide variety of symptoms that cover most brain functions, including sensorimotor, affective, cognitive, and social functions. For instance, patients with major depressive disorder (MDD) show a wide variety of symptoms: cognitive changes are manifest in ruminations and increased self-focus, affective changes predominate here with anhedonia, sensorimotor changes are manifest in terms of psychomotor agitation or retardation, and social functions are affected in the often observed social withdrawal and isolation.

This suggests a close link between psychopathological symptoms on the one hand and sensorimotor, affective, social, and cognitive functions on the other. For that reason, neuroimaging often focuses on searching the neural correlates underlying the abnormalities in the sensorimotor, affective, cognitive, and social functions. Various kinds of affective, sensorimotor, cognitive, and social tasks are applied to probe abnormal changes in the brain's extrinsic activity, otherwise known as stimulus-induced or task-evoked activity (see Northoff, 2014a, 2014b, 2014c, 2014d; Raichle, 2009). These studies yielded novel and important insights into the relationship between extrinsic activity and psychopathological symptoms, and has led to what one may wish to describe as cognitive (Frith, 1992; Kahn and Keefe, 2013) and affective (Panksepp, 2004) approaches to psychopathology.

For all the progress in investigating the brain's extrinsic activity and its various functions, diagnostic or therapeutic markers still remain nevertheless, elusive in both affective and cognitive psychopathology. In its search for these specific markers, recent neuroimaging in psychiatry has shifted to the brain's intrinsic activity, its so-called resting state activity. Roughly, the brain's resting state activity describes the brain's neural activity in the absence of any specific tasks or stimuli (Logothetis et al., 2009). The brain's intrinsic activity can spatially be characterized by various neural networks consisting of regions showing close functional connectivity thus yielding a particular spatial structure (see below for details). The same applies to the temporal domain, where fluctuations in different frequency ranges are coupled with each other, providing 'neural synchrony' (see below). One should be aware, however, that the understanding of the resting state activity's spatial and temporal structure is in its infancy. It shall be pointed out that the concepts of spatial and temporal structure do not refer to merely anatomical and structural features but rather to physiological and functional features; the resting state's spatiotemporal structure may therefore not be directly observable as such but rather existing in a virtual (and statistically-based) sense (see Northoff, 2014a, 2014c).

Neuroimaging reports a variety of changes in both functional connectivity and neural synchrony (see below) in various psychiatric disorders. Both the origin of the resting state abnormalities, as well as their relevance for yielding psychiatric symptoms such as cognitive deficits, however, remains unclear. Setting aside their origin for future discussion, I argue that spatiotemporal abnormalities in resting state activity lead to abnormal spatiotemporal organization of the various internal and external cognitive contents. This, in turn, produces various cognitive deficits and psychopathological symptoms as they can be observed in MDD.

Without conducting a thorough literature review, this will be paradigmatically illustrated by linking cognitive symptoms, such as ruminations in depression and thought disorder, to specific spatial and temporal abnormalities in resting state activity as recently reported. I conclude that such a spatiotemporal approach may lead to a novel psychopathological one, namely a spatiotemporal psychopathology to MDD that, unlike its cognitive and affective siblings, may be able to bridge the gap between the brain and psychopathological symptoms. Finally, I will touch upon the potential diagnostic and therapeutic implications of such a spatiotemporal approach to MDD.

2. Intrinsic activity and its spatiotemporal structure

2.1. Determination of intrinsic activity

How can we determine the brain's resting state activity? The term resting state is often used interchangeable with the ones intrinsic activity or spontaneous activity. Moreover, one should be aware that the concept of the brain's intrinsic or resting state activity is a rather heterogenous one and raises methodological and physiological issues (see also Northoff, 2014a, 2014c). Resting state activity can be measured in different ways: metabolic investigations using PET focus on measuring quantitatively the brain's energetic metabolism indicating the resting state's utilization and distribution of for instance glucose (Shulman et al., 2014). In contrast, fMRI as relying on the BOLD effects as a neuro-vascular (rather than metabolic) signal targets different resting state's neural networks as based on statistical, i.e., correlative relationships between different regions' voxel signifying functional connectivity (Cabral et al., 2013; Menon, 2011; Raichle et al., 2001) (which may also depend on some methodological specifics such as global signal regression; (Gotts et al., 2013; Saad et al., 2012). Finally, resting state activity can also concern electrophysiological or magnetic activity as measured with EEG or MEG (Deco et al., 2013; Ganzetti and Mantini, 2013) that targets neural activity changes in different frequency ranges. Hence, reference to the brain's resting state requires to specify the exact operational measure used in the respective studies.

The different measures of resting state activity may be characterized as spatial, temporal or spatiotemporal. PET, for instance provides spatial resolution while basically showing no temporal resolution. The focus is on spatial resolution in fMRI too though functional connectivity is based on calculating time series of voxel thus introducing a temporal component. EEG/MEG show excellent temporal resolution but low spatial resolution. This makes clear-cut segregation of spatial and temporal features in resting state activity impossible.

Moreover, the resting state's integrated spatiotemporal nature makes the assumption that its abnormalities are spatiotemporal almost trivially true. Resting state abnormalities are by their very nature, i.e., by default spatiotemporal. The central point in this paper though is not about the resting state itself but rather about its linkage

Please cite this article as: Northoff, G., Spatiotemporal psychopathology I: No rest for the brain's resting state activity in depression? Spatiotemporal psychopathology of.... Journal of Affective Disorders (2015), http://dx.doi.org/10.1016/j.jad.2015.05.007

to or translation into psychopathological symptoms: the abnormal spatiotemporal nature of the brain's resting state translates into spatiotemporal abnormalities on the symptomatic, i.e., psychopathological level. This provides a novel perspective on psychopathological symptoms, i.e., a resting state-based spatiotemporal perspective rather than a task-evoked-based sensorimotor, affective, cognitive, or social one (see Section 5 for further more detailed discussion).

2.2. Intrinsic activity and spatial structure

Resting state activity can be characterized by both spatial and temporal dimensions.

Spatially, the brain's intrinsic activity can be characterized by different neural networks such as the default-mode network (DMN), the cognitive-executive network (CEN), the salience network (SN), and the sensorimotor network (see Cabral et al., 2013; Deco et al., 2013; Ganzetti and Mantini, 2013; Menon, 2011; Raichle, 2009; Raichle et al., 2001). The DMN concerns mainly cortical midline regions and the bilateral posterior parietal cortex (Buckner et al., 2008; Raichle et al., 2001). These regions seem to show high resting state activity, dense functional connectivity, and strong low frequency fluctuations (0.001–0.1 Hz) in the resting state. One should be careful, however, not to equate the DMN with resting state activity ('DMN is not the resting state network') since the latter can be found throughout the whole brain and its various networks.

The executive network comprises the lateral prefrontal cortex, the supragenual anterior cingulate, and posterior lateral cortical regions as core regions, as these are involved in higher-order cognitive and executive functions. The executive network is often subdivided into the fronto-parietal network and dorsal attention network (Ganzetti and Mantini, 2013). The salience network includes regions like the insula, the ventral striatum, and the dorsal anterior cingulate cortex, which are associated with reward, empathy, intero/exteroception and other processes involving salience (see Fan and Duncan, 2011; Menon, 2011; Wiebking et al., 2011). Finally, there is the sensorimotor network that is often subdivided into the auditory, somatomotor, and visual networks (see for instance Ganzetti and Mantini, 2013 for a recent review).

In addition to the strong functional connectivity between regions within each network, there are also plenty of interactions between networks. For instance, the DMN and the executive network are often observed to be anticorrelated meaning that the functional connectivity of their respective regions correlate negatively with each other (see Ganzetti and Mantini, 2013). Both networks, DMN and CNE stand in a negative, i.e., anti-correlating relation to each other which has been associated with the distinction between internal (e.g., own thoughts) and external (e.g. perceptions of external environment) contents in (see Carhart-Harris; et al., 2013; Northoff, 2014c, 2014b, 2014d; Vanhaudenhuuyse et al., 2010; Wiebking et al., 2014). We will see later that this negative or anticorrelating relation between DMN and CEN that is especially central in anterior regions may be crucial in accounting for some of the most basic psychopathological symptoms in depression and schizophrenia. One has to be careful though at this point in time: it can currently not be excluded that the anticorrelation between DMN and CEN may be do due methodological reasons, i.e., global signal regression, rather than being genuinely physiological (Gotts et al., 2013; Saad et al., 2012).

2.3. Intrinsic activity and temporal structure

There appears to be quite an elaborate temporal structure to the brain's intrinsic activity as it is manifest in the fluctuations of intrinsic activity in different frequency ranges. Spontaneous fluctuations of neural activity in the resting state are often observed, especially in the default-mode network (DMN) where they are characterized predominantly by low frequencies (<0.1 Hz). However, low (and high) frequency fluctuations in neural activity can also be observed in regions other than the DMN such as the sensory cortices, motor cortex, insula, and subcortical regions like the basal ganglia and thalamus (see Buckner et al., 2008; Freeman, 2003; Hunter et al., 2006; Shulman et al., 2009a, 2009b; Wang et al., 2007; Zuo et al., 2010). Rather than being specific to the DMN, low frequency fluctuations appear to be a hallmark feature of neural activity in general.

Further support for spontaneous resting state activity across the whole brain comes from electrophysiological studies showing spontaneous neuronal oscillations and synchronizations in various parts of the brain including the hippocampus and visual cortex (Arieli et al., 1996; Buzsaki, 2006; Buzsaki and Draguhn, 2004; Fries et al., 2007, 2001; Llinas, 1988). This suggests that spontaneous fluctuations—and thus intrinsic activity—may be prevalent throughout the whole brain in both humans and animals, and not limited to the DMN.

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). 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 artefacts caused by sweating, movements, and electrode drift; their measurement therefore requires a more direct approach by so-called DC (direct current) recording. There is some evidence that what is measured as SCP in EEG corresponds to, or is even identical to the low frequency fluctuations obtained in fMRI (see He and Raichle, 2009 as well as He and Raichle, 2009; Khader et al., 2008 for reviews).

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) (see Mantini et al., 2007; Sadaghiani et al., 2010). This raises the question how low and high frequencies are related to each other in the brain's resting state (see also the recent reviews by 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, e.g., during rest, where, using DC-EEG, low frequency oscillations were recorded. All subjects showed infraslow oscillations (0.02–0.2 Hz); these were detected across 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). Such phase-locking of high frequency oscillations' power to the phases of lower ones is described as *phase-power coupling*, with phase-phase and power-power coupling also being possible (see Canolty and Knight, 2010 as well as Sauseng and Klimesch, 2008 for excellent reviews). Generally, the coupling seems to occur in the direction from low to high frequency fluctuations as well from phase to amplitude/power (see Buzsaki, 2006; Buzsaki et al., 2013)—the phase of the lower frequency entrains the amplitude of the higher frequency.

3. Spatial dysbalance and 'increased self-focus' in MDD

3.1. Spatial dysbalance between medial/DMN and lateral/CEN networks in resting state activity

Major depressive disorder (MDD) is a psychiatric disorder that is characterized by extremely negative emotions, suicidal thoughts,

Please cite this article as: Northoff, G., Spatiotemporal psychopathology I: No rest for the brain's resting state activity in depression? Spatiotemporal psychopathology of.... Journal of Affective Disorders (2015), http://dx.doi.org/10.1016/j.jad.2015.05.007

hopelessness, diffuse bodily symptoms, lack of pleasure, i.e., anhedonnia, ruminations, and enhanced stress sensitivity (see Hasler and Northoff, 2011 as well as Northoff et al., 2011 for a recent overview and Kuhn and Gallinat, 2013 as well as Northoff, 2014a, 2014b, 2014c, 2014d). We here focus only on MDD while leaving aside bipolar disorder and its many neural overlaps with both schizophrenia and MDD which will be subject to future spatiotemporal investigation.

How about the resting state activity in MDD? (Alcaro et al., 2010b) conducted a meta-analysis of all imaging studies in human MDD that focused on resting-state activity. This yielded hyperactive regions like PACC, VMPFC, thalamic regions like the dorsomedial thalamus and the pulvinar, pallidum/putamen and midbrain regions like VTA, Substantia nigra (SN), the Tectum and the PAG. In contrast, resting-state activity was hypoactive and thus reduced in the dorsolateral prefrontal cortex (DLPFC), the posterior cingulate cortex (PCC) and adjacent precuneus/cuneus (Alcaro et al., 2010a) (see also Kuhn and Gallinat, 2013 for similar results). The PACC and anterior midline resting state hyperactivity seems to be somehow specific for depression since in schizophrenia there is rather hypoactivity (see Kuhn and Gallinat, 2013; Zhu et al., 2012).

These results are well in accord with other meta-analyses (see Fitzgerald et al., 2006, 2007; Price and Drevets, 2010; Savitz and Drevets, 2009). Also, Price and Drevets (2010) and Savitz and Drevets (2009a, 2009b) emphasized the role of the hippocampus, parahippocampus and the amygdala where resting-state hyperactivity was also evident in MDD. Interestingly, the very same regions and the PACC also show structural abnormalities with reduced grey matter volume in imaging studies and reduced cell counts markers of cellular function in post-mortem studies (see Price and Drevets, 2010; Savitz and Drevets, 2009a, 2009b).

Involvement of these regions in MDD is further corroborated by the investigation of resting-state activity in animal models of MDD. Reviewing evidence for resting-state hyperactivity in various animal models, yielded diverse participating brain regions—the anterior cingulate cortex, the central and basolateral nuclei of the amygdala, the bed nucleus of the stria terminalis, the dorsal raphe, the habenula, the hippocampus, the hypothalamus, the nucleus accumbens, the PAG, the DMT, the nucleus of the solitary tract, and the piriform and prelimbic cortex (Alcaro et al., 2010b). In contrast, evidence of hypoactive resting-state activity in animal models remains sparse with no clear results (Alcaro et al., 2010b).

How do these regional changes translate onto the network level? As illustrated above, anterior and posterior midline regions like especially PACC and VMPFC are core regions of the DMN while the DLPFC is part of the CEN. A recent meta-analysis of resting state functional connectivity observed the following abnormal changes in DMN and CEN in MDD (see 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 functional hyperconnectivity between DMN and CEN; (Kaiser et al., 2015).

In sum, the data provide evidence for abnormal resting state hyperactivity in anterior midline regions in depression while there is reduced activity, e.g., hypoactivity in the resting state in lateral regions like the DLPFC. A recent study in healthy subjects (Chen et al., 2013) observed direct causal interaction between midline and lateral networks, e.g., DMN and CEN: inhibition of neural activity in for instance the DLPFC (by using transcranial magnetic stimulation) increased DMN/PACC–VMPFC functional connectivity as measured in fMRI. In contrast, excitation of DLPFC neural activity reduced PACC–VMPFC functional connectivity. This is well compatible with the observation in MDD where increased functional connectivity in PACC–VMPFC and thus DMN is accompanied by decreased functional connectivity in lateral prefrontal cortex and the CEN (Hasler and Northoff, 2011; Northoff, 2014c, 2014a; Zhu et al., 2012). One can thus speak of functional dysbalance between DMN and CEN with their spatial balance tilting abnormally towards the former at the expense of the latter.

3.2. Resting state and spatial dysbalance between self- and environment-focus

How is such abnormal spatial structure in resting state activity manifest in experience and mental contents (and subsequently in psychopathological symptoms) in depression? As indicated earlier, the anterior midline network has been associated with internal mental contents as occurring during random thoughts, consciousness, mind wandering, and self-referential activity (Northoff, 2014c, 2014b, 2014d). In contrast, neural activity in the lateral network or the CEN is rather related to external mental contents originating in the environment as distinguished from those related to the self. If now the anticorrelation between midline and lateral networks, between DMN and CEN is shifted abnormally towards the former, the DMN at the expense of the latter, the CEN, one would expect analogous shift between internal and external mental contents, e.g., between self- and environment-related contents: internal, e.g., self-related contents should become more prominent in awareness, e.g., consciousness while external, e.g., environment-related contents should be weaken and recede (see Fig. 1a and b).

Such shift towards internal, e.g., self-related mental contents has been described as ‘increased self-focus’ (Northoff, 2007). This abnormal shift towards self-related contents results in ruminations that revolve around the own self, as is illustrated in the following: “She sat by the window, looking inward rather than looking out. Her thoughts were consumed with her sadness. She viewed her life as a broken one, and yet she could not place her finger on the exact moment it fell apart. ‘How did I get to feel this way?’ she repeatedly asked herself. By asking, she hoped to transcend her depressed state; through understanding, she hoped to repair it. Instead, her questions led her deeper and deeper inside herself –further away from the path that would lead to her recovery.” (Treynor et al., 2003)

The concept of increased self-focus describes that attention to and awareness of internal, e.g., self-related mental contents predominate and are rather strong in MDD patients. The increased self-focus may be related to the abnormally increased resting state activity in PACC/VMPFC and the increased functional connectivity within the DMN. The former is indeed supported by recent data. Paradigms requiring a self-reference task show abnormal activity in anterior midline regions in response to pictures or nouns to which an abnormally high degree of self-reference is attributed (see Grimm et al., 2011, 2009a; Lemogne et al., 2012, 2009) though only indirectly (on the basis of deactivation), such abnormal task-induced activity was shown to be related to abnormally high resting state activity in the midline regions (Grimm et al., 2011).

In addition to the increased self-focus, the attention may also focus on the own body. Psychologically this is for instance manifest in increased perception of the own body and its changes as related to stress, autonomic nervous systems (as measured with the Body Perception Questionnaire; Wiebking et al., 2010). How about the underlying neural mechanisms? Interoceptive stimuli as stemming from the own body are processed in the insula and the salience network (see above) in balance with exteroceptive stimuli (see above). MDD patients show decreased activity in insula in response to exteroceptive stimuli which leads to relative predominance of interocepetive stimulus processing in the same region (Wiebking et al., 2010).

Please cite this article as: Northoff, G., Spatiotemporal psychopathology I: No rest for the brain’s resting state activity in depression? Spatiotemporal psychopathology of.... Journal of Affective Disorders (2015), http://dx.doi.org/10.1016/j.jad.2015.05.007

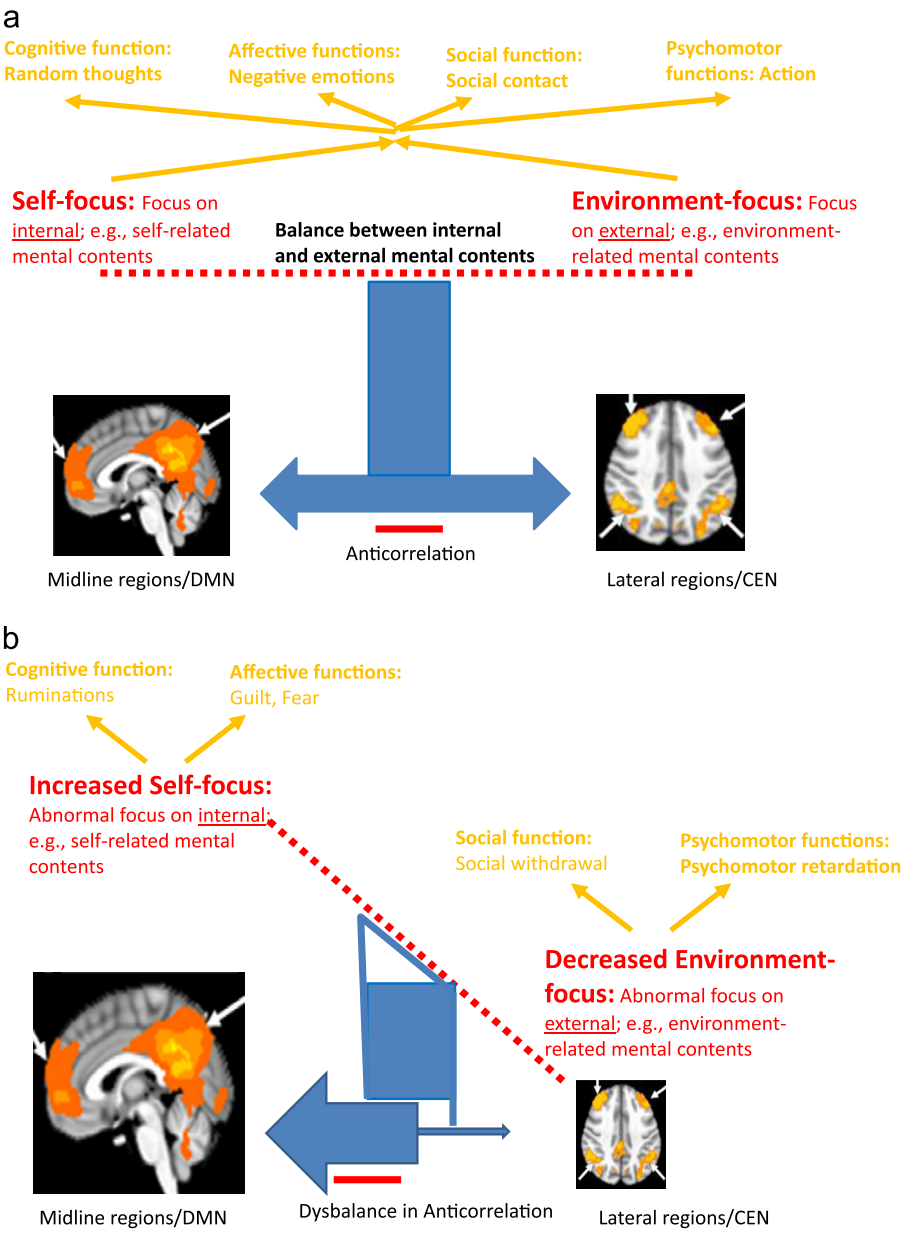

Fig. 1. Spatial structure of resting state activity and spatial dysbalance between self- and environment-focus in depression. (a) and (b): The lower part shows, on the left, the typical regions of the default-mode network (DMN) with the image displaying the medial prefrontal cortex (anterior white arrow) and the posterior cingulate cortex (posterior white arrow). While on the lower right the regions of the central executive network (CEN) are shown with the lateral prefrontal cortex (anterior white arrows) and the lateral parietal cortex (posterior white arrows) being displayed in the image. The blue horizontal bar represents the relationship between medial regions (DMN) and lateral regions (CEN). The – sign indicates negative correlation as in healthy subjects between DMN and CEN. The anticorrelation may be tilted towards the DMN as it is the case in depression where especially the anterior DMN is hyperactive and the CEN hypoactive; this is indicated by the right and left differences in the horizontal arrow. The middle part of the figure (in red) shows the spatial balance (or dysbalance) between internal and external mental contents and hence between self- and environment-focus. The DMN mainly processes internal mental contents as originated and related to the own self, while the CEN mediates external mental contents from the environment. The red dotted vertical line represents the distinction between internal and external mental contents in consciousness or awareness (see (a)). There is reciprocal modulation and balance between internal and external mental contents and thus between self- and environment-focus in healthy subjects, as indicated by the red horizontal dotted line and the underlying blue bar. Due to the shift of the anticorrelation towards the DMN (as indicated by the enlarged brain image with the midline regions) at the expense of the lateral regions and their executive network (as indicated by small brain image), this balance between internal and external mental contents is abnormally tilted towards the former in depression (see (b)), resulting in increased self-focus and decreased-environment focus. The upper part in both figures illustrates the manifestations of self- and environment focus in cognitive, affective, social and psychomotor functions (see (a)) and the resulting psychopathological symptoms in MDD (see (b)). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Interestingly, the insula also show resting state functional hyperconnectivity to the anterior midline regions (like the subgenual anterior cingulate) of the DMN (Avery et al., 2014). The intero-exteroceptive dysbalance in the insula and its abnormally high functional connectivity to the anterior DMN may mean that the attention may also focus on the own body resulting in increased body-focus (see Northoff, 2014b, 2014d; Northoff and Qin, 2011). The concept of the increased body-focus describes that mental contents concern mainly bodily contents. However, future studies are needed to investigate the exact relationship between salience network and DMN as well as between self- and body-focus in both healthy and MDD subjects.

One may need to be careful though. Alternatively to experiencing diverse unspecific somatic symptoms, the own body may also be experienced as heavy, failed, slowed, lifeless and ultimately dead ('something struck in my throat'. 'head congested', 'stomach

Please cite this article as: Northoff, G., Spatiotemporal psychopathology I: No rest for the brain's resting state activity in depression? Spatiotemporal psychopathology of.... Journal of Affective Disorders (2015), http://dx.doi.org/10.1016/j.jad.2015.05.007

fallen down', 'head crocked', 'I am dead', 'I stink') (Stanghellini et al., 2014).

In that case the body is no longer experienced as mental content that by definition is alive (and subjective), i.e., the lived body, but rather as mere physical object, i.e., as objective body. One may then no longer want to speak of an increased body-focus but rather the opposite, decreased body-focus. Future investigation may want to search for the relationship between self-focus and body-focus whether there is for instance reciprocal relationship: increase in self-focus may go along with decrease in body-focus and vice versa which neuronally may eventually be related to the relationship between insula/salience network and PACC–VMPFC/DMN.

Finally, the functional hypoconnectivity within the CEN and its decreased functional connectivity to posterior parietal regions involved in the attention towards the environment may translate into decreased focus on the environment. This results in a decreased environment-focus that can be described by the decreased occurrence of mental contents stemming from the environment, i.e., external rather than internal mental contents (Northoff, 2014b, 2014d; Northoff and Qin, 2011). Specifically, the increased resting state activity in anterior midline regions may tilt the anticorrelation with lateral regions/networks unilaterally towards the midline regions.

This shifts the reciprocal balance between internal and external mental contents towards the former at the expense of the latter: the patients' focus more on the internal mental contents, e.g., self-related content while the external mental contents recede into the background. The reported increased functional connectivity between DMN and CEN may further 'enslave' the environment-focus by the self-focus. This results in an increased self-focus and concomitantly decreased environment-focus and thus in spatial dsybalance between self- and environment-related, i.e., internal and external mental contents.

3.3. Spatial dysbalance and psychopathological symptoms

I described so far three basic features (see in Section 5 for brief discussion), increased self-focus, increased body-focus, and decreased environment-focus. How do these now translate into the psychopathological symptoms one can observe in these patients? Let us start with the increased self-focus. The increased self-focus concerns internal mental contents as they are manifest in the own thoughts and cognition, the random thoughts and mindwandering that continuously occur in the resting state. Increase in these internal mental contents is consecutively manifest in an abnormal increase in the own thoughts and cognitions which psychopathologically is manifest in ruminations and, if extreme, in brooding. Hence, ruminations can be considered the cognitive manifestation of the increased self-focus.

In addition, the increased self-focus may also be manifest in affective functions. Data suggest abnormal functional connectivity between anterior DMN regions and regions (like the amygdala) implicated in emotional processing (see Kaiser et al., 2015). The increased self-focus may then be accompanied by excessive feelings of guilt and eventually of sadness which abnormally related and assigned to the own self. The increased self-focus is consequently manifest and extends in cognitive functions, i.e., ruminations, and affective functions, i.e., guilt and sadness.

How about the increased body-focus? The increased attention to the own body and its interoceptive processing including its abnormally close relation to the self (as mediated by increased functional connectivity from insula to anterior DMN) may results in hypersensitive perception of the own body and hence the various unspecific somatic symptoms (like accelerated heart and breathing rate, pain, etc.) including hypochondria in MDD. The increased body-focus consecutively becomes manifest in the vegetative functions of the body as in anergia, lack of energy, lack of appetite, and loss of libido. The same may hold for the opposite, the decreased body-focus which psychopathologically may be manifest in hyperenergy, increased appetite, and libido as in mania (see also Fig. 1a and b in upper part for the different functions and their respective symptoms).

The decreased environment-focus as related to the decreased CEN concerns external mental contents from the environment. If the external mental contents are decreased, goal-orientations may no longer be as available leading to deficits in executive functions (and also working memory) as they can indeed be observed. Moreover, as described above, the decreased functional connectivity from CEN to the posterior parietal attention system related to the external environment may strongly contribute to the lack of goal-orientation and the deficits in attention that can often be observed in MDD.

Finally, the decreased environment-focus may also be manifest in lack of motivation and volition to act in the external environment which ultimately may result in psychomotor retardation and social withdrawal on the psychopathological side. However, to further substantiate that, one may want to investigate the relationship between DMN and CEN with the especially the sensorimotor network: one may assume that both DMN and CEN show resting state functional hypoconnectivity to the sensorimotor network. In sum, the spatial dysbalance between the three networks may thus translate into spatial dsybalance between self and body on the one hand, and environment on the other which psychopathollogically may translate into dysbalance between internally-oriented cognitive and externally-oriented psychomotor activity.

In sum, there is strong evidence for abnormal spatial structure in resting state activity in MDD with abnormal shift of the anticorrelation between medial and lateral networks towards the medial, e.g., the DMN, at the expense of the lateral ones, the CEN. That entails abnormal reciprocal balance between internal, e.g., self-related, and external, e.g., environment-related, mental contents. The patients may consequently suffer from 'increased self-focus' and 'decreased environment-focus' as "basic spatial disturbance" in MDD.

4. Temporal dysbalance and 'increased past—Focus' in MDD

4.1. Temporal dysbalance between slow and fast oscillations in resting state activity

The temporal structure of the resting state activity can be measured using EEG. EEG is predominantly used to measure event-related potentials (ERP) in response to specific stimuli thus targeting stimulus-induced or task-evoked activity. Additionally, EEG can also measure the power in different frequency oscillations including delta (1–4 Hz), theta (5–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (30–180 Hz) in resting state as during eyes open and closed. Resting state investigations in MDD showed consistently power increase in the lower frequency ranges like delta and especially theta (see Baskaran et al., 2012; Fingelkurts and Fingelkurts, 2014b; Iosifescu, 2011; Olbrich and Arns, 2013). In contrast, power in higher frequencies like gamma does not seem to be really altered in MDD. Together, this suggests (tentatively) that the relative balance in power shifts towards low frequency oscillations that relative predominate over higher ones.

The well documented of especially theta power is of particular interest. A combined EEG-FDG-PET study observed that resting state theta power was high in PACC/subgenual anterior cingulate (as measured with current source density in EEG) and correlated well with glucose metabolism in that same region (as measured with FDG-PET) (Pizzagalli et al., 2003). This suggests that the increase in theta in MDD seems to be directly related to the increase in resting state activity in PACC–VMPFC as described above. Hence, the resting state's spatial dysbalance towards the anterior DMN, i.e., PACC–VMPFC, may be

Please cite this article as: Northoff, G., Spatiotemporal psychopathology I: No rest for the brain's resting state activity in depression? Spatiotemporal psychopathology of.... Journal of Affective Disorders (2015), http://dx.doi.org/10.1016/j.jad.2015.05.007

closely related with to temporal dysbalance between lower and higher frequency oscillations.

In addition to the low frequencies, i.e., delta and theta, intermediate frequency like alpha seems to be consistently elevated in MDD (see Baskaran et al., 2012; Fingelkurts and Fingelkurts, 2014a; Iosifescu, 2011; Olbrich and Arns, 2013 for reviews). Moreover, when shifting from EC to EO, alpha power shows a typical decrease, the alpha blockade. Interestingly, this alpha decrease or blockade during the shift from EC to EO is significantly lower in MDD. Alpha power has been associated with inhibition of processing and attending external stimuli while its decrease is related to disinhibition as for instance during the shift from EC to EO (Klimesch, 2012).

Increase in alpha power as in MDD thus suggests increased inhibition while the decreased alpha blockade may be related to the decreased capacity to disinhibit the ongoing resting state activity. This suggests that external stimuli (as for instance during EO) can no longer properly disinhibit the ongoing resting state's alpha power anymore thus showing decreased resting state reactivity; that in turn may lead to the decreased (external) stimulus processing resulting subsequently in decreased attention towards external stimuli, i.e., the decreased environment-focus (see above). However, for that to be validated one need to combine spatial (fMRI) and temporal (EEG) measures of resting state activity to show that increased alpha power is related to increased resting state activity (i.e., variability, functional connectivity, metabolism) in especially the anterior midline regions, i.e., PACC–VMPFC.

In addition to the power of frequencies, one can also investigate the functional connectivity between different areas using measures of coherence or synchronization. Fingelkurts et al. (2007) and Leuchter et al. (2012) observed increased coherence between frontopolar electrodes and posterior parietal and temporal electrodes in theta and alpha bands (but also in delta and beta bands) in MDD. Lee et al. (2011) demonstrated that stronger coherence, e.g., functional connectivity strength in delta and theta in frontopolar electrodes predicted subsequent non-response to antidepressant treatment. Olbrich et al. (2014) measured functional connectivity in EEG by the degree of synchronization between phase onsets, i.e., lagged phased synchronization. This revealed increased alpha phase-lagged synchronization between subgenual/pregenual anterior cingulate cortex and medial prefrontal cortex (VMPFC, DMPC) and DLPFC in unmedicated MDD patients before treatment (see Olbrich et al., 2014). Interestingly, increase alpha coherence also predicted subsequent treatment response which went along with shift of phase-lagged synchronization shifted to a higher frequency namely beta.

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

4.2. Experience of 'Slowing' and temporal dysbalance between past and future-focus

How is the resting state's temporal dysbalance manifest in experience of time and associated mental contents (and ultimately in psychopathological symptoms)? For that let us go briefly to descriptions of subjective experience of time. In his "General Psychopathology" Jaspers (1964/1997) points out the extreme slowing of the subjective experience of time flow in MDD; time no longer flows as fast and comes almost to a "standstill". This is for instance reflected in the experience that time is "dragging and endless" and that "everything including the own movements are "slowed up" (see also Stanghellini et al., 2015). The slowing down of the flow of time in subjective time experience is a well described (see also Fuchs, 2013) for a more recent phenomenological description) documented phenomenon in MDD: this is confirmed on the grounds of many single subjective reports (Fuchs, 2013; Jaspers, 1964/1997), semi-quantitative analyses of qualitative interviews (Stanghellini et al., 2015), and quantitative investigation (using visual analogue scales (VAS) or questionnaires for measuring subjective time experience (Bschor et al., 2004; Mahlberg et al., 2008; Thönes and Oberfeld, 2015).

Where do the subjective time experience abnormalities originate? One hypothesis is that they may stem from abnormal time judgment so that objectively time can no longer be properly judged. One way to test that is to use different time judgment tasks (like time production, reproduction, estimation, and duration discrimination) where time intervals have to be estimated, produced, reproduced (i.e., recalled), or distinguished (i.e., discriminated). A recent meta-analyses of the various studies (Thönes and Oberfeld, 2015) shows though no clear evidence for abnormalities in time judgment. In contrast, meta-analytic evidence stands for abnormalities in subjective experience of time flow which is experienced in a slowed or decelerated way as distinguished from the fastened or accelerated way in mania (see Bschor et al., 2004; Mahlberg et al., 2008; Thönes and Oberfeld, 2015).

Taken together, these data suggest dissociation between subjective and objective time. Objective time as measured in time judgment tasks seems to remain normal whereas subjective time, the experience of slowing of time flow, is abnormal. Phenomenologically, such dissociation between objective and subjective time has been described as dissociation or desynchronziation between world, i.e., world-related time and own, i.e., self-related time, which has also been described as 'intersubjective time'. (see Fuchs, 2013; Minkowski, 1930/1993). World-related time reflects objective time as can be observed and judged in the outside world or environment while self-related time concerns the subjective experience of for instance the flow of time.

In the healthy subject, both world- and self-related time usually correspond to a high degree and thus synchronized. This though changes in MDD where self-related time becomes slowed or decelerated compared and henceforth relative to world-related time (while in mania the opposite takes place with the abnormal fastening or acceleration of self-related time). Self- and world-related time dissociate or desychronize from each other (see Fig. 1 in Fuchs, 2013) in MDD. The focus is consequently shifted towards the abnormal slowing of time in self-related time which can no longer be linked or coupled to, i.e., synchronized with, world-related time; that implies that the increased self-focus as described above and its dsybalance with the decreased environment-focus is not only spatial but also temporal.

The extreme slowing of time can lead to the subjective experience of complete "standstill" with the subjective experience that time is no longer real and existent. This is reflected in quotes like "*as if there were always the same instant, as if there was a void free of time*"(Jaspers, 1964/1997), time is "void", "absent", "non-existing", "black", or a "complete shadow" (Stanghellini et al., 2015) who also confirms the subjective experience of standstill and non-existence in a semi-quantiative way based on qualitative interviews). However, despite the subjective experience of the non-existence of time in their own self, MDD patients know well

Please cite this article as: Northoff, G., Spatiotemporal psychopathology I: No rest for the brain's resting state activity in depression? Spatiotemporal psychopathology of.... Journal of Affective Disorders (2015), http://dx.doi.org/10.1016/j.jad.2015.05.007

that time exists in the world: they do not subjectively experience time whose objective existence they though know well.

Such standstill in subjective experience of time is closely related to the extreme focus on past events in MDD patients while at they same time they remain unable to project themselves into the future. This is reflected in the following: "the present has nothing for them, and the future lies horrifyingly before them (Jaspers, 1964/1997), "I understand that the time may be past, but the past is still present as accusation. …. One has said things which cannot be made unsaid; one can no longer escape from what one has done." (Fuchs, 2013), 98). One can consequently speak of a temporal dysbalance between past and future in subjective experience of time: the past including the recall of past actual mental contents predominates over the future with the anticipation of future possible (rather than actual) mental contents. Therefore I speak of a temporal dysbalance with increased past-focus and decreased future-focus in MDD.

The concepts of increased past focus and decreased future focus describe that the temporal balance between past, present and future mental contents in experience, e.g., consciousness, is unilaterally shifted towards past mental contents which overshadow and predominate present and future mental contents. Note that such shift in subjective time experience towards the past, the increased past-focus, needs to be distinguished from the subjective experience of disruption of time in schizophrenia: subjective experience of temporal continuity is still preserved in MDD but abnormally staunched or tilted towards the past at the expense of its opposite end, the future. This is no longer in case in schizophrenia where temporal continuity is itself disrupted resulting in the fragmentation of subjective time experience (see Northoff, 2014a, 2014b, 2014c, 2014d, 2015b; Stanghellini et al., 2015).

4.3. Resting state, subjective experience, and temporal dysbalance

How can we now link the abnormalities in subjective experience of time to the temporal dysbalances observed in resting state activity? Let us start with the well documented and validated extreme slowing or deceleration in subjective experience of time flow. Resting state data showed abnormally strong power in lower or slow frequencies like delta and especially theta and alpha (see above). This shifts the relative power balance between slow (delta, theta, alpha) and fast (beta and especially gamma) frequency oscillations towards the slower pole implying temporal dysbalance with increased slow and (relatively) decreased fast oscillations.

The (relative) increase in slow oscillations means that changes in neural activity, e.g., the phases of an oscillation with low and high excitability periods, do no longer occur as often. Neural activity shows consequently a higher degree of temporal continuity that describes the number of time points during which neuronal activity remains the same and does not change (see Northoff, 2014a, 2014c, 2014d, 2014b) for the concept of temporal continuity). In contrast, the relative decrease in fast oscillations means that the degree of temporal flow of neural activity, the number of points in time after which neural activity changes (see Northoff, 2014a, 2014b, 2014c, 2014d) for the concept of temporal flow), is rather low. The temporal dysbalance between slow and fast freqeuncy oscillations entails temproal dysbalance between temporal continuity and temproal flow in neural activity.

MDD patients show apparently an abnormal increase in their resting state's temporal continuity while its temporal flow is decreased. Resting state activity remains the same and does not change to a higher degree in these patients which may be subjectively experienced as the slowing of time. Let us be more specific. Due to the predominance of slow oscillations with their longer phase durations, time is extended and stretched which can then is subjectively experienced as slowing or deceleration of time: the lower the freqeuncy in which the power increase can be observed, the longer its phase durations, and the higher degrees of slowing down of time may be experienced by the patients. In short, one would expect proportional relationship between frequency range/phase duration and degree of slowing in subjective time experience (see Fig. 2a).

How about the temporal dysbalance between increased past-focus and decreased future-focus in MDD? We recall the abnormally increased functional connectivity, i.e., coherence and phase-lagged synchronization in the whole brain resting state in very slow, i.e., infra-slow (fMRI) and slow (EEG) frequency oscillations (see above). Increased functional connectivity across the whole brain means that neural activity in specific regions (as triggered by either internal or external stimuli) can no longer change as much indicating higher degrees of temporal continuity and temporal flow (see above for definitions) in the overall resting state. The abnormal increase in temporal continuity of the brain's overall resting state activity is especially fostered by the infraslow frequency fluctuations showing increased functional connectivity (as measured in fMRI) (see above) because their extremely long phase durations (up to 100 s) contribute strongly to an abnormally high degree of temporal continuity.

The infraslow and slow frequency coherence' extremely high degree of temporal continuity in resting state activity may be related to the subjective experience of "standstill": due to the abnormal functional connectivity in infraslow and slow functional connectivity, "nothing moves anymore in neural activity" which subjectively is experienced as "standstill". That, in turn, is related to the increased past-focus and decreased future-focus with the former based on abnormally high degrees of temporal continuity and the latter on low degrees of temporal flow of neural activity. One would consequently expect proportional relationship between the degree of increase in infraslow and slow frequency functional connectivity and the subjective experience of "standstill" and increased past-focus: the higher the increase in infraslow and slow frequency functional connectivity, the stronger the degree of subjective experience of a "standstill", and the more the past-focus is increased and the future-focus decreased (see Fig. 2b).

How about the nosological specificity of these neurophenomenal relationships? Mania shows the opposite pattern with fastening/acceeleration of time and an increased future-focus and decreased past-focus. A recent study in bipolar mania did indeed obserevd decreased theta and increased beta oscillations (Painold et al., 2014) indicating that the temporal balance is shifted towards the faster oscillations. Moreover, global coherence or synchronization is decreased in infraslow (Magioncalda et al., 2014) (as in fMRI) and slow (as in EEG; Fingelkurts and Fingelkurts, 2014a; Kim et al., 2013) frequency ranges. This may be related to the opposite temporal dysbalance with decreased past-focus and increased future-focus.

How about schizophrenia? As indicated above schizophrenic patients can experience abnormal slowing and "standstill" of time which though is based on the organisation (or articulation as Stanghellini et al., 2015 say) of time, i.e., temporal fragementation and disruption rather than a primary deficit in the speed of time (see Northoff, 2014a, 2014b, 2014c, 2014d, 2015a; Stanghellini et al., 2015). Data indicate that the relationship between the different freqeuncy oscillations is not only shifted towards either pole, i.e., fast or slow, but that their relationship itself as for instance engineered by cross-frequency phase-phase or phase-power coupling may be disrupted (see Northoff, 2014a, 2014b, 2014c, 2014d, 2015a; Stanghellini et al., 2015). In contrast to schizophrenia, one would not expect analogous disruptions in cross-frequency coupling in MDD which though remains to be investigated.

4.4. Temporal dysbalance and psychopathological symptoms

How are the experience of 'slowing', 'standstill' and increased past-focus and their underlying resting state temporal dysbalances

Please cite this article as: Northoff, G., Spatiotemporal psychopathology I: No rest for the brain's resting state activity in depression? Spatiotemporal psychopathology of.... Journal of Affective Disorders (2015), http://dx.doi.org/10.1016/j.jad.2015.05.007

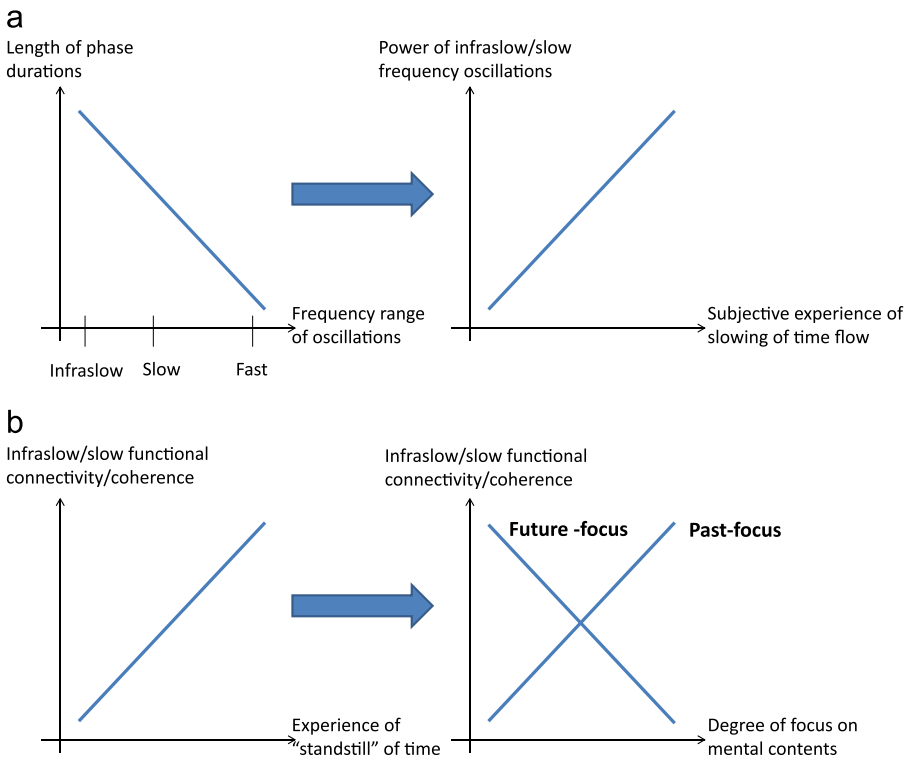

Fig. 2. Relationship between oscillations and subjective experience. (a) demonstrates how the relationship between infraslow/slow and fast oscillations is related to phase durations (left) and subjective experience of slowing of time (right): the lower the frequency of the oscillations, the longer its phase durations, entailing that stronger power in infraslow/slow oscillations leads to stronger subjective experience of slowing of time flow. (b) shows the relationship between infraslow-slow oscillations and the experience of "standstill" and the balance between past- and future-focus. The stronger the power of infraslow/slow oscillations, the stronger the past-focus and the lower the future-focus.

manifest in sensorimotor, affective, cognitive and social functions and their respective psychopathological symptoms? Let us start with the affective symptoms. The recent meta-analysis of MDD fMRI–based resting state networks by Kaiser et al. (2015) investigated what they describe as affective network (that as part of the salience network) includes regions like PACC–VMPFC, the insula, the amygdala, and ventral striatum. MPFC showed decreased functional connectivity from PACC–VMPFC to ventral striatum (and reward system) which may be related to the decrease in positive emotions. While functional connectivity from PACC–VMPFC to amygdala is increased as it may be related to the abnormal increase in negative emotions.

Functional connectivity is here obtained in fMRI and taps therefore into the infraslow freqeuncy fluctuation range as characterized by extremely long phase durations (up to 100 s) suggesting high degree of temproal continuity. That does apparently not only result in subjective experience of slowing and ultimately "standstill' in the flow of time (see above) but is also related to abnormal increase in negative emotions like hopelessness, grief, sadness, and guilt and ultiamtely even the subjective experience of death ("I am slowly dying" resulting in Cotard syndrome that refers to the denial of being alive or existent) and decay (Fuchs, 2013; Stanghellini et al., 2015). To put in an even more accentuated way, neural shift towards infraslow and slow frequency oscillations seems to be closely associated with negative emotions and the corresponding changes in the underlying neural systems like the affective network. The opposite can again be obserevd in mania where positive emotions like excitement, happiness and joy prevail (see Fig. 3a and b).

How about cognitive functions? The predominance of infraslow and slow frequency oscillations may make cognitive operations that require temporal precision with respect to both internal thoughts and external goals rather difficult. This is neuropsychologically well reflected in the various cognitive deficits including executive functions, attention, and working memory in MDD (see for instance Snyder, 2013). While neuronally, this may be related to the decreased functional connectivity within the CEN and its abnormally increased functional connectivity to the PACC–VMPFC with both changes occuring in infraslow and slow frequency ranges. One may consequently assume that stronger anterior DMN/PACC–VMPFC power and PACC/VMPFC–DLPFC functional connectivity in infraslow and slow oscillation ranges may lead to abnormal slowing of neural activity, i.e., increased temporal continuity which in turn is manifest in cognitive deficits.

Social functions may also be affected. As described above, slowing and "standstill" of subjective time flow dissociates or desynchronizes self- and world-related time. The discrepancy in speed between self- and world-related time make it more difficult for the depressed patient to connect and related to others, his social environment, and the world in general. He consecutively withdraws from his social context and the world resulting in psychopathological symptoms like social withdrawal, anergy and apathy that go along with changes in the underlying neural correlates. Increased whole brain coherence may make the brain less flexible to adapt to environmental changes resulting in increased social withdrawal and decreased behavioral adaptation. This is well reflected in the following quote by Olbrich and Arns (2013) from their meta-analysis of EEG saying that the brain "might reflect a rigid and less flexible CNS (central nervous system) that leads to impaired behavioral adaptation o the whole organism ot the requirements of the environment in MDD" (Olbrich and Arns, 2013).

Finally, psychomotor functions may be strongly altered. The predominance of infraslow and low frequency oscillations may extend from the DMN to the sensorimotor network. Using fMRI Abou (Abou Elseoud et al., 2014) in patients with seasonal affective disorder increased functional connectivity in sensorimotor network (and visual and attentional networks). Since functional connectivity was here measured in the infraslow range (using fMRI), this would

Please cite this article as: Northoff, G., Spatiotemporal psychopathology I: No rest for the brain's resting state activity in depression? Spatiotemporal psychopathology of.... Journal of Affective Disorders (2015), http://dx.doi.org/10.1016/j.jad.2015.05.007

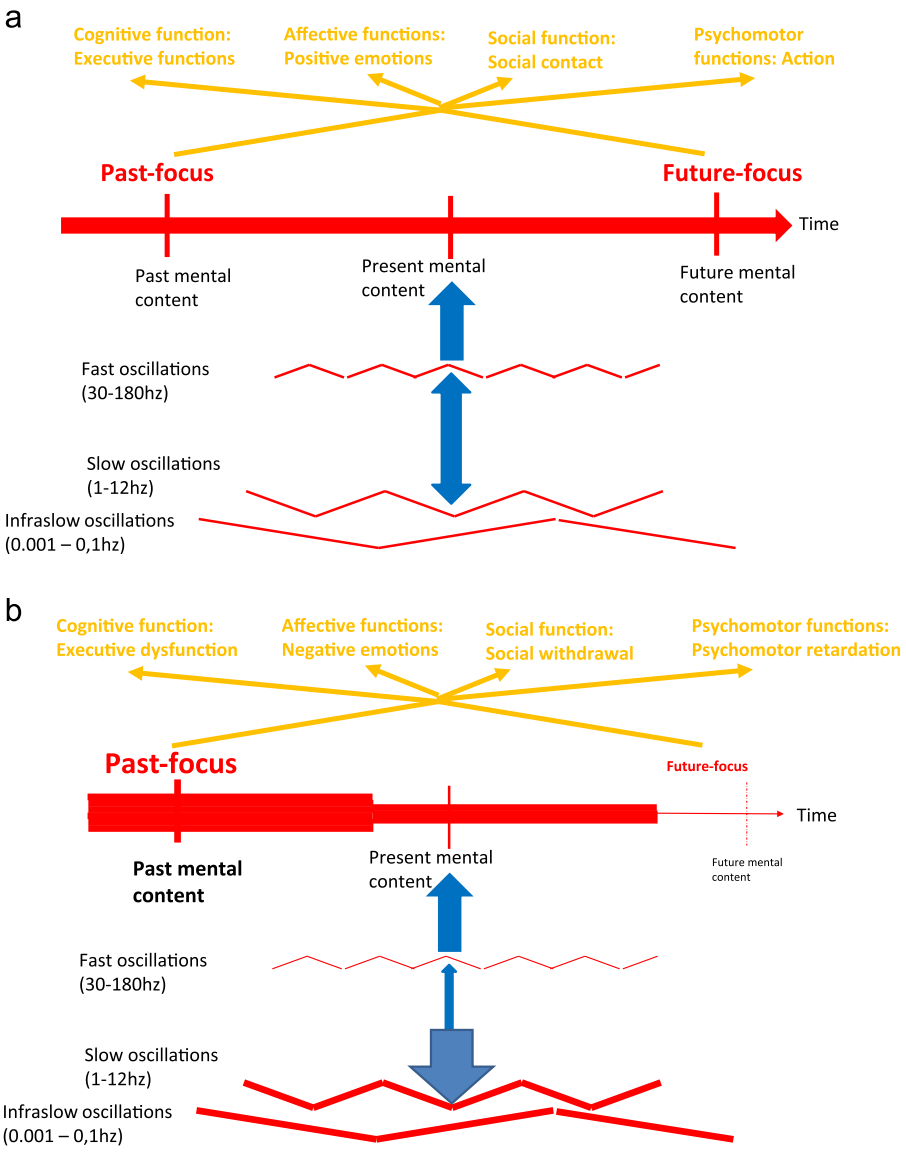

Fig. 3. Temporal balance between infraslow/slow and fast oscillations and past- and future-focus. The lower part represents the oscillations in the different (infraslow, slow, fast) frequency ranges including their balance in healthy subjects (a) and dysbalance (b) in depression. That in turn establishes a temporal balance between past, present and future mental contents as in the red line in the middle of the figure. Due to the altered temporal balance between infraslow/slow and fast oscillations, this temporal balance is shifted towards the past in depression resulting in increased past-focus and decreased future-focus (middle part in b). Finally, the altered temporal structure impacts the different functions, social, affective, cognitive, and psychomotor (upper part) leading to the various kinds of psychopathological symptoms in depression (upper part in b). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

be consistent with the assumption that the sensorimotor network too shows strong infraslow oscillations (unfortunately Kaiser et al., 2015) did not include the sensorimotor network in their meta-analysis of MDD resting state studies). Psychopathologically the predominance of infraslow oscillations may be manifest in psychomotor slowing and retardation as often obsered in MDD. One would consequently expect the degree of psychomotor slowing to be directly proportional to the degree of infraslow oscillation power and functional connectivity in the sensorimotor network.

5. Conclusion: Why do we need "Spatiotemporal Psychopathology"?

How can we characterize the approach taken here? I traced back psychopathological symptoms in MDD (and also in schizophrenia; see Northoff, 2014a, 2014c, 2015a) to underlying spatial and temporal abnormalities which in turn are supposed to be based on abnormalities in the resting state's spatial and temporal structure. One may consequently want to speak of what I describe as "Spatiotemporal Psychopathology". Put in a nutshell (and awaiting future more detailed development), the concept of "Spatiotemporal Psychopathology" conceives psychopathological symptoms in spatial and temporal terms which makes it possible to link them to the brain and its resting state's spatiotemporal structure. Taken in this sense Spatiotemporal Psychopathology stands in the tradition of the history of psychopathology and, at the same time, extends and links it to the brain and its resting state activity (see second paper for details).

What can the spatiotemporal approach to depressive symptoms provide that other approaches cannot? In nutshell, current psychopathology still suffers from the divide between psyche and brain, between psychopathological symptoms and neural activity. Traditionally, psychopathology is 'located' on the side of the psyche as it is well reflected in both historical approaches like descriptive psychopathology (Jaspers, 1964/1997) and current approaches including phenomenological psychopathology (Fuchs, 2013; Parnas et al., 2013;

Please cite this article as: Northoff, G., Spatiotemporal psychopathology I: No rest for the brain's resting state activity in depression? Spatiotemporal psychopathology of.... Journal of Affective Disorders (2015), http://dx.doi.org/10.1016/j.jad.2015.05.007

Stanghellini, 2009a, 2009b) and more operational systems like DSM and ICD. This leaves us still with the question how the psychopathological symptoms (regardless how they are categorized) are related to the brain.

Other approaches like affective (Panksepp, 2004) and cognitive (Frith, 1992; Halligan and David, 2001) psychopathology as well as the more recent Research Domain categorization (RDoC) (Cuthbert and Insel, 2013) aims explicitly to bridge the gap between brain and psyche, neural circuits and psychopathological symptoms. However, even in these approaches the question how neural changes in for instance the resting state as in depression can be translated and transformed into psychopathological symptoms like ruminations remains still unclear. While these approaches have considerably added to our understanding, the neuropsychopathological pathogenesis of the various symptoms remains still unclear.

This is the moment where the here suggested spatiotemporal approach, i.e., Spatiotemporal Psychopathology, steps in. Spatiotemporal Psychopathology conceives the brain and especially its intrinsic activity in purely a formal way, i.e., in terms of spatiotemporal features rather than in terms of specific contents like affective, cognitive, sensorimotor, or social. Ruminations in depression are then traced not to abnormal contents but rather to abnormal shift in the spatial balance between internal and external mental contents (see above). What in the perspective of for instance a cognitive approach appears as a disorder of abnormal cognitive contents, i.e., ruminations, reveals itself in the spatiotemporal approach as an underlying spatial dysbalance between internal and external mental contents which neutrally can be traced back to abnormal spatial dysbalance between DMN and CEN.

The spatiotemporal approach offers a pathogenetic approach to psychopathological symptoms which are conceived primarily as spatiotemporal symptoms of the brain's resting state. As demonstrated in this paper, this provides direct link between the neural level of the brain, the subjective or phenomenal level of experience, and the behavioral level of psychopathological symptoms. Metaphorically put, the spatiotemporal structure provides the hitherto missing glue between the three levels, neural, phenomenal, and behavioral level which makes understandable why and how for instance resting state abnormalities translate into abnormal experiences and behavior as in depression.

Why and how though is the spatiotemporal approach relevant for clinical diagnosis and therapy of depression (and ultimately of other psychiatric disorders)? If developed further in more detail, we may categorize and classify psychopathological symptoms based on their spatial and temporal features. Symptoms like ruminations, psychomotor retardation and social withdrawal will be categorized no longer according to their contents, i.e., cognitive, affective, sensorimotor or social, but rather based on their spatiotemporal features. Space-time-based diagnoses may ultimately replace the current function-based (i.e., cognitive, affective, social, sensorimotor, vegetative) diagnostic criteria. We might then for instance establish rhythm- or oscillation-based diagnosis as related to the power ratio between the different oscillations (as measured with EEG) ranging from delta over theta, alpha, and beta to gamma. This may also allow for better individualization of clinical diagnosis and psychopathological symptoms as well as of the respective person's resting state.

Therapeutically, we may then base our therapeutic interventions like transcranial magnetic stimulation (TMS), deep brain stimulation, and many others including pharmacotherapy (Buzsaki et al., 2013) and music therapy (Müller et al., 2014) on the respective individual's spatiotemporal profile of their resting state. If for instance one subject show abnormal oscillation ratio shifted towards especially delta, we may then target to restore 'normal' delta oscillation with consecutive normalization of the overall frequency ratio. Such "rhythm-based therapy" (see also Buzsaki et al., 2013) for a more less analogous notion) requires though much more detailed insight into the resting state's spatiotemporal features and how they transform and translate into psychopathological symptoms. This will be the future task of Spatiotemporal Psychopathology.

Acknowledgments

I am thankful to Benedetta Conio, Annemarie Wolf, Francesca Ferri, and Wendy Carter who commented in a very helpful way on prior versions of this paper. I am also grateful to the CIHR No 4566, the ISAN-HDRF No 462, the EJLB-CIHR 05, and the Michael Smith Foundation for their generous financial support.

References

Abou Elseoud, A., Nissilä, J., Liettu, A., Remes, J., Jokelainen, J., Takala, T., Aunio, A., Starck, T., Nikkinen, J., Koponen, H., 2014. Altered resting-state activity in seasonal affective disorder. Hum. Brain Mapp. 35, 161–172.

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, 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, 592–605.

Arieli, A., Sterkin, A., Grinvald, A., Aertsen, A., 1996. Dynamics of ongoing activity: explanation of the large variability in evoked cortical responses. Science 273, 1868–1871.

Avery, J.A., Drevets, W.C., Moseman, S.E., Bodurka, J., Barcalow, J.C., Simmons, W.K., 2014. Major depressive disorder is associated with abnormal interoceptive activity and functional connectivity in the insula. Biol. Psychiatry 76, 258–266.

Baskaran, A., Milev, R., McIntyre, R.S., 2012. The neurobiology of the EEG biomarker as a predictor of treatment response in depression. Neuropharmacology 63, 507–513.

Bschor, T., Ising, M., Bauer, M., Lewitzka, U., Skerstupeit, M., Müller-Oerlinghausen, B., Baethge, C., 2004. Time experience and time judgment in major depression, mania and healthy subjects. A controlled study of 93 subjects. Acta Psychiatr. Scand. 109, 222–229.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. Ann. N.Y. Acad. Sci. 1124, 1–38.

Buzsaki, G., 2006. Rhythms of the Brain. Oxford University Press.

Buzsaki, G., Draguhn, A., 2004. Neuronal oscillations in cortical networks. Science 304, 1926–1929.

Buzsaki, G., Logothetis, N., Singer, W., 2013. Scaling brain size, keeping timing: evolutionary preservation of brain rhythms. Neuron 80, 751–764.

Cabral, J., Kringelbach, M.L., Deco, G., 2013. Exploring the network dynamics underlying brain activity during rest. Prog. Neurobiol..

Canolty, R.T., Knight, R.T., 2010. The functional role of cross-frequency coupling. Trends Cogn. Sci. 14, 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, 1343–1351.

Chen, A.C., Oathes, D.J., Chang, C., Bradley, T., Zhou, Z.W., Williams, L.M., Glover, G. H., Deisseroth, K., Etkin, A., 2013. Causal interactions between fronto-parietal central executive and default-mode networks in humans. Proc. Natl. Acad. Sci. U.S.A. 110, 19944–19949.

Cuthbert, B.N., Insel, T.R., 2013. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med. 11, 126.

Deco, G., Jirsa, V.K., McIntosh, A.R., 2013. Resting brains never rest: computational insights into potential cognitive architectures. Trends Neurosci. 36, 268–274.

Fan, Y., Duncan, N.W., de Greck, M., Northoff, G., 2011. Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. Neurosci. Biobehav. Rev. 35, 903–911.

Fell, J., Axmacher, N., 2011. The role of phase synchronization in memory processes. Nat. Rev. Neurosci. 12, 105–118.

Fingelkurts, A.A., Fingelkurts, A.A., 2014a. Altered structure of dynamic 'EEG Oscillatory Pattern'in major depression. Biol. Psychiatry.

Fingelkurts, A.A., Fingelkurts, A.A., 2014b. EEG oscillatory states: universality, uniqueness and specificity across healthy-normal, altered and pathological brain conditions. PLoS One 9, e87507.

Fingelkurts, A.A., Fingelkurts, A.A., Rytsälä, H., Suominen, K., Isometsä, E., Kähkönen, S., 2007. Impaired functional connectivity at EEG alpha and theta frequency bands in major depression. Hum. Brain Mapp. 28, 247–261.

Fitzgerald, P.B., Oxley, T.J., Laird, A.R., Kulkarni, J., Egan, G.F., Daskalakis, Z.J., 2006. An analysis of functional neuroimaging studies of dorsolateral prefrontal cortical activity in depression. Psychiatry Res. 148, 33–45.

Fitzgerald, P.B., Sritharan, A., Daskalakis, Z.J., de Castella, A.R., Kulkarni, J., Egan, G., 2007. A functional magnetic resonance imaging study of the effects of low frequency right prefrontal transcranial magnetic stimulation in depression. J. Clin. Psychopharmacol. 27, 488–492.

Freeman, W.J., 2003. The wave packet: an action potential for the 21st century. J. Integr. Neurosci. 2, 3–30.

Fries, P., 2009. Neuronal gamma-band synchronization as a fundamental process in cortical computation. Annu. Rev. Neurosci. 32, 209–224.

Fries, P., Nikolić, D., Singer, W., 2007. The gamma cycle. Trends Neurosci. 30, 309–316.
Fries, P., Reynolds, J.H., Rorie, A.E., Desimone, R., 2001. Modulation of oscillatory neuronal synchronization by selective visual attention. Science 291, 1560–1563.
Frith, C.D., 1992. The Cognitive Neuropsychology of Schizophrenia. Psychology Press.
Fuchs, T., 2013. Temporality and psychopathology. Phenomenol. Cogn. Sci. 12, 75–104.
Ganzetti, M., Mantini, D., 2013. Functional connectivity and oscillatory neuronal activity in the resting human brain. Neuroscience 240, 297–309.
Gotts, S.J., Saad, Z.S., Jo, H.J., Wallace, G.L., Cox, R.W., Martin, A., 2013. The perils of global signal regression for group comparisons: a case study of Autism Spectrum Disorders. Front. Hum. Neurosci. 7.
Grimm, S., Ernst, J., Boesiger, P., Schuepbach, D., Boeker, H., Northoff, G., 2011. Reduced negative BOLD responses in the default-mode network and increased self-focus in depression. World J. Biol. Psychiatry 12, 627–637.
Grimm, S., Ernst, J., Boesiger, P., Schuepbach, D., Hell, D., Boeker, H., Northoff, G., 2009a. Increased self-focus in major depressive disorder is related to neural abnormalities in subcortical-cortical midline structures. Hum. Brain Mapp. 30, 2617–2627.
Halligan, P.W., David, A.S., 2001. Cognitive neuropsychiatry: towards a scientific psychopathology. Nat. Rev. Neurosci. 2, 209–215.
Hasler, G., Northoff, G., 2011. Discovering imaging endophenotypes for major depression. Mol. Psychiatry 16, 604–619.
He, B.J., Raichle, M.E., 2009. The fMRI signal, slow cortical potential and consciousness. Trends Cogn. Sci. 13, 302–309.
Hunter, M., Eickhoff, S., Miller, T., Farrow, T., Wilkinson, I., Woodruff, P., 2006. Neural activity in speech-sensitive auditory cortex during silence. Proc. Natl. Acad. Sci. U.S.A. 103, 189–194.
Iosifescu, D.V., 2011. Electroencephalography-derived biomarkers of antidepressant response. Harvard Rev. Psychiatry 19, 144–154.
Jaspers, K., 1964/1997. General Psychopathology. University of Chicago Press, Chicago.
Kahn, R.S., Keefe, R.S., 2013. Schizophrenia is a cognitive illness: time for a change in focus. JAMA Psychiatry 70, 1107–1112.
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.
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, 252–261.
Kim, D.-J., Bolbecker, A.R., Howell, J., Rass, O., Sporns, O., Hetrick, W.P., Breier, A., O'Donnell, B.F., 2013. Disturbed resting state EEG synchronization in bipolar disorder: a graph-theoretic analysis. NeuroImage: Clin. 2, 414–423.
Klimesch, W., 2012. Alpha-band oscillations, attention, and controlled access to stored information. Trends Cogn. Sci. 16, 606–617.
Kuhn, S., Gallinat, J., 2013. Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis. Schizophr. Bull. 39, 358–365.
Lee, T.-W., Wu, Y.-T., Yu, Y.W.-Y., Chen, M.-C., Chen, T.-J., 2011. The implication of functional connectivity strength in predicting treatment response of major depressive disorder: a resting EEG study. Psychiatry Res.: NeuroImaging 194, 372–377.
Lemogne, C., Delaveau, P., Freton, M., Guionnet, S., Fossati, P., 2012. Medial prefrontal cortex and the self in major depression. J. Affect. Disord. 136, e1–e11.
Lemogne, C., le Bastard, G., Mayberg, H., Volle, E., Bergouignan, L., Lehericy, S., Allilaire, J.F., Fossati, P., 2009. In search of the depressive self: extended medial prefrontal network during self-referential processing in major depression. Soc. Cogn. Affect. Neurosci. 4, 305–312.
Leuchter, A.F., Cook, I.A., Hunter, A.M., Cai, C., Horvath, S., 2012. Resting-state quantitative electroencephalography reveals increased neurophysiologic connectivity in depression. PLoS One 7, e32508.
Llinas, R.R., 1988. The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. Science 242, 1654–1664.
Logothetis, N.K., Murayama, Y., Augath, M., Steffen, T., Werner, J., Oeltermann, A., 2009. How not to study spontaneous activity. NeuroImage 45, 1080–1089.
Magioncalda, P., Martino, M., Conio, B., Escelsior, A., Piaggio, N., Presta, A., Marozzi, V., Rocchi, G., Anastasio, L., Vassallo, L., Ferri, F., Huang, Z., Roccatagliata, L., Pardini, M., Northoff, G., Amore, M., 2014. Functional connectivity and neuronal variability of resting state activity in bipolar disorder-reduction and decoupling in anterior cortical midline structures. Hum. Brain Mapp..
Mahlberg, R., Kienast, T., Bschor, T., Adli, M., 2008. Evaluation of time memory in acutely depressed patients, manic patients, and healthy controls using a time reproduction task. Eur. Psychiatry 23, 430–433.
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, 13170–13175.
Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn. Sci. 15, 483–506.
Minkowski, E., 1930/1993. La depression ambivalents, Structures des depressions. Nouvel, Paris, France.
Müller, W., Haffelder, G., Schlotmann, A., Schaefers, A.T., Teuchert-Noodt, G., 2014. Amelioration of psychiatric symptoms through exposure to music individually adapted to brain rhythm disorders–a randomised clinical trial on the basis of fundamental research. Cogn. Neuropsychiatry 19, 399–413.
Northoff, G., 2007. Psychopathology and pathophysiology of the self in depression—neuropsychiatric hypothesis. J. Affect. Disord. 104, 1–14.
Northoff, G., 2014a. Do cortical midline variability and low frequency fluctuations mediate William James' "Stream of Consciousness"? "Neurophenomenal Balance Hypothesis" of "Inner Time Consciousness. Conscious Cogn. 30C, 184–200.
Northoff, G., 2014b. How is our self altered in psychiatric disorders? A neurophenomenal approach to psychopathological symptoms. Psychopathology.
Northoff, G., 2014c. Unlocking the Brain. Coding, vol. 1. Oxford University Press.
Northoff, G., 2014d. Unlocking the Brain. Consciousness, vol. II. Oxford University Press, Oxford.
Northoff, G., 2015a. Is schizophrenia a spatiotemporal disorder of the brain's resting state? World Psychiatry 14, 34–35.
Northoff, G., 2015b. Resting state activity and the "stream of consciousness" in schizophrenia—neurophenomenal hypotheses. Schizophr. Bull. 41, 280–290.
Northoff, G., Qin, P., 2011. How can the brain's resting state activity generate hallucinations? A 'resting state hypothesis' of auditory verbal hallucinations. Schizophr. Res. 127, 202–214.
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, 1929–1945.
Olbrich, S., Arns, M., 2013. EEG biomarkers in major depressive disorder: discriminative power and prediction of treatment response. Int. Rev. Psychiatry 25, 604–618.
Olbrich, S., Tränkner, A., Chittka, T., Hegerl, U., Schönknecht, P., 2014. Functional connectivity in major depression: increased phase synchronization between frontal cortical EEG-source estimates. Psychiatry Res.: NeuroImaging 222, 91–99.
Painold, A., Faber, P.L., Milz, P., Reininghaus, E.Z., Holl, A.K., Letmaier, M., Pascual-Marqui, R.D., Reininghaus, B., Kapfhammer, H.P., Lehmann, D., 2014. Brain electrical source imaging in manic and depressive episodes of bipolar disorder. Bipolar Disord. 16, 690–702.
Panksepp, J., 2004. Textbook of biological psychiatry. Wiley Online Lib..
Parnas, J., Sass, L.A., Zahavi, D., 2013. Rediscovering psychopathology: the epistemology and phenomenology of the psychiatric object. Schizophr. Bull. 39, 270–277.
Pizzagalli, D.A., Oakes, T.R., Davidson, R.J., 2003. Coupling of theta activity and glucose metabolism in the human rostral anterior cingulate cortex: an EEG/PET study of normal and depressed subjects. Psychophysiology 40, 939–949.
Price, J.L., Drevets, W.C., 2010. Neurocircuitry of mood disorders. Neuropsychopharmacology 35, 192–216.
Raichle, M.E., 2009. A brief history of human brain mapping. Trends Neurosci. 32, 118–126.
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, 676–682.
Saad, Z.S., Gotts, S.J., Murphy, K., Chen, G., Jo, H.J., Martin, A., Cox, R.W., 2012. Trouble at rest: how correlation patterns and group differences become distorted after global signal regression. Brain Connect. 2, 25–32.
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, 1001–1013.
Savitz, J., Drevets, W.C., 2009. Bipolar and major depressive disorder: neuroimaging the developmental-degenerative divide. Neurosci. Biobehav. Rev. 33, 699–771.
Savitz, J., Drevets, W.C., 2009a. Bipolar and major depressive disorder: neuroimaging the developmental-degenerative divide. Neurosci. Biobehav. Rev. 33, 699–771.
Savitz, J.B., Drevets, W.C., 2009b. Imaging phenotypes of major depressive disorder: genetic correlates. Neuroscience 164, 300–330.
Shulman, G.L., Astafiev, S.V., Franke, D., Pope, D.L., Snyder, A.Z., McAvoy, M.P., Corbetta, M., 2009a. Interaction of stimulus-driven reorienting and expectation in ventral and dorsal frontoparietal and basal ganglia-cortical networks the official journal of the Society for Neuroscience. J. Neurosci. 29, 4392–4407.
Shulman, R.G., Hyder, F., Rothman, D.L., 2009b. Baseline brain energy supports the state of consciousness. Proc. Natl. Acad. Sci. U.S.A. 106, 11096–11101.
Shulman, R.G., Hyder, F., Rothman, D.L., 2014. Insights from neuroenergetics into the interpretation of functional neuroimaging: an alternative empirical model for studying the brain's support of behavior. J. Cereb. Blood Flow Metab. 34, 1721–1735.
Snyder, H.R., 2013. Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. Psychol. Bull. 139, 81.
Stanghellini, G., 2009a. A hermeneutic framework for psychopathology. Psychopathology 43, 319–326.
Stanghellini, G., 2009b. The meanings of psychopathology. Curr. Opin. Psychiatry 22, 559–564.
Stanghellini, G., Ballerini, M., Blasi, S., Mancini, M., Presenza, S., Raballo, A., Cutting, J., 2014. The bodily self: a qualitative study of abnormal bodily phenomena in persons with schizophrenia. Comprehen. Psychiatry 55, 1703–1711.
Stanghellini, G., Ballerini, M., Presensa, S., Macini, M., Raballo, A., Blasi, S., J, CPlease check author name for correctness., 2015. Psychopathology of lived time: abnormal time experience in persons with Schizophrenia. Schizophr. Bull., in press.
Thönes, S., Oberfeld, D., 2015. Time perception in depression: a meta-analysis. J. Affect. Disord..
Treynor, W., Gonzalez, R., Nolen-Hoeksema, S., 2003. Rumination reconsidered: a psychometric analysis. Cogn. Ther. Res. 27, 247–259.

Please cite this article as: Northoff, G., Spatiotemporal psychopathology I: No rest for the brain's resting state activity in depression? Spatiotemporal psychopathology of.... Journal of Affective Disorders (2015), http://dx.doi.org/10.1016/j.jad.2015.05.007

ARTICLE IN PRESS

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, 5053–5057.

Vanhaudenhuyse, A., Noirhomme, Q., Tshibanda, L.J., Bruno, M.A., Boveroux, P., Schnakers, C., Soddu, A., Perlbarg, V., Ledoux, D., Brichant, J.F., Moonen, G., Maquet, P., Greicius, M.D., Laureys, S., Boly, M., 2010. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. Brain 133, 161–171.

Wang, F., Duratti, L., Samur, E., Spaelter, U., Bleuler, H., 2007. A computer-based real-time simulation of interventional radiology. In: Conference proceedings:... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference 2007, pp. 1742–1745.

Wiebking, C., Bauer, A., de GRECK, M., Duncan, N.W., Tempelmann, C., Northoff, G., 2010. Abnormal body perception and neural activity in the insula in depression: an fMRI study of the depressed "material me". World J. Biol. Psychiatry 11, 538–549.

Wiebking, C., de Greck, M., Duncan, N.W., Heinzel, A., Tempelmann, C., Northoff, G., 2011. Are emotions associated with activity during rest or interoception? An exploratory fMRI study in healthy subjects. Neurosci. Lett. 491, 87–92.

Wiebking, C., Duncan, N.W., Tiret, B., Hayes, D.J., Marjańska, M., Doyon, J., Bajbouj, M., Northoff, G., 2014. GABA in the insula—a predictor of the neural response to interoceptive awareness. NeuroImage 86, 10–18.

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, 611–617.

Zuo, X.-N., Kelly, C., Adelstein, J.S., Klein, D.F., Castellanos, F.X., Milham, M.P., 2010. Reliable intrinsic connectivity networks: test–retest evaluation using ICA and dual regression approach. NeuroImage 49, 2163–2177.

Please cite this article as: Northoff, G., Spatiotemporal psychopathology I: No rest for the brain's resting state activity in depression? Spatiotemporal psychopathology of.... Journal of Affective Disorders (2015), http://dx.doi.org/10.1016/j.jad.2015.05.007