5 Anxiety Disorders and the Brain's Resting State Networks: From Altered Spatiotemporal Synchronization to Psychopathological Symptoms

Georg Northoff

Introduction

Anxiety and depression are among the most common symptoms. According to the World Health Organization (WHO), 20 million North Americans suffer from depression which also causes major economic burden with an estimated €92 billion [1]. Importantly, depression and anxiety can be associated with different disorders. Most typically, depression and anxiety occur in those psychiatric disorders that are classified as anxiety disorders in DSM V; these include mainly panic disorder (PD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), agoraphobia, and specific phobias – our review focuses on GAD, PD, and SAD.

In addition to cognitive and affective symptoms, subjects suffering from PD, GAD, and SAD often also show (i) reduced heart rate variability (HRV) [2–4]; (ii) abnormal perception of their own heart beat [5–8]; (iii) somatic and especially cardiac symptoms like racing heart rate, heart palpitations, and chest pain [2, 3, 7, 8]; and (iv) increased risk for coronary artery disease and atrial fibrillation [9]. Taken together, the combination of both affective and somatic-cardiac symptoms in anxiety disorders suggests abnormal coupling of the brain's neural and the heart's cardiac activity.

The present paper focuses on how the brain's resting state and its functional connectivity process and monitor the cardiac inputs from the heart. The main and overarching hypothesis is that abnormalities in the brain's resting state activity lead to dysfunctional coupling between the heart and brain in anxiety disorders. That, as we elaborate on the basis of recent findings in both healthy and anxiety subjects, can be traced to alterations in those mechanisms that allow for spatiotemporal synchronization between neural and cardiac activity within the brain's resting state.

G. Northoff (✉)
EJLB-Michael Smith Chair for Neuroscience and Mental Health, Royal Ottawa Healthcare Group, University of Ottawa Institute of Mental Health Research, Ottawa, ON, Canada
e-mail: georg.northoff@theroyal.ca; http://www.georgnorthoff.com

Y.-K. Kim (ed.), *Anxiety Disorders*, Advances in Experimental Medicine and Biology 1191, https://doi.org/10.1007/978-981-32-9705-0_5

The first part of the paper focuses on recent findings in healthy subjects on how neural and cardiac activity are coupled and synchronized both spatially and temporally within the brain's ongoing resting state activity. We will establish various hypotheses about various mechanisms of spatiotemporal synchronization of neural and cardiac activity within the brain's spontaneous activity. That provides the basis for the second part about anxiety disorders. We here review recent findings on resting state abnormalities in various networks in anxiety disorders. That provides the basis for suggesting abnormal expression of spatiotemporal synchronization of neural and cardiac activity within the brain's spontaneous activity in these disorders. We thus establish a set of experimentally testable hypothesis about abnormal spatiotemporal brain-heart synchronization in anxiety disorders which provide direct link to the psychopathological symptoms like anxiety, unstable self, and increased bodily awareness.

The here suggested approach sets anxiety disorders within the framework of the recently introduced "Spatiotemporal Psychopathology." Spatiotemporal Psychopathology suggests primarily spatiotemporal (rather than affective or cognitive) mechanisms to provide the link between the brain's neural changes and the mind's psychopathological symptoms [10–16].

Part I: Brain-Heart Coupling – Spatiotemporal Synchronization in the Healthy Brain

Spatial Relationship Between Neural and Cardiac Variability

Initial investigations using brain imaging with functional magnetic resonance imaging (fMRI) during the so-called resting state (i.e., absence of specific tasks or stimuli) show close coupling between the heart and brain in healthy subjects [17]. observed direct relation between heart rate variability (HRV) and resting state functional connectivity in the brain, specifically in the insula, amygdala, and dorsal anterior cingulate cortex (dACC) see also [18, 19].

Others have observed close coupling of neural activity in ventromedial prefrontal cortex (VMPFC) (and adjacent perigenual anterior cingulate cortex (PACC)), somatosensory and somatomotor cortex, and subcortical regions (like periaqueductal gray (PAG), thalamus, and lentiform nucleus as part of the so-called central autonomic network (CAN)) with the high-frequency content of HRV recordings [18–20].

Other investigations of the brain using magnetoencephalography (MEG, a technique with high temporal resolution) show direct temporal coupling between the brain's oscillatory activity and heart rhythm during the brain's resting state [21–26] (see below for mechanistic details). Such coupling can specifically be observed in the insula, the somatosensory cortex, and the PACC and VMPFC – the MEG (which cannot capture subcortical regions) thus confirm the cortical regions involved in brain-heart coupling.

The very same regions and SN are also recruited during task-evoked activity related to the awareness of the heartbeat, i.e., interoceptive awareness (see [27, 28] for the recent distinction between interoceptive accuracy, sensitivity, and awareness as well as physiological interoception). Studies by others [29, 30] and our group [5, 31, 32] demonstrated strong involvement of the insula, dACC, thalamus, and somatosensory/motor cortex during heartbeat counting which requires awareness of one's own heart. Moreover, VMPFC and PACC are less deactivated (in fMRI) during interoceptive awareness of the own heartbeat [31].

Taken together, the regions mediating brain-heart coupling in the healthy brain can be subsumed under three main neural networks as they have been identified in the brain's resting state [33]. (i) The insula, amygdala, dACC, and thalamus form the salience network (SN) [34]; (ii) the somatosensory cortex and its associated regions are at the core of the somatosensory-motor network (SMN); and finally (iii) VMPFC and PACC are part of the default-mode network (DMN) [35, 36].

The involvement of these networks in brain-heart coupling raises the question for the exact mechanisms how the neural activity of these regions couples to the ongoing cardiac input. The findings suggest that neural variability in the brain's resting state activity is related to cardiac variability, e.g., heartrate variability (HRV). That is further supported by the fact that the frequency range in which fMRI resting state neuronal variability is typically measured (0.01–0.1 Hz) corresponds well to the frequency range of slow and fast HRV (0.01–0.1). Our first neuro-cardiac hypothesis is thus that there is a direct relationship between neural and cardiac variability in the brain's resting state activity in regions of SN, SMN, and DMN. The coupling between neural and cardiac variabilities raises the question for the underlying temporal mechanisms which shall be the focus in the following.

Phase-Based Temporal Synchronization of the Heart and Brain

We so far discussed the regions/networks and their resting state and task-evoked activity implicated in brain-heart coupling in anxiety disorders. This leaves open (i) the neuronal mechanisms underlying brain-heart coupling and (ii) how the latter can account for the psychopathological symptoms observed in anxiety disorders. Let us start with the first point, the neuronal mechanisms of brain-heart coupling, for which we briefly go back to the healthy brain.

As said above, the group around Tallon-Baudry conducted several MEG and intracranial EEG studies on brain-heart coupling and how that is related to perception and our sense of self (see [37] for an excellent overview). Thereby we need to understand two different mechanisms, first, the one that allows for the coupling between neuronal and cardiac activity in the brain and, second, how that transforms into mental features like perception, emotion, and self. Let us start with the first mechanism, that is, neuro-cardiac coupling.

Park et al. [21–24] conducted several studies using MEG or intracranial EEG (iEEG) while at the same time recording the heartbeat with ECG. It is well known that

the heartbeat induces an event-related potential in the brain which is described as heartbeat-evoked potential (HEP) [38]. Since the HEP is time-wise related to the heartbeat, it must reflect the coupling of the brain's ongoing neuronal activity, e.g., its so-called resting state or spontaneous activity, with the heart-related rhythmic activity.

The brain's ongoing neuronal activity, that is, its spontaneous or resting state activity, can be characterized by continuous fluctuations and oscillation with varying phase onsets [39, 40]. Various investigations demonstrated that the brain can shift its phase onsets according to the onset of external stimuli as in music – this is described as entrainment [41] or alignment [42]. Phase shift can thus be seen as mechanisms by means of which the brain can actively align its own neural activity to external stimuli. This raises the question whether such active alignment also underlies the resting state's activity coupling to the continuous cardiac input. Specifically, one may now want to investigate whether the phase onsets in the brain's spontaneous activity are temporally coupled and ultimately synchronized with the onsets of the heartbeats (and ultimately the amplitude of the HEP) as they are processed by the brain.

[21–24] observed that the phase onset of the brain's ongoing neuronal fluctuations is locked to the timing of the ongoing heartbeat, e.g., the R-peak as measured in ECG. The phase onset in the brain's ongoing neuronal fluctuations was coherent across numerous heartbeats and thus temporally phase-locked to the latter – this could be measured by and was reflected in high values of the brain's intertrial coherence (ITC) (as in the frequency range between 4 and 7 Hz) relative to the heartbeat onset [24]. This strongly suggests that the timing of both the brain, e.g., phase onset as measured by ITC, and the heart, e.g., heartbeat onset including HRV, is coupled and thus synchronized with each other.

The ITC, in turn, was directly related to the amplitude of the HEP with higher ITC leading to higher amplitude in the HEP [24] therefore concluded that the amplitude of HEP can, at least in some major part, be linked to the phase shift, i.e., ITC. The ITC reflecting the coupling between the brain's phase onsets and the timing of the heartbeat (as processed by the brain) can thus be conceived a marker of brain-heart coupling. Moreover, as ITC mediates the amplitude of HEP, the latter can be conceived a second marker. That needs to be distinguished from mere power changes as measured by event-related spectral perturbation (ERSP) as these do not mediate the amplitude of HEP [24].

Taken together, the data suggest that temporal synchronization is a central mechanism in coupling neural and cardiac activity in the brain. Specifically, as such synchronization is mediated by coherence or phase, we speak of phase-based temporal synchronization between the rhythms of both the brain and the heart – this is manifested in the amplitude of HEP. Low temporal synchronization, e.g., low ITC, will reduce HEP amplitude, while high degrees of temporal synchronization with high ITC will enhance the amplitude of HEP (see Fig. 5.1a).

We can thus formulate yet another neuro-cardiac hypothesis. The temporal coupling of neural and cardiac activity in the brain's resting state activity is mediated by phase shift resulting in neuro-cardiac phase entrainment or alignment as it can be measured

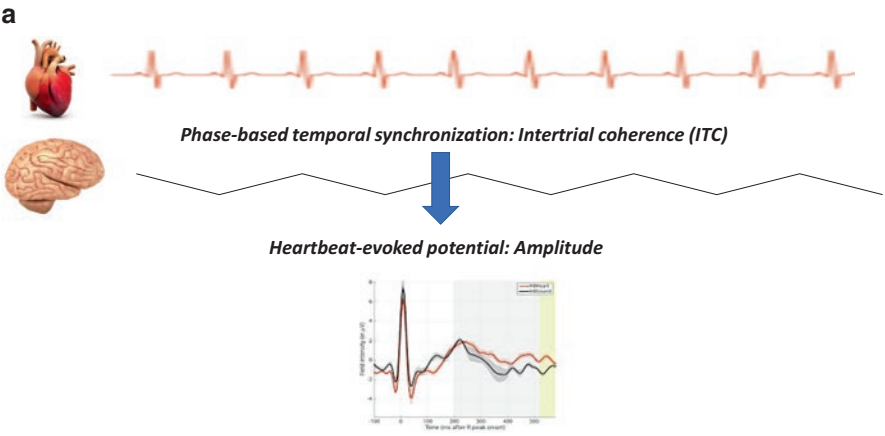

Fig. 5.1a Neuro-cardiac phase-based temporal synchronization and the heartbeat-evoked potential (HEP)

by intertrial coherence (ITC). The phase shift, in turn, mediates the amplitude of the heartbeat-evoked potential (HEP). The temporal phase alignment thus modulates the amplitude the cardiac input can induce in the brain's resting state activity.

Spatiotemporal Brain-Heart Synchronization Shapes Mental Functions (Emotion, Bodily Awareness, and the Sense of Self)

We identified phase-based temporal synchronization as core mechanism in coupling neural and cardiac activity. This allows us to proceed to our second question, namely, how temporal synchronization impacts and shapes mental features like perception, emotion, bodily awareness, and sense of self. To test that, Park included tasks for visual perception [21, 22], body awareness [24], and sense of self [23, 25, 26] and related them to neuro-cardiac coupling, namely, the HEP, as investigated in various MEG or iEEG studies (see [37] for an overview).

[21, 22] observed that visual perception, e.g., visual consciousness, is directly dependent upon the degree of neuro-cardiac temporal synchronization in specifically visual cortex and insula. The same holds for bodily awareness: different degrees in the amplitude of HEP in the insula (as region of SN) and the somatosensory cortex (as part of SMN) were related to different degrees of bodily awareness (as tested for by synchronous vs asynchronous brush stroke) [24].

Finally, [25, 26] and [23] could show that the subjects' experience of their own self as either "I" or "me" is directly related to the amplitude of the HEP and its underlying neuro-cardiac temporal synchronization in specifically the VMPFC as part of DMN. The DMN is well known to be involved in our sense of self [43, 44], the SMN has been related to bodily awareness [45], and the SN is central in mediating both sense of self [46, 47] and emotions [48]. Given the findings by the group

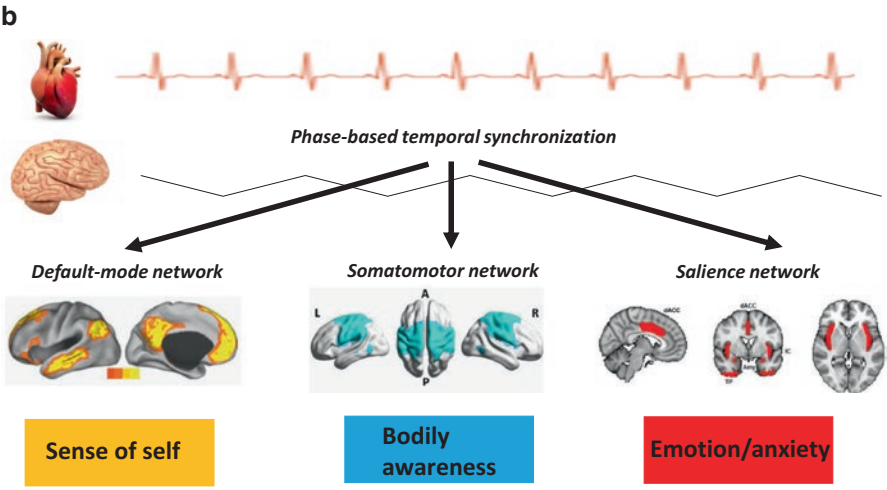

Fig. 5.1b Neuro-cardiac phase-based temporal synchronization in different networks and related psychological functions

around Tallon-Baudry, one may now want to assume that these regions'/networks' involvement in mental features like emotions, bodily awareness, and sense of self may, in part, be related to phase-based temporal synchronization between neural and cardiac activity (see [37] who makes this point) (see Fig. 5.1b).

In sum, the findings by the group around Tallon-Baudry shows that phase-based temporal synchronization in specific networks like SN, SMN, and DMN between neuronal and cardiac rhythms may not only allow for brain-heart coupling but, at the same time, also strongly shape mental features like perception, bodily awareness, and sense of self. We therefore speak of spatiotemporal synchronization as mechanism of brain-heart coupling which (i) allows connecting, e.g., synchronizing neuronal and cardiac activity, and (ii) shaping mental features like emotions, bodily awareness, and sense of self.

One would consequently expect that changes in these networks, e.g., DMN, SN, and SMN, as in anxiety disorders, are (i) based on altered phase-based temporal synchronization between neuronal and cardiac activity, which, in turn, (ii) should lead to abnormalities in the respective mental features like emotion, bodily awareness, and sense of self with the corresponding psychopathological symptoms. That is indeed the case in anxiety disorder as we will discuss in the following.

Part II: Brain-Heart Coupling – Spatiotemporal Hypo- and Hyper-synchronization and Its Psychopathology in Anxiety Disorders

Resting State Abnormalities in SN, DMN, and SMN

Several studies on resting state functional connectivity in PD have been conducted (see [3, 49–51] for reviews). [52] reported increased rsFC in the midline regions

including perigenual and posterior cingulate cortex (PACC, PCC) as typical default-mode network (DMN) regions. Corresponding changes in midline regions of DMN were observed by [53] who found increased rsFC especially in the PCC and precuneus (see also [54]).

In addition to midline DMN regions, other studies observed major changes in sensory and motor regions that are included in the salience network (SN) and, in part, the sensorimotor network (SMN). A whole-brain approach observed increased rsFC between the thalamus and postcentral cortex, i.e., sensory cortex which also correlated with the degree of anxiety (as measured in the Spielberger trait-state anxiety) [7] (see also [55]).

The SN is also a major focus in PD. Various resting state fMRI studies of the brain's functional connectivity in PD demonstrate alterations in the regions of the SN with changes in the amygdala and MPFC, dACC, and insula being most prominent [7, 49, 56–58]. Moreover, [59] demonstrated abnormal change in resting state functional connectivity in the amygdala and medial prefrontal cortex during induction of perseverative cognition (i.e., excessive worry) in PD patients.

A recent review by [3] (see also [51]) compared resting state functional connectivity (rsFC) in panic and social anxiety disorders. They demonstrate that SAD and PD share abnormalities, e.g., reductions in rsFC, in DMN in specifically PACC and VMPFC that are closely connected to the insula [47]. At the same time, SAD and PD also differ from each other. In addition to DMN changes, SAD exhibits increased rsFC in SN including especially the amygdala, insula, and dorsal anterior cingulate. PD, in contrast, while sharing abnormal rsFC in DMN with SAD, exhibits additional rsFC changes, e.g., increases, in specifically the SMN with a specific focus on primary and secondary somatosensory cortex.

In sum, the resting state data in anxiety disorders like PD, SAD, and GAD show shared rsFC abnormalities, e.g., reductions, in DMN including anterior midline regions like PACC and VMPFC that are known to be closely connected to the insula [47, 48]. At the same time, rsFC changes, e.g., increases, can be observed in other networks like salience network and somatosensory network that, unlike DMN, are rather restricted to one of the anxiety disorders (see Fig. 5.2).

In sum, anxiety disorders show abnormalities in DMN, SN, and SMN. Specifically, DMN rsFC is reduced in all anxiety disorders, whereas connected networks like SN and SMN exhibit rsFC increases that are more specific to GAD, PD, or SAD. This suggests that the resting state balance of each of these networks, e.g., SMN and SN, relative to the DMN may be abnormal in the different anxiety disorders: the balance shifts away from the generally shared reduction in DMN toward increases in either SN (SAD) or SMN (PD). We will see later that such abnormal DMN/SMN or DMN/SN balances may be central in yielding both shared and differential psychopathological symptoms in GAD, SAD, and PD (see also [3]).

Most interestingly, these networks also mediate the brain's processing of the cardiac input (see above). Given the supposed relationship between neural and cardiac variability (see above), these findings in anxiety disorders raise the question whether the abnormalities in their resting state's functional connectivity go along with abnormal neuronal variability in the same regions. Following our neuro-cardiac hypothesis in healthy subjects (see above), one would expect first that neuronal

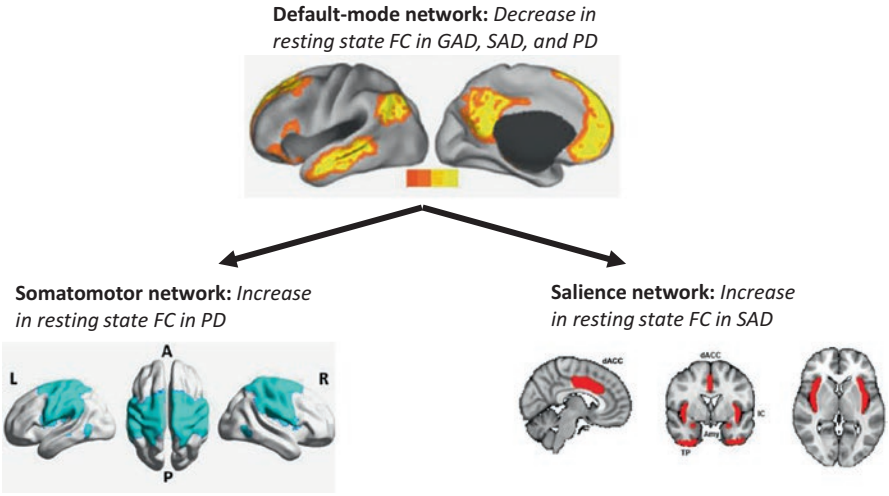

Fig. 5.2 Changes in resting state functional connectivity (FC) in different neural networks in anxiety disorders

variability in regions of DMN, SN, and SMN is abnormal and, second, that abnormal neuronal variability is related to abnormal HRV in anxiety disorders.

There is indeed some support for abnormal neuronal variability in DMN, SN, and SMN in anxiety disorders which though is tentative given the low number of studies [60–62]. Moreover, as indicated in the introduction, HRV is abnormal, e.g., reduced in anxiety disorders [2, 3]. What remains unclear is whether the potentially altered neuronal variability in DMN, SN, and SMN is related to the reduced HRV in anxiety disorders.

Hence, future investigation may want to (i) investigate neuronal variability in resting state activity of DMN, SMN, and SN; (ii) demonstrate relationship between altered rsFC and resting state neuronal variability in DMN, SMN, and SN in anxiety disorder; (iii) connect potentially altered neuronal variability to the changes in HRV; and (iv) investigate neuronal variability in different infraslow frequency ranges (slow 5, 0.01–0.027 Hz; slow 4, 0.27–0.073 Hz; slow 3, 0.073–0.198 Hz; slow 2, 0.198–0.2 Hz) as they are related to different frequency ranges of HRV (very slow, slow, fast). This may allow for detecting frequency-specific alterations in coupling between neuronal and cardiac variability in anxiety disorder (which may vary from patient to patient as well as between the different anxiety disorders).

Task-Evoked Abnormalities of Brain-Heart Coupling in SN, DMN, and SMN

Task-evoked activity during brain-heart coupling can be measured by employing the abovementioned paradigm of interoceptive awareness of the own heartbeat (see above). While this has been done in healthy subjects [29, 31, 32], there is only one

recent study in anxiety disorders like GAD, SAD, and PD (see though [63] in phobia) measuring task-evoked activity during interoceptive awareness of the own heartbeat [8]. As we here only focus on task-evoked studies that specifically test for the neural correlates of interoceptive awareness of the own heart, we leave out others that investigate task-evoked activity during emotional processing in anxiety disorders (see [50] for a recent review).

Applying fMRI, [8] investigated both rsFC and task-evoked activity during interoceptive awareness in drug-naïve subjects with GAD [8]. They firstly observed that GAD subjects showed an abnormally increased sensitivity in their body perception (as measured with the Body Perception Questionnaire, BPQ) which concerned dimensions as autonomous nervous system, awareness, and stress. These findings confirm that these subjects (and that applies to PD and SAD too) suffer from an abnormally increased perception related to their own vegetative or autonomous nervous system that monitors the vegetative input to the brain from the body including the heart.

The same subjects also underwent task-evoked and resting state activity in fMRI. Task-evoked activity was measured during the abovementioned interoceptive awareness task where subjects are required to monitor and count their own heartbeat (when compared to the monitoring and counting of an external tone). Most interestingly, the GAD subjects showed increased task-evoked activity in various subregions of the insula including both the anterior insula (as closely connected to the PACC and VMPFC) and the posterior insula (as closely connected to the secondary somatosensory cortex and thus the SMN). The abnormally increased task-evoked activity in specifically left anterior insula was positively correlated with the severity of symptoms such as "psychic anxiety." In addition to task-evoked activity, the same subjects also underwent rsFC. RsFC from anterior and posterior insula to other regions such as VMPFC was reduced which was related negatively to the severity of somatic anxiety.

Taken together, this study in GAD demonstrates abnormally increased task-evoked activity in regions of SN and SMN during interoceptive awareness (of the own heartbeat) (see also Fonzo et al. 2015 for more or similar regions being involved in task-evoked activity of positive and negative emotions) while, at the same time, rsFC from these regions to those of the DMN (VMPFC) is reduced. Importantly, both increased task-evoked activity in SMN and SN regions as well as their reduced rsFC to DMN correlated with psychopathological symptoms, e.g., psychic and somatic anxiety. Confirming and extending the resting state data, these findings further point out the central role of an abnormal balance of DMN with SN and/or SMN in anxiety disorders like GAD, SAD, and PD.

Moreover, these findings support the above suggested assumption that the resting state abnormalities in these networks are related to abnormal brain-heart coupling and HRV in anxiety disorders. Future investigations may thus want to demonstrate (i) how resting state neuronal variability in SMN, DMN, and SN changes during specifically task-evoked activity related to interoceptive awareness; (ii) how HRV changes during the transition from rest to task; and (iii) how the frequency ranges of neuronal variability change during the transition from rest to task including their relationship to the HRV changes.

Spatiotemporal Hypo- and Hyper-synchronization in DMN, SMN, and SN

The findings show abnormal resting state and task-evoked activity in regions of DMN, SMN, and SN in anxiety disorders (see above). At the same time, we demonstrated that the very same regions and networks are central in mediating phase-based temporal synchronization between neuronal and cardiac activity in the healthy brain (see above). This raises the question whether, and, if so, how the changes in resting state and task-evoked activity in these networks in anxiety disorders are related to abnormal phase-based temporal synchronization between neuronal and cardiac activity.

The resting state findings in anxiety disorders are mostly based on functional connectivity, e.g., rsFC. RsFC describes the correlation between two or more regions' time series [36]. Importantly, recent investigation in both fMRI [39, 64] and iEEG [65] show that rsFC is based on phase and, more specifically, phase-based coherence or synchronization between the different regions' time series: the more, for instance, two regions' phase are coherent and thus synchronized, the higher their resulting rsFC [39] which directly probed and compared different ways of calculating rsFC.

The phase-based nature of rsFC carries far-reaching implications for interpreting the abnormalities of rsFC in anxiety disorders. All anxiety disorders share the decrease of rsFC in DMN. Given the presumably phase-based nature of rsFC, one would now assume that the DMN regions are less synchronized with each other in anxiety disorders resulting in their decreased spatiotemporal synchronization with reduced rsFC. One can thus speak of "spatiotemporal hypo-synchronization" of DMN resting state activity in anxiety disorders. The converse seems to hold in SMN and SN. The findings suggest that SN and SMN show increased rsFC and thus increased spatiotemporal synchronization in SAD and PD, respectively – we therefore speak of "spatiotemporal hyper-synchronization" of SMN and SN resting state activity in SAD and PD.

Putting all together, one may want to speak of a spectrum of different possible degrees of spatiotemporal synchronization. What we observe as "normal" degree of spatiotemporal synchronization, e.g., rsFC, in the healthy brain may reflect an intermediate or average value. In contrast, the abnormally high or low degrees of rsFC, indexing spatiotemporal hypo- or hyper-synchronization, may reflect extreme values on the spectrum of different possible degrees of spatiotemporal synchronization. Accordingly, future phase-based analysis of rsFC in DMN, SN, and SMN in anxiety disorders is needed to support our hypothesis.

Abnormal Cross-Frequency Coupling in DMN, SMN, and SN

Based on the data on healthy subjects, we now traced rsFC abnormalities in DMN, SN, and SMN anxiety disorders to an underlying abnormal phase-based coherence or synchronization. Interestingly, as pointed out above, the same networks that show

rsFC in anxiety disorders are also central to processing in temporal synchronization between neuronal and cardiac activity. This raises the question whether abnormal spatiotemporal hypo- or hyper-synchronization, e.g., rsFC, in DMN, SN, and SMN is related to abnormal temporal synchronization between neuronal and cardiac activity in anxiety disorders. We thus search for connecting rsFC-related spatiotemporal (hypo- and hyper-) synchronization with neuro-cardiac temporal (de) synchronization.

We first and foremost have to say that both rsFC-based spatial synchronization and neuro-cardiac temporal synchronization operate in different frequency ranges. The rsFC findings were obtained in fMRI which operates in the infraslow frequency domain between 0.01 and 0.1 Hz, whereas the ITC and HEP findings were observed in MEG/iEEG that operate in a much faster frequency domain from 1 to 180 Hz with the ITC being observed between 4 and 7 Hz (while the slower frequencies around the heartbeat itself and its HRV (e.g., 1 Hz and lower) were filtered for methodological reasons). Due to such difference in frequency ranges, we cannot directly link and relate rsFC-related spatial (hypo- or hyper-)synchronization to neuro-cardiac temporal (de)synchronization in anxiety disorders.

However, impossible direct linkage does not preclude indirect connection. One mechanism could be cross-frequency coupling (CFC) [66]. For instance, the phase of the slower frequency around 0.01–0.1 Hz (as measured with rsFC in fMRI) could bind and thus synchronize with the amplitude of the faster frequencies (0.1–4 and 7 Hz) (as measured in MEG/iEEG) which indeed has been demonstrated in combined fMRI-EEG studies [67]. Moreover, as shown by [39], there is also cross-frequency coupling within the infraslow frequency range as measured with fMRI. Accordingly, CFC seems to be important in synchronizing neuronal activity between different frequency ranges.

Such temporal synchronization between different frequency ranges within the neuronal activity itself in terms of CFC raises the question whether analogous CFC also occurs between neuronal and cardiac activity. For instance, CFC could mediate temporal synchronization between the infraslow frequencies (0.01–0.1 Hz) of the ongoing brain's resting state activity and the faster frequencies of the heartbeat (0.1–1 Hz). This is especially important in anxiety disorders. The clearly observed resting state abnormalities in the infraslow range of 0.01–0.1 Hz may alter CFC within the brain's neuronal activity which, in turn, may alter temporal synchronization between neural and cardiac activity. The resting state FC abnormalities would then directly impact neuro-cardiac temporal synchronization. That remains to be tested though.

We therefore hypothesize that anxiety disorders can be characterized by abnormal cross-frequency coupling between infraslow and faster frequency ranges as that is important for temporal synchronization of neural and cardiac activity. Specifically, following rsFC and its spatial hypo- and hyper-synchronization, we hypothesize decreased CFC in DMN but increased CFC in SMN and SN in anxiety disorders. That, in turn, as it needs to be investigated in the future, may strongly impact neuro-cardiac temporal synchronization in the 0.1/4–7 Hz range including its measures like ITC and HEP. Specifically, one would expect that decreased CFC leads to

decreases in both ITC and HEP, as we assume it to be the case in DMN, while increased CFC should lead to increases in both ITC and HEP as it may be the case in SN and SMN in anxiety disorders.

Spatiotemporal Hypo-synchronization in DMN and Instability of Self

We demonstrated that rsFC is most likely related to spatiotemporal synchronization reflecting phase-based coherence between different regions within a specific network like DMN. Decreased rsFC in DMN, as observed in anxiety disorders, may thus reflect spatiotemporal hypo-synchronization such that the various DMN regions are no longer as strongly tied and connected together as network. Due to such spatiotemporal hypo-synchronization, the DMN as one phase-based coherent network may thus become more instable, e.g., less synchronized, on neuronal grounds. This carries major neuronal and psychological implications.

Spatiotemporal hypo-synchronization means that the DMN as network becomes more unstable in its neuronal activity as its various regions, being less synchronized with each other, are "now more on their own" and independent of each other. That introduces instability into DMN neuronal activity in the infraslow range of 0.01–0.1 Hz. That very same infraslow neuronal instability may make the coupling of the infraslow to faster frequencies more difficult resulting in decreased CFC. The decrease in CFC, in turn, may also impair temporal synchronization between neuronal and cardiac activity (in faster frequencies) such that both become desynchronized from each other in regions like VMPFC and PACC as core regions of DMN. The DMN's spatiotemporal hypo-synchronization in the resting state's rsFC would then lead to reduction in neuro-cardiac temporal hypo-synchronization – the latter should be manifested in lower phase locking with reduced intertrial coherence (ITC) (in the 0.1/4–7 Hz range) in the brain's resting state activity.

Accordingly, put in a nutshell, we assume that spatiotemporal hypo-synchronization in DMN leads to neuro-cardiac temporal desynchronization in anxiety disorders. The neuronal instability of DMN may thus affect the neuro-cardiac coupling which, analogously, may then also become unstable if not resulting in neuro-cardiac temporal desynchronization. While such neuro-cardiac temporal desynchronization remains to be investigated in anxiety disorders, it has already been reported in fMRI of posttraumatic stress disorders (PTSD) [18, 19]. Since PTSD is also featured by strong anxiety, one would expect more or less analogous findings in anxiety disorders.

The instability of both DMN network neuronal activity and neuro-cardiac coupling may carry major psychological implications. As pointed out the DMN is central in mediating internal cognition like sense of self [43], episodic simulation with prospection into the future and retrospection into the past, and mind wandering [13, 68]. Moreover, the above-presented findings by the group around Tallon-Baudry clearly demonstrate that neuro-cardiac coupling in VMPFC/PACC as core regions of DMN is related to the sense of self, e.g., "I" vs "me" [25, 26] (see above for details).

Given the DMN findings, one would expect the sense of self to be less synchronized and thus instable as based on spatiotemporal hypo-synchronization within DMN as manifested in reduced rsFC. Moreover, one would expect that the self can no longer integrate different time scales as it has no access to different frequency ranges beyond itself due to reduced CFC in DMN. Finally, one would expect that the self is no longer aligned with the own body as related to decreased neuro-cardiac temporal synchronization. Together, this leads to an increased spatial and temporal instability in self as it is indeed a hallmark feature in anxiety disorders which may be manifested in abnormal internal cognition as in episodic simulation (as in abnormal foresight of the futures) [69] and mind wandering [68–70] (see Fig. 5.3a).

Spatiotemporal Hyper-synchronization in SMN/SN and Increased Emotions/Anxiety (SAD) and Bodily Awareness (PD)

In addition to rsFC decrease in DMN, the findings show increased rsFC in SMN (PD) and SN (SAD) (see above). One would consequently assume spatiotemporal hyper-synchronization in SMN or SN accompanying DMN spatiotemporal hypo-synchronization. Following the neuronal and psychological results of brain-heart coupling in the healthy brain (see above), one would assume the following hypotheses.

Spatiotemporal hyper-synchronization means that the SMN/SN as network becomes more stable in its neuronal activity as its various regions, being more synchronized with each other, are "now more with each other" and thus more dependent on each other. That increases network stability in the infraslow range of 0.01–0.1 Hz. Increased infraslow neuronal stability may make the coupling of the infraslow to faster frequencies easier resulting in increased CFC. The increase in CFC, in turn, may enhance temporal synchronization between neuronal and cardiac activity (in faster frequencies) such that both become hyper-synchronized with each other in regions like insula, amygdala, thalamus (SN), and somatosensory cortex (SMN).

The spatiotemporal hyper-synchronization of SMN/SN in the 0.01–0.1 Hz range of rsFC should lead to higher CFC and ultimately higher neuro-cardiac temporal synchronization in the 0.1/4–7 Hz range. The spatiotemporal hyper-synchronization of SMN/SN in the 0.01–0.1 Hz range of rsFC should lead to higher CFC and ultimately higher neuro-cardiac temporal synchronization in the 0.1/4–7 Hz range. The increased rsFC indexing spatiotemporal hyper-synchronization in SMN/SN should then be accompanied by increased neuro-cardiac temporal synchronization as manifested in higher phase synchronization with increased intertrial coherence (ITC) (in the 0.1/4–7 Hz range) in the brain's resting state activity.

Accordingly, put in a nutshell, we assume that spatiotemporal hyper-synchronization in SMN/SN leads to temporal hyper-synchronization between the brain and the heart in anxiety disorders. The increased neuronal stability of SMN/SN may thus affect the neuro-cardiac coupling which, analogously, may then also become increasingly stable resulting in increased neuro-cardiac coupling mediated by phase-based temporal hyper-synchronization. Such neuro-cardiac temporal

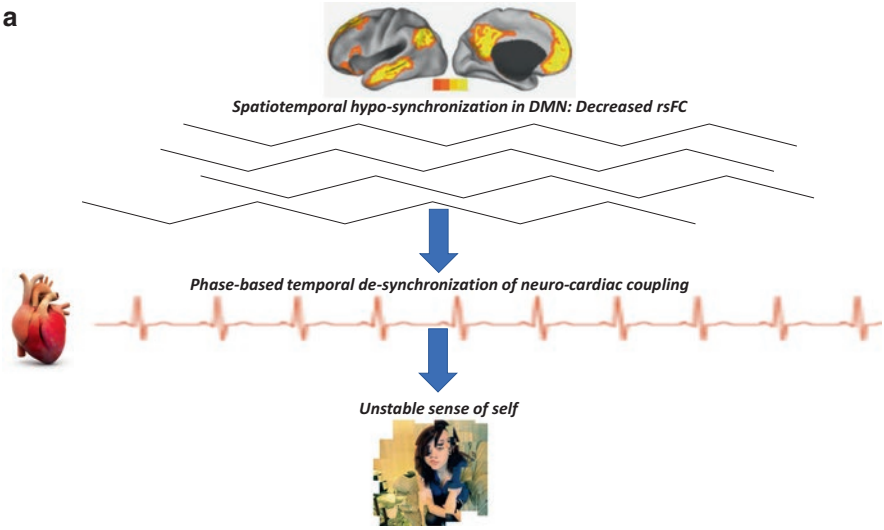

Fig. 5.3a Altered default-mode network (DMN) and its psychopathological symptoms

hyper-synchronization remains to be investigated in SMN and SN in anxiety disorders though. The increased stability of both SMN/SN network neuronal activity and neuro-cardiac coupling may carry major psychological implications.

The SN and specifically the insula, thalamus, dACC, and amygdala including their neuro-cardiac coupling are strongly associated with emotions like anxiety. Increased stability of both SN and neuro-cardiac coupling in specifically amygdala and insula may abnormally enhance emotions and especially anxiety – that is exactly what one can observe psychopathologically in specifically SAD (see also [71] and [39] as well as [57, 59, 72]) where increases in SN rsFC have been reported. Moreover, since SN and especially insula are central in processing the heartbeat (see above), one would expect abnormally increased SN function to go along with increased neuro-cardiac coupling in this region resulting in increased perception or awareness of the own heartbeat, e.g., increased interoceptive awareness (see [73, 74]), in specifically SAD (where the insula and SN are abnormal) (see Fig. 5.3b).

The SMN and its neuro-cardiac coupling are involved in proprioception and awareness of the own body (see [24, 45]). Increased stability of both SMN and its neuro-cardiac coupling may result in increased awareness of the own body's proprioceptive stimuli and ultimately in higher awareness of the own body, e.g., increased bodily awareness, and various somatic symptoms (see also [75]). This is well compatible with the psychopathological symptoms of PD (where the SMN is abnormally increased) where increased awareness of bodily sensation and the own body as a whole are core symptoms (see, as described above, 8 for support). However, the link between SMN spatiotemporal hyper-synchronization, increased neuro-cardiac coupling, and increased bodily awareness remains to be demonstrated (see Fig. 5.3c).

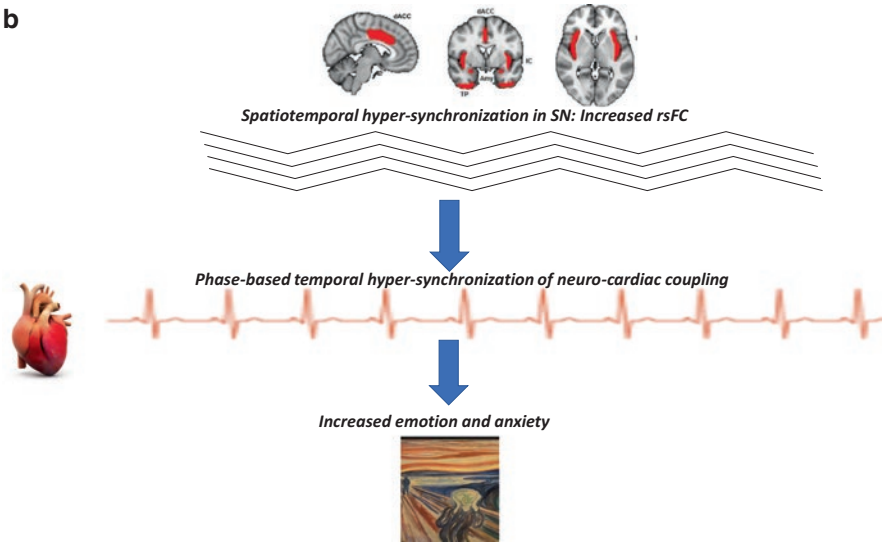

Fig. 5.3b Altered salience network (SN) and its psychopathological symptoms. Altered somatomotor network (SMN) and its psychopathological symptoms

Conclusion

We here reviewed recent rsFC and task-evoked findings, conducted mainly in fMRI, in anxiety disorders. Core findings include altered rsFC in DMN, SN, and SMN which suggests disbalances in their relationships with the tilting of DMN/SN and DMN/SMN ratios toward the non-DMN networks. These findings suggest spatiotemporal hypo-synchronization between the regions' rsFC in the infraslow frequency range in DMN (all anxiety disorders), while one may assume spatiotemporal hyper-synchronization in SMN (PD) and SN (SAD). That, as we hypothesize, may be related to increased or decreased neuro-cardiac coupling as mediated by phase-based temporal synchronization (as demonstrated in healthy subjects in MEG and iEEG).

Taken together, we assume two spatiotemporal mechanisms to play a central role in yielding psychopathological symptoms in anxiety disorders. First, the findings suggest spatiotemporal hypo- and/or hyper-synchronization in the neural activity of networks like DMN< SMN and SN. Secondly, based on clinical finding in anxiety disorders and neuronal observations in healthy subjects, we suggest these network abnormalities to lead to abnormal, e.g., increased or decreased, phase-based temporal synchronization of neuronal and cardiac activity. Together, spatiotemporal hypo- or hyper-synchronization in the different resting state networks, e.g., DMN, SMN, and SN, and associated increased/decreased neuro-cardiac temporal synchronization are shown to most likely underlie core psychopathological symptoms such as unstable self, increased emotions/anxiety, and/or increased interoceptive and/or bodily awareness in anxiety disorders.

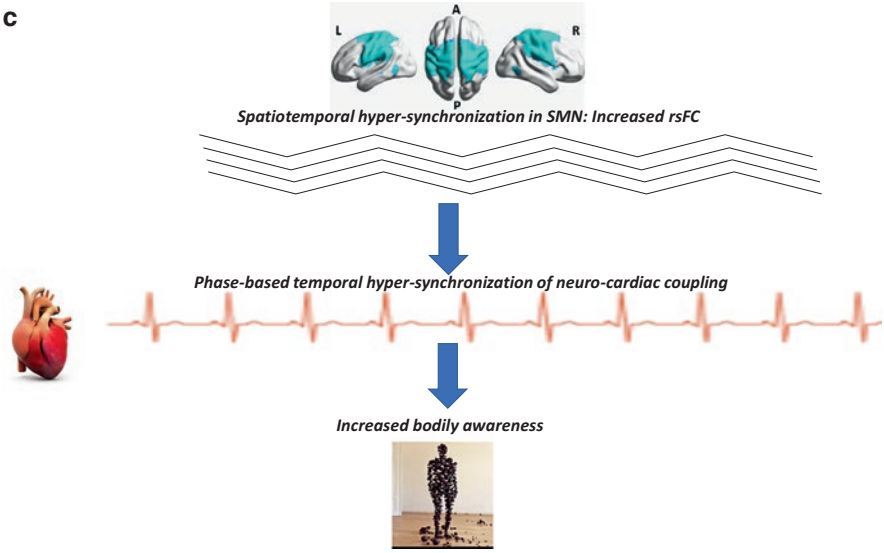

Fig. 5.3c Altered somatomotor network (SMN) and its psychopathological symptoms

Psychopathological symptoms in the different domains of self (unstable self), emotions (increased anxiety), and bodily awareness (increased interoceptive and bodily awareness) may thus be based primarily on spatiotemporal mechanisms in the brain's neuronal activity, e.g., its resting state networks' spatiotemporal synchronization, and its neuro-cardiac coupling, e.g., phase-based temporal synchronization. Such spatiotemporal (rather than primarily affective or cognitive) basis of psychopathological symptoms in anxiety disorders is well compatible with the recent suggestion of "Spatiotemporal Psychopathology" [10–13, see also 14–16].

References

1. Olesen KKW, Madsen M, Lip GYH, Egholm G, Thim T, Jensen LO, et al. Coronary artery disease and risk of adverse cardiac events and stroke. Eur J Clin Invest. 2017 Nov;47(11):819–28.
2. Kim EY, Lee MY, Kim SH, Ha K, Kim KP, Ahn YM. Diagnosis of major depressive disorder by combining multimodal information from heart rate dynamics and serum proteomics using machine-learning algorithm. Prog Neuropsychopharmacol Biol Psychiatry. 2017 Jun;76:65–71.
3. Kim Y-K, Yoon H-K. Common and distinct brain networks underlying panic and social anxiety disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2018 Jan;80(Pt B):115–22.
4. Chalmers JA, Quintana DS, Abbott MJ-A, Kemp AH. Anxiety disorders are associated with reduced heart rate variability: a meta-analysis. Front Psychiatry. 2014;5:80.
5. Wiebking C, de Greck M, Duncan NW, Heinzel A, Tempelmann C, Northoff G. Are emotions associated with activity during rest or interoception? An exploratory fMRI study in healthy subjects. Neurosci Lett. 2011 Mar;491(1):87–92.

6. Avery JA, Drevets WC, Moseman SE, Bodurka J, Barcalow JC, Simmons WK. Major depressive disorder is associated with abnormal interoceptive activity and functional connectivity in the insula. Biol Psychiatry. 2014 Aug;76(3):258–66.
7. Cui H, Zhang J, Liu Y, Li Q, Li H, Zhang L, et al. Differential alterations of resting-state functional connectivity in generalized anxiety disorder and panic disorder. Hum Brain Mapp. 2016 Apr;37(4):1459–73.
8. Cui S, Len J, Zhang J, Li C, Northoff G. Alterations in interceptive awareness and the brain's resting state and task-evoked activity in generalized anxiety disorder. Biol Psychiatry Cogn Neurosci Neuroimaging. In review. 2019
9. Emdin CA, Odutayo A, Wong CX, Tran J, Hsiao AJ, Hunn BHM. Meta-analysis of anxiety as a risk factor for cardiovascular disease. Am J Cardiol. 2016 Aug;118(4):511–9.
10. Northoff G. Spatiotemporal psychopathology I: no rest for the brain's resting state activity in depression? Spatiotemporal psychopathology of depressive symptoms. J Affect Disord. 2016 Jan;190:854–66.
11. Northoff G. Spatiotemporal psychopathology II: how does a psychopathology of the brain's resting state look like? Spatiotemporal approach and the history of psychopathology. J Affect Disord. 2016 Jan;190:867–79.
12. Northoff G. "Paradox of slow frequencies" – are slow frequencies in upper cortical layers a neural predisposition of the level/state of consciousness (NPC)? Conscious Cogn. 2017 Sep;54:20–35.
13. Northoff G. The brain's spontaneous activity and its psychopathological symptoms – "spatiotemporal binding and integration". Prog Neuropsychopharmacol Biol Psychiatry. 2018 Jan;80(Pt B):81–90.
14. Northoff G, Duncan NW. 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. 2016 Oct;145–146:26–45.
15. Northoff G, Stanghellini G. How to link brain and experience? Spatiotemporal psychopathology of the lived body. Front Hum Neurosci. 2016;10:76.
16. Fingelkurts AA, Fingelkurts AA. Brain space and time in mental disorders: paradigm shift in biological psychiatry. Int J Psychiatry Med. 2018 Aug;91217418791438
17. Chang C, Metzger CD, Glover GH, Duyn JH, Heinze H-J, Walter M. Association between heart rate variability and fluctuations in resting-state functional connectivity. Neuroimage. 2013 Mar;68:93–104.
18. Thome J, Densmore M, Frewen PA, McKinnon MC, Theberge J, Nicholson AA, et al. Desynchronization of autonomic response and central autonomic network connectivity in posttraumatic stress disorder. Hum Brain Mapp. 2017 Jan;38(1):27–40.
19. Rabellino D, D'Andrea W, Siegle G, Frewen PA, Minshew R, Densmore M, et al. Neural correlates of heart rate variability in PTSD during sub- and supraliminal processing of trauma-related cues. Hum Brain Mapp. 2017 Oct;38(10):4898–907.
20. Jennings JR, Sheu LK, Kuan DC-H, Manuck SB, Gianaros PJ. Resting state connectivity of the medial prefrontal cortex covaries with individual differences in high-frequency heart rate variability. Psychophysiology. 2016 Apr;53(4):444–54.
21. Park H-D, Correia S, Ducorps A, Tallon-Baudry C. Spontaneous fluctuations in neural responses to heartbeats predict visual detection. Nat Neurosci. 2014 Apr;17(4):612–8.
22. Park H-D, Tallon-Baudry C. The neural subjective frame: from bodily signals to perceptual consciousness. Philos Trans R Soc Lond B Biol Sci. 2014 May;369(1641):20130208.
23. Park H-D, Bernasconi F, Bello-Ruiz J, Pfeiffer C, Salomon R, Blanke O. Transient modulations of neural responses to heartbeats covary with bodily self-consciousness. J Neurosci. 2016 Aug;36(32):8453–60.
24. Park H-D, Bernasconi F, Salomon R, Tallon-Baudry C, Spinelli L, Seeck M, et al. Neural sources and underlying mechanisms of neural responses to heartbeats, and their role in bodily self-consciousness: an intracranial EEG study. Cereb Cortex. 2018 Jul;28(7):2351–64.

25. Babo-Rebelo M, Wolpert N, Adam C, Hasboun D, Tallon-Baudry C. Is the cardiac monitoring function related to the self in both the default network and right anterior insula? Philos Trans R Soc Lond B Biol Sci. 2016 Nov;371(1708)
26. Babo-Rebelo M, Richter CG, Tallon-Baudry C. Neural responses to heartbeats in the default network encode the self in spontaneous thoughts. J Neurosci. 2016 Jul;36(30):7829–40.
27. Garfinkel SN, Seth AK, Barrett AB, Suzuki K, Critchley HD. Knowing your own heart: distinguishing interoceptive accuracy from interoceptive awareness. Biol Psychol. 2015 Jan;104:65–74.
28. Forkmann T, Scherer A, Meessen J, Michal M, Schachinger H, Vogele C, et al. Making sense of what you sense: disentangling interoceptive awareness, sensibility and accuracy. Int J Psychophysiol. 2016 Nov;109:71–80.
29. Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ. Neural systems supporting interoceptive awareness. Nat Neurosci. 2004 Feb;7(2):189–95.
30. Kuehn E, Mueller K, Lohmann G, Schuetz-Bosbach S. Interoceptive awareness changes the posterior insula functional connectivity profile. Brain Struct Funct. 2016 Apr;221(3):1555–71.
31. Wiebking C, Duncan NW, Tiret B, Hayes DJ, Marjanska M, Doyon J, et al. GABA in the insula – a predictor of the neural response to interoceptive awareness. Neuroimage. 2014 Feb;86:10–8.
32. Wiebking C, Duncan NW, Qin P, Hayes DJ, Lyttelton O, Gravel P, et al. External awareness and GABA – a multimodal imaging study combining fMRI and [18F]flumazenil-PET. Hum Brain Mapp. 2014 Jan;35(1):173–84.
33. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci. 2011 Oct;15(10):483–506.
34. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci. 2007 Feb;27(9):2349–56.
35. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci USA. 2001 Jan;98(2):676–82.
36. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci USA. 2003 Jan;100(1):253–8.
37. Tallon-Baudry C, Campana F, Park H-D, Babo-Rebelo M. The neural monitoring of visceral inputs, rather than attention, accounts for first-person perspective in conscious vision. Cortex. 2018 May;102:139–49.
38. Pollatos O, Herbert BM, Mai S, Kammer T. Changes in interoceptive processes following brain stimulation. Philos Trans R Soc Lond B Biol Sci. 2016 Nov;371(1708)
39. Huang Z, Zhang J, Longtin A, Dumont G, Duncan NW, Pokorny J, et al. Is there a nonadditive interaction between spontaneous and evoked activity? Phase-dependence and its relation to the temporal structure of scale-free brain activity. Cereb Cortex. 2017 Feb;27(2):1037–59.
40. He BJ. Spontaneous and task-evoked brain activity negatively interact. J Neurosci. 2013 Mar;33(11):4672–82.
41. Lakatos P, Schroeder CE, Leitman DI, Javitt DC. Predictive suppression of cortical excitability and its deficit in schizophrenia. J Neurosci. 2013 Jul;33(28):11692–702.
42. Northoff G, Huang Z. How do the brain's time and space mediate consciousness and its different dimensions? Temporo-spatial theory of consciousness (TTC). Neurosci Biobehav Rev. 2017 Sep;80:630–45.
43. Northoff G, Heinzel A. First-Person Neuroscience: a new methodological approach for linking mental and neuronal states. Philos Ethics Humanit Med. 2006 Mar;1(1):E3.
44. Qin P, Northoff G. How is our self related to midline regions and the default-mode network? Neuroimage. 2011 Aug;57(3):1221–33.
45. Blanke O. Multisensory brain mechanisms of bodily self-consciousness. Nat Rev Neurosci. 2012 Jul;13(8):556–71.

46. Enzi B, de Greck M, Prosch U, Tempelmann C, Northoff G. Is our self nothing but reward? Neuronal overlap and distinction between reward and personal relevance and its relation to human personality. PLoS One. 2009 Dec;4(12):e8429.
47. Northoff G, Wiebking C, Feinberg T, Panksepp J. The "resting-state hypothesis" of major depressive disorder-a translational subcortical-cortical framework for a system disorder. Neurosci Biobehav Rev. 2011 Oct;35(9):1929–45.
48. Craig AD. The sentient self. Brain Struct Funct. 2010 Jun;214(5–6):563–77.
49. Peterson A, Thome J, Frewen P, Lanius RA. Resting-state neuroimaging studies: a new way of identifying differences and similarities among the anxiety disorders? Can J Psychiatry. 2014 Jun;59(6):294–300.
50. Fonzo GA, Etkin A. Affective neuroimaging in generalized anxiety disorder: an integrated review. Dialogues Clin Neurosci. 2017 Jun;19(2):169–79.
51. MacNamara A, DiGangi J, Phan KL. Aberrant spontaneous and task-dependent functional connections in the anxious brain. Biol psychiatry Cogn Neurosci neuroimaging. 2016 May;1(3):278–87.
52. Shin Y-W, Dzemidzic M, Jo HJ, Long Z, Medlock C, Dydak U, et al. Increased resting-state functional connectivity between the anterior cingulate cortex and the precuneus in panic disorder: resting-state connectivity in panic disorder. J Affect Disord. 2013 Sep;150(3):1091–5.
53. Lai C-H, Wu Y-T. The alterations in inter-hemispheric functional coordination of patients with panic disorder: the findings in the posterior sub-network of default mode network. J Affect Disord. 2014 Sep;166:279–84.
54. Pannekoek JN, van der Werff SJA, Stein DJ, van der Wee NJA. Advances in the neuroimaging of panic disorder. Hum Psychopharmacol. 2013 Nov;28(6):608–11.
55. Lai C-H, Wu Y-T. The changes in the low-frequency fluctuations of cingulate cortex and postcentral gyrus in the treatment of panic disorder: the MRI study. World J Biol Psychiatry. 2016;17(1):58–65.
56. Mochcovitch MD, da Rocha Freire RC, Garcia RF, Nardi AE. A systematic review of fMRI studies in generalized anxiety disorder: evaluating its neural and cognitive basis. J Affect Disord. 2014;167:336–42.
57. Makovac E, Meeten F, Watson DR, Herman A, Garfinkel SN, D Critchley H, et al. Alterations in amygdala-prefrontal functional connectivity account for excessive worry and autonomic dysregulation in generalized anxiety disorder. Biol Psychiatry. 2016 Nov;80(10):786–95.
58. Hilbert K, Lueken U, Beesdo-Baum K. Neural structures, functioning and connectivity in generalized anxiety disorder and interaction with neuroendocrine systems: a systematic review. J Affect Disord. 2014 Apr;158:114–26.
59. Makovac E, Watson DR, Meeten F, Garfinkel SN, Cercignani M, Critchley HD, et al. Amygdala functional connectivity as a longitudinal biomarker of symptom changes in generalized anxiety. Soc Cogn Affect Neurosci. 2016 Nov;11(11):1719–28.
60. Zhang Y, Zhu C, Chen H, Duan X, Lu F, Li M, et al. Frequency-dependent alterations in the amplitude of low-frequency fluctuations in social anxiety disorder. J Affect Disord. 2015 Mar;174:329–35.
61. Wang W, Hou J, Qian S, Liu K, Li B, Li M, et al. Aberrant regional neural fluctuations and functional connectivity in generalized anxiety disorder revealed by resting-state functional magnetic resonance imaging. Neurosci Lett. 2016 Jun;624:78–84.
62. Yuan C, Zhu H, Ren Z, Yuan M, Gao M, Zhang Y, et al. Precuneus-related regional and network functional deficits in social anxiety disorder: A resting-state functional MRI study. Compr Psychiatry. 2018 Apr;82:22–9.
63. Caseras X, Murphy K, Mataix-Cols D, Lopez-Sola M, Soriano-Mas C, Ortriz H, et al. Anatomical and functional overlap within the insula and anterior cingulate cortex during interoception and phobic symptom provocation. Hum Brain Mapp. 2013 May;34(5):1220–9.
64. Zhang J, Magioncalda P, Huang Z, Tan Z, Hu X, Hu Z, et al. Altered global signal topography and its different regional localization in motor cortex and hippocampus in mania and depression. Schizophr Bull. 2018 Oct;

65. Wen H, Liu Z. Broadband electrophysiological dynamics contribute to global resting-state fMRI signal. J Neurosci. 2016 Jun;36(22):6030–40.
66. He BJ, Zempel JM, Snyder AZ, Raichle ME. The temporal structures and functional significance of scale-free brain activity. Neuron. 2010 May;66(3):353–69.
67. Ganzetti M, Mantini D. Functional connectivity and oscillatory neuronal activity in the resting human brain. Neuroscience. 2013 Jun;240:297–309.
68. Christoff K, Irving ZC, Fox KCR, Spreng RN, Andrews-Hanna JR. Mind-wandering as spontaneous thought: a dynamic framework. Nat Rev Neurosci. 2016 Nov;17(11):718–31.
69. Miloyan B, Bulley A, Suddendorf T. Episodic foresight and anxiety: proximate and ultimate perspectives. Br J Clin Psychol. 2016 Mar;55(1):4–22.
70. Miloyan B, Pachana NA, Suddendorf T. The future is here: a review of foresight systems in anxiety and depression. Cogn Emot. 2014;28(5):795–810.
71. Paulus MP, Stein MB, Craske MG, Bookheimer S, Taylor CT, Simmons AN, et al. Latent variable analysis of positive and negative valence processing focused on symptom and behavioral units of analysis in mood and anxiety disorders. J Affect Disord. 2017 Jul;216:17–29.
72. Makovac E, Meeten F, Watson DR, Garfinkel SN, Critchley HD, Ottaviani C. Neurostructural abnormalities associated with axes of emotion dysregulation in generalized anxiety. NeuroImage Clin. 2015;10:172–81.
73. Khalsa SS, Adolphs R, Cameron OG, Critchley HD, Davenport PW, Feinstein JS, et al. Interoception and mental health: a roadmap. Biol psychiatry Cogn Neurosci Neuroimaging. 2018 Jun;3(6):501–13.
74. Quadt L, Critchley HD, Garfinkel SN. The neurobiology of interoception in health and disease. Ann NY Acad Sci. 2018 Sep;1428(1):112–28.
75. Mallorqui-Bague N, Bulbena A, Pailhez G, Garfinkel SN, Critchley HD. Mind-body interactions in anxiety and somatic symptoms. Harv Rev Psychiatry. 2016;24(1):53–60. 71.