Molecular Psychiatry
https://doi.org/10.1038/s41380-021-01029-w

REVIEW ARTICLE

# Out-of-step: brain-heart desynchronization in anxiety disorders

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Received: 19 June 2020 / Revised: 30 December 2020 / Accepted: 12 January 2021


## Abstract

Imaging studies in anxiety disorders (AD) show abnormal functional connectivity primarily in the salience network (SN), somatomotor network (SMN), and default mode network (DMN). However, it is not clear how precisely these network changes occur including their relation to psychopathological symptoms. Here, we show that the functional networks affected in AD overlap with cortical regions that receive visceral inputs (the so-called central/visceral autonomic network). Focusing on cardiac afferents, we suggest that network changes in AD may be due to reduced phase synchronization between ongoing neural and cardiac activity. This neuro-cardiac desynchronization occurs due to the abnormal phase resetting of neural activity at the onset of each heartbeat, as measured by a lower intertrial coherence and heartbeat-evoked potential. Biochemically, cardiac afferents reach subcortical serotonergic raphe nuclei and noradrenergic locus coeruleus (among others) which, in turn, are known to reciprocally modulate the DMN and SMN/SN on the cortical level. Consistent with the network changes in AD, decreases in serotonergic and noradrenergic activity are known to increase connectivity in both SMN and SN while, at the same time, they decrease DMN connectivity. SMN and SN increases, in turn, lead to increased emotional arousal/anxiety and bodily awareness whereas decreased DMN connectivity leads to an unstable sense-of-self in AD. Finally, we integrate our proposal with interoceptive predictive processing models suggesting neuro-cardiac desynchronization as a mechanism for "noisy" bottom-up information leading to a persistently uncertain bodily state in top-down models. In sum, integrating theories on active interference and hyperarousal, we propose a precise neuro-cardiac and biochemically -driven mechanisms for key psychopathological symptoms of AD.

## Introduction

Anxiety disorders (AD) include panic disorder (PD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), and specific phobias, which share symptoms of excessive worry or fearful responses to benign stimuli [1]. In addition to uncontrollable worry, somato-cardiac symptoms such as heart palpitations and lower heart rate variability (HRV) are also common across these disorders [2]. Imaging studies in these disorders show changes in large scale functional networks/regions during rest [3] and various tasks [4]. However, it remains unclear how these neural changes occur and how they may be related to the various symptoms in these disorders.

Here, we suggest that functional network changes in AD may be due to an abnormal biochemically -driven interaction between neural activity and cardiac inputs to the brain. Specifically, we show that (1) regions in the affected networks receive cardiac and other visceral inputs, (2) cardiac activity resets the phase of neural activity in these regions, and may be abnormal in AD, (3) the impaired phase-resetting process affects the flow of information from the body to the brain, which leads to increased uncertainty of the bodily state, which (4) induces top-down corrective signals to enhance 'noisy' bodily signals, (5) resulting in altered phase coherence (functional connectivity) within functional networks, as well as causing anxious apprehension and somatic symptoms of anxious arousal such as palpitations. (6) Lastly, we suggest that the subcortical monoaminergic neurotransmitter system including serotonin and noradrenaline may modulate the reciprocal balance in the activity on the cortical level leading to the specific network findings in AD.

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Published online: 27 January 2021

We base our suggestion on evidence that converges upon the role of abnormal spatiotemporal mechanisms of cardiac interoception in anxiety. We focus more on AD rather than primarily on anxiety as a trans-diagnostic symptom because of the relative strength of evidence in these disorders for our proposal. We also focused on cardiac function rather than on interoceptive abnormalities in general because recent advances show how cardiac activity influences neural activity at a high temporal resolution. More generally, our proposal attributes psychopathological symptoms of AD to spatiotemporal mechanisms, such as brain-heart synchronization, rather than to affective or cognitive abnormalities [5–11].

## Anxiety—an asymmetric response to benign stimuli

Anxiety may be defined as a state of worry due to the anticipation of uncertain or undesirable outcomes [12]. This can be useful in healthy individuals as uncertainty may prompt increased attention and arousal in order to avoid negative events. However, persistent worry where innocuous stimuli are considered threatening constitutes a mental disorder and limits day-to-day functioning. Anxiety may be subdivided into anxious apprehension (enduring worry of negative events) and anxious arousal (hyperarousal and exaggerated response to benign stimuli) [13]. These constructs are regarded as traits, suggesting that individuals have a propensity for anxiety.

The above view considers psychological processes of prospecting and uncertainty reduction to underlie anxiety; a broader view suggests abnormal interoceptive processing as a basis for anxiety [14–16]. In this view, behavioral and autonomic symptoms are attributed to top-down modulation from brain regions that monitor interoceptive signals [14, 15, 17, 18]. It has been hypothesized that the central nervous system implements active inference perceptual processing hierarchically and bi-directionally [19], i.e., models at a lower level of the hierarchy serve as evidence for models at a higher level, i.e., bottom-up modulation. In turn, higher-level models modify lower-level models, i.e., top-down modulation, to match their prediction. Minimization of the energetic cost, i.e., the free energy principle proposed by Friston, aims to provide a computational explanation for how the brain optimizes (selects) perceptions in the presence of multiple expectations and models [20]. Via the active inference process, the brain ultimately settles on a perception that results in the least divergence between the available evidence and the predicted model.

A consequence of active inference models is that certain psychiatric disorders, especially those characterized by chronic and unrelenting anxiety, are preferentially susceptible to "top-down constructed dysfunctions", i.e., they are the consequences of a persistent mismatch between top-down predicted body states and bottom-up afferent signals from the body. It has been proposed that sustained and exaggerated mismatches dysregulate the ability to accurately sense what is happening in the body, resulting in a turbulent reference state (i.e., a "noisy baseline") [21], attentional bias toward threats [22], increased worry and self-related cognitions, dysfunctional learning about bodily states over time [23], and increased allostatic load leading to increased stress and mental illness [24, 25].

In an adaptive individual, corrective action in the presence of somatic error can be achieved by adjusting the expectations (priors) to match the current physiological state, or by engaging in regulatory actions which change the afferent signal, leading the current physiological state to conform more closely with the expectations. In either case, successful corrective action reduces somatic error, which results in homeostatic balance within the nervous system. This can break down in two ways. Firstly, hyperprecise priors, i.e., having very strong beliefs that a certain model is correct driven by prolonged periods of worry and rumination, may not get appropriately updated by the evidence, which can create persistent somatic errors or a "noisy" baseline state [21]. Secondly, context rigidity, i.e., the lack of one's ability to adjust expectation as a function of context, may contribute to the persistent experience of somatic error because the individual does not adjust her belief about different models in a new environment. In its most severe form, the somatic error becomes so pervasive that the only corrective action that seems to quell the error is avoidance of all perceived triggers (i.e., agoraphobia).

The symptoms of AD are considered as responses either to reduce uncertainty or to avoid consequent symptoms [12, 26]. However, each of the disorders show a constellation of overlapping and distinct symptoms (see Box 1). GAD maybe described by the presence of internally focused apprehension without prominent external symptoms. Patients with PD, on the other hand, suffer from sudden unpredictable bouts of extreme anxiety, a sense of impending doom, and overwhelming somatic symptoms. In the context of interoceptive basis for anxiety, the prominent cardiac symptoms and heightened bodily awareness are especially noteworthy. In contrast to GAD and PD, feelings of anxiety in SAD and specific phobias are cue-specific. Overt anxiety in SAD is limited to specific circumstances such as social settings or public-speaking, which may lead patients to avoid these situations or endure them with distress. In both PD and SAD, the somatic or "external" symptoms are more prominent than in GAD where the symptoms are more internally oriented. This heterogeneity

**Box 1.** Anxiety disorders: specific-symptom constellations

GAD is characterized by presence of excessive worry over multiple issues and anxious apprehension of untoward outcomes [1]. Despite the absence of specific sources, feelings of anxiety are difficult to control. Somatic symptoms are less prominent than other AD and include restlessness, excessive fatigue, irritability, difficulty concentrating, muscle tension, sleep disturbance, headaches, and gastrointestinal symptoms. These symptoms must be present for more than 6 months. The internally oriented rumination over varied concerns with mild physical symptoms differentiate GAD from other AD that are triggered by external cues.

SAD is characterized by fear or worry limited to social situations in which either the individual may be scrutinized or are afraid of acting in a way that elicits negative responses from others [1]. To avoid the symptoms, social situations are avoided or endured under distress. Somatic symptoms are typically limited to social situations, and may include palpitations, excessive sweating, tremors, blushing, or muscle tension.

PD is characterized by sudden and unexpected attacks of extreme anxiety accompanied by strong somatic symptoms including palpitations, tightness of chest, feeling short of breath, sweating, and trembling [1]. Patients feel a fear of losing control and a fear of death. An attack is followed by a persistent fear of a recurrence. The abrupt nature of the attack along with dominant somatic (especially cardiac) symptoms distinguish PD from GAD and SAD.

in symptom clusters of AD along with a commonality in anxiety symptoms is also reflected on the neural level where these disorders show common as well as specific brain changes [27].

## Decoupled networks: brain changes in anxiety disorders

### Resting state abnormalities in DMN, SN, and SMN—functional connectivity

The large number of functional imaging studies on AD implicate a variety of regions (see [3, 28–32] for reviews and meta-analyses). Broadly speaking, the aggregate changes in functional connectivity across these disorders appear to be reduced [3]. However, like their symptoms, these disorders show common and distinct patterns of connectivity changes [29]. These regions include the amygdala, insula, somatosensory cortex, ventromedial prefrontal cortex (VMPFC), and the precuneus and posterior cingulate cortex. Together, these regions are part of three canonical functional networks—the salience network (SN), the somatomotor network (SMN), and the default mode network (DMN) [33, 34]. Broadly, the DMN shows reduced RSFC in GAD, and SAD, whereas in PD, studies show both increased and decreased RSFC. The SN shows increased RSFC specifically in SAD; and the SMN shows increased RSFC specifically in PD [35–37].

In GAD, RSFC is reduced between the midline regions of the DMN—the perigenual and posterior cingulate cortex (pgACC, PCC) [38]. However, another study found both increased and decreased RSFC within regions of the DMN [39]. In a resting state and task-based intervention study in GAD, resting state scans were obtained before and after a perseverative cognition task asking subjects to recall worrying episodes [40]. A greater increase in worry was associated with a greater decline in amygdala—VMPFC connectivity.

In SAD, midline regions of the DMN showed reduced RSFC [41, 42]. Specifically, RSFC is consistently reduced between the amygdala and the medial prefrontal cortex and posterior cingulate cortex [41, 43–46]. Whole-brain RSFC studies also report similar results [42, 47]. However, albeit in a small sample, increased RSFC in the amygdala has been reported [36]. In PD, both increased and reduced RSFC within the DMN were reported [45, 48, 49]. In the SMN, changes in RSFC appear to be specific to PD. Using a whole-brain approach, Cui et al. [50] observed increased RSFC between the postcentral cortex (i.e., sensory cortex) and the thalamus, which also correlated with the degree of anxiety (see also [37]).

Thus, studies in AD show a shared reduction in RSFC in the midline regions of DMN and SN. In addition, RSFC between networks (DMN to executive network, SN to SMN) is also reduced, whereas RSFC between the amygdala and anterior DMN appears to be increased [3, 29]. In individual disorders, changes in the SN and SMN appear to be relatively more specific—increased RSFC in SN in SAD, and increased RSFC from SMN to thalamus in PD (Fig. 1).

### Task-evoked abnormalities in SN, DMN, and SMN during interoception of heartbeats

The anterior insula, cingulate cortex, and somatomotor cortex, which show abnormal RSFC in AD, are 'activated' when healthy subjects are asked to focus on their heartbeat [51–55]. Awareness of heartbeats is also exaggerated in anxiety and AD [15, 56], which may be linked to the neural changes in these disorders. Indeed, interoceptive tasks in AD show increased activation, which is correlated to anxiety symptoms [57–59]. Furthermore, this increased activation maybe linked to RSFC in GAD [60]. In drug-naïve patients, the insula showed increased activity during a cardiac interoception task as well as reduced RSFC to the VMPFC. In addition, the task-evoked activity was correlated with 'psychic anxiety' and reduced RSFC was negatively correlated with 'somatic anxiety' (on the Hamilton Anxiety Rating Scale). Although more studies are needed, this result shows that interoception in AD may be related to abnormalities in the same regions affected in the resting state.

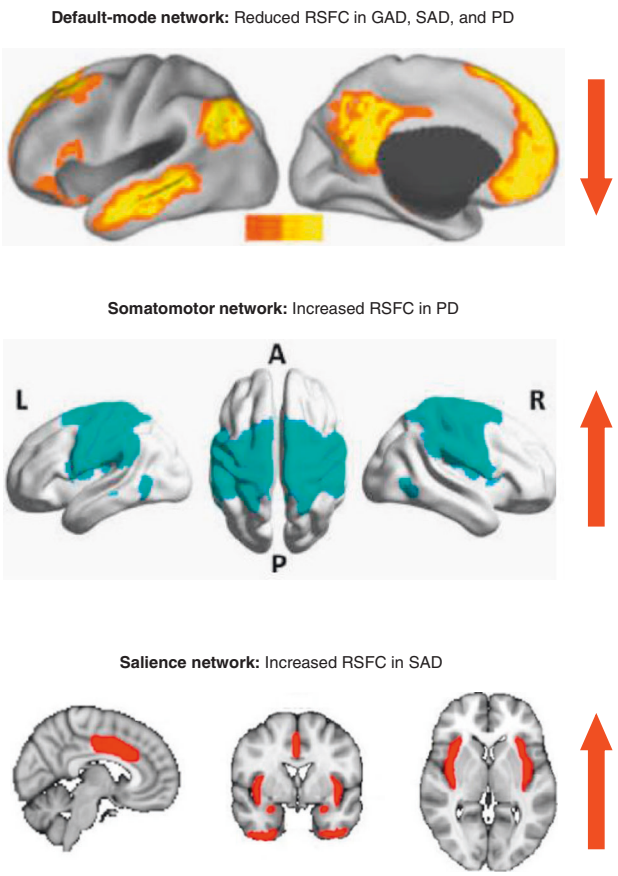


**Fig. 1 Altered resting state functional connectivity (RSFC) in different neural networks in anxiety disorders.** Systematic and meta-analytic reviews show that anxiety disorders are associated with reduced functional connectivity within and between the salience network, the somatomotor network, and the default mode network. However, a closer look shows disorder-specific network changes such as a higher RSFC in the salience network in social anxiety disorder and in the somatomotor network in panic disorder.

The SN and specifically the insula are implicated in AD by other task paradigms, such as emotion regulation, emotion recognition, and fear regulation [28–30, 61, 62] (GAD-specific studies [63–65], and SAD-specific studies [66, 67]). Abnormal activation in the amygdala is found in GAD, SAD, and PD whereas the medial prefrontal cortex and posterior insula changes are specifically associated with PD [27, 68].

Taken together, neural changes in AD can be localized to affective regions such as the amygdala, regions in the SN—particularly the insula, the anterior and posterior DMN regions, and regions in the primary somatosensory cortex. RSFC changes within these networks are mostly reduced, though disorder-specific increase in RSFC also occurs. Importantly, the neural correlates of interoception in healthy and anxious individuals also localize to these regions. However, it is not clear how abnormal interoceptive processing in AD is related to its network changes.

## Mechanisms of neuro-cardiac coupling in the healthy brain

### Regions showing neuro-cardiac coupling are part of the DMN, SN, and SMN

Regions in the DMN, SMN, and SN receive visceral inputs such as those from the heart, lungs, and gastric activity (see [69, 70] for recent reviews). Together, these regions are termed as the 'visceral/central autonomic network', which monitor the internal state of the body [71]. As described below, studies show that cardiac activity modulates neural activity in these regions through a phase-based mechanism [72].

In healthy subjects, HRV is correlated with variability in neural activity in the insula, amygdala, and anterior cingulate cortex [73–75]. The high-frequency component of HRV in particular is correlated with the variability of RSFC in the regions of the 'central autonomic network'—the VMPFC (and adjacent perigenual anterior cingulate cortex/PACC), somatosensory and somatomotor cortex, and subcortical regions (like periaquaeductal gray, thalamus, and lentiform nucleus) [74–77]. Considering that cardiac interoceptive tasks also evoke activity in the same regions [51–53, 78–81], these findings further suggest that cardiac and neural activity share a temporal inter-dependence in these regions.

In the context of AD, the overlap between regions involved in processing cardiac activity and neural activity in affected functional networks suggests that the ongoing integration of cardiac inputs in these regions may underlie the changes in RSFC (Fig. 2). Furthermore, the mechanism for neuro-cardiac synchronization in these regions may account for the abnormal interoceptive processing in these disorders.

### Temporal synchronization of heart and brain—heartbeat-evoked potential and intertrial coherence

Magnetoencephalography and intracranial electroencephalography studies show that cardiac activity modulates neural activity as well as functions ranging from perception to the sense-of-self (see [70, 82, 83] for reviews). These studies suggest that neural activity in these regions are phase-locked to cardiac inputs [72, 84]. Similar to a task stimulus, each heartbeat induces an event-related potential in the brain, termed as 'heartbeat-evoked potential' (HEP) [70, 85, 86]. The HEP is the increased amplitude of neural activity that is time-locked to the R-wave of cardiac activity.

Park et al. [72, 87–89] observed that the HEP induces a reset in the phase of ongoing neural activity resulting in the phase of ongoing neural fluctuations being locked to the timing of heartbeats. This phase-locking (between 4 and 7 Hz frequencies) can be measured by intertrial coherence (ITC), and is high after each HEP [72]. Moreover, higher values of ITC were associated with a higher HEP. The

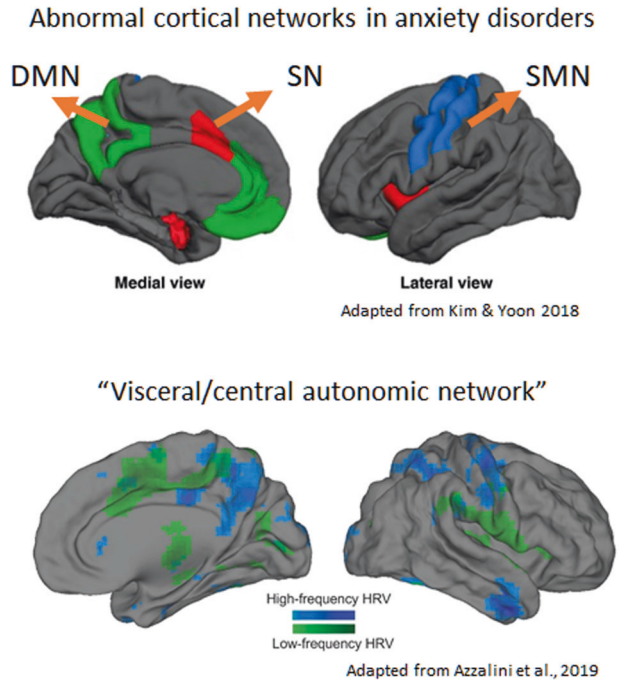


**Fig. 2 Overlap in regions processing cardiac activity and regions affected in anxiety disorders.** The regions underlying the functional networks altered in anxiety disorders show a significant overlap with regions that are associated with low and high-frequency heart rate variability. These regions are also suggested to receive viscerceptive inputs, and are proposed to form a visceral or central autonomic network. Regions in this network modulate lower and higher cognitive functions such as perception and sense of self.

authors therefore conclude that the amplitude of HEP can, at least partly, be linked to the phase of neural activity [72]. Both HEP and ITC can therefore be regarded as markers of neuro-cardiac synchronization

Neuro-cardiac phase coupling may also be related to RSFC, which is typically derived from fMRI data in the ~0.1 Hz frequency range. Using fMRI, Pfurtscheller et al. [90, 91] demonstrated that the vascular component of the BOLD signal could be separated from neural oscillations based on their timing, with the former preceding the latter. Moreover, in healthy subjects with high anxiety levels in the fMRI scanner, neuro-cardiac phase coupling in the insula and precentral gyrus as well as between the amygdala and medial prefrontal cortex was increased. These findings allow us to extend phase-resetting, a M/EEG measure of neuronal communication and information transfer [92, 93] to fMRI data for abnormal neuro-cardiac synchronization in AD.

More generally, neural activity comprises of continuous fluctuations and oscillations [94, 95]. The phase of this rhythmic activity shifts in response to external stimuli such as when listening to music—described as entrainment [96, 97] or alignment [98]. A similar response to continuous internal stimuli like heartbeats appear to entrain neural activity in regions supporting allostasis.

## Is neuro-cardiac phase synchronization related to functional connectivity?

The relation between neuro-cardiac synchronization and brain-wide functional networks is less clear. We suggest a theoretical-computational and biochemical basis relating visceral inputs such as from the heart to the brain's functional connectivity. The alignment between rhythmic neural and cardiac activity feeds information about the visceral state to the brain. As per active inference-based theories, top-down predictive models are matched with this bottom-up information. Visceral inputs ascend to the brainstem nuclei and are relayed forward to the thalamus and the cortex, where the posterior insula and primary somatosensory cortex are its primary targets. This information is fed to the anterior insula, which is regarded as a primary visceromotor cortex, i.e., the higher-level region generating predictions of the bodily state and modulating interoceptive inputs to match predicted states [14, 21, 55].

Changes in the bodily state increase the mismatch error leading to increased interoceptive awareness. This change is accompanied by activation of monoaminergic brainstem nuclei that receive this input—namely the serotonergic raphe nucleus and noradrenergic locus coeruleus, which in turn increase activity in the amygdala, insula, and orbitofrontal cortex (the so-called 'fear circuit'). Tracer studies show strong reciprocal connections between these regions—ascending inputs from brainstem nuclei are relayed to the thalamus and then to the posterior insula and primary somatosensory cortex. The posterior insula modulates connectivity of the anterior insula, which shows bi-directional connections to dorsal anterior cingulate cortex, orbitofrontal cortex, and the amygdala [55, 69]. Taken together, the visceral (including cardiac) input to the brain, and its prediction and modulation by both top-down processes and neurotransmitters provide a basis to explain how abnormal interoception may lead to altered functional networks.

## Neurotransmitter systems—targets of visceral inputs and opposite modulators of SMN/SN and DMN

Monoaminergic neurotransmitter systems originate in brainstem nuclei and are targets of visceral afferents, which ascend through the spinal cord to reach them (Fig. 3, see [55] for a detailed description of interoceptive pathways). Projections from these nuclei carry the afferents forward to the thalamus and then to primary viscerceptive cortical regions. These structures include the serotonergic raphe nucleus and the noradrenergic locus coeruleus, which are implicated in AD

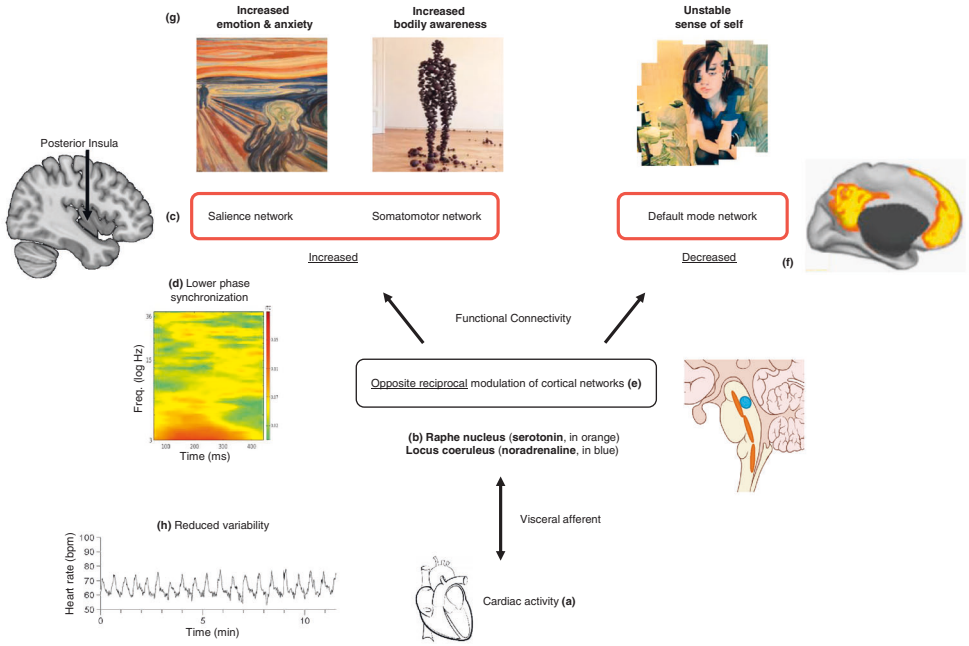


**Fig. 3 Neuro-cardiac desynchronization, functional networks, and symptoms of anxiety disorders.** Cardiac afferents (**a**) first reach the serotonergic raphe nucleus and noradrenergic locus coeruleus (**b**), and are then relayed onwards to the primary visceral cortex (posterior insula and primary somatosensory cortex) (**c**), which are abnormal in anxiety disorders. We suggest that synchronization between the cardiac and neural regions is abnormal in these disorders and can be measured by lower intertrial coherence (ITC) (**d**), and heartbeat-evoked potential. This desynchronization alters serotonergic and noradrenergic activity and leads to opposite reciprocal modulation of cortical networks (**e**) with increased RSFC in the salience network and in the somatomotor network whereas RSFC decreases in the DMN (**f**). These network changes manifest as heightened emotions and anxiety, increased bodily awareness, and an unstable sense-of-self (**g**). Notably, anxiety disorders are also associated with lower cardiac variability (**h**) potentially indicating visceromotor modulation.

[99]. These nuclei modulate functional networks and may help explain the network changes seen in AD.

Conio et al. [100] demonstrate that the serotonergic raphe nucleus modulate SMN/SN and DMN connectivity in an opposite reciprocal manner. They suggest that increased serotonergic signaling is associated with decreased SMN activity and increased DMN activity. Although the locus coeruleus was not directly associated with cortical network modulation by Conio et al., it is worth noting that it receives visceral afferents, is activated by stress and in AD, and increases connectivity in multiple networks including the SN, SMN, and amygdala [101–103]. Together, the findings show opposite modulation of cortical SMN/SN and DMN by subcortical serotoninergic raphe nucleus with potential involvement of noradrenergic locus coeruleus. This is consistent with AD where opposite changes in these networks as well as abnormalities in serotonergic and noradrenergic systems occur.

## Brain-heart synchronization shapes mental functions—emotion, bodily awareness, and the mental self

The aforementioned studies show that phase-resetting of neural activity may underlie neuro-cardiac coupling. Moreover, this process shapes mental features such as visual perception [87, 89], emotion, bodily awareness [72], and sense-of-self [88, 104, 105]. The degree of neuro-cardiac synchronization in the visual cortex and insula was associated with visual perception [87, 89]. Similarly, the amplitude of HEP in the insula and the somatosensory cortex were related to bodily awareness [88]. Higher-order functions such as subjects' experience of their self as either "I" ('subjective self' referring to thoughts with the self as the agent) or "me" ('objective self' referring to thoughts about themselves) was related to the amplitude of the HEP specifically in the VMPFC ('Me'), and in the PCC and right anterior insula ('I') [88, 105].

The DMN is known to be involved in our sense-of-self [106–108], the SMN is related to bodily awareness [109], and the SN is central to mediating the sense-of-self [110, 111] and emotions [112]. Given the findings by Tallon-Baudry et al., neuro-cardiac synchronization can be said to modulate mental features like emotions, bodily awareness, and sense-of-self (see [83] who make this point; also see [69, 113]). In the context of interoceptive deficits in AD, reduced neuro-cardiac synchronization may reduce the efficacy of functions localized to these regions/networks.

## Brain-heart desynchronization and abnormal cortical networks in AD

It was recently suggested that neuro-cardiac synchronization underlies the RSFC changes and symptoms of AD [114]. Here, we expand this proposal by describing the process that may underlie the observed dysfunctions in each network.

### Reduced heart rate variability in anxiety disorders

HRV, a marker of health [115, 116], is consistently reduced in AD [2]. HRV is also reduced in major depressive disorder, where anxiety is common [117]. It is measured either by the root mean square of the successive differences (RMSSD) or by high (HF) and low frequency (LF) variability. Studies in GAD, PD, and SAD show lower RMSSD and HF HRV (medium effect size) but normal LF HRV, which suggests a stronger parasympathetic input to the heart [2].

Reduced HRV in AD contributed to an influential model of neurovisceral integration [71, 118, 119], which describes how cardiac and other visceral activity is regulated across the neural hierarchy. In this model, the relation between cardiac (visceral) activity, and emotional and cognitive functions is explained using concepts from dynamical systems theory and predictive coding. Deviations (or predictive errors) in cognitive or sensory inputs are proposed to reduce cortical inhibitory input (parasympathetic/vagal tone) to the heart, leading to reduced HRV.

### Serotonergic and noradrenergic systems—opposite reciprocal modulators of abnormal functional networks in AD

The monoaminergic transmitters play a key role in the understanding and treating AD through their innervation of the so-called "fear circuit" (amygdala, insula, and orbitofrontal cortex) [99]. They may also explain how cardiac inputs from the periphery affect cortical networks. As described above, the serotonergic raphe nuclei and noradrenergic locus coeruleus receive cardiac inputs, and relay it forward to the thalamus and then to the primary visceral cortex (Fig. 3). In AD, lower serotonergic activity is consistently reported [99] (though this has been questioned recently [120, 121]). This lower serotonergic activity, as per Conio et al. [100], suggests increased SMN RSFC and lower DMN RSFC. Similarly, increased noradrenergic activity suggests increased SN RSFC and decreased DMN RSFC. These predictions are consistent with the observed network abnormalities in AD. Thus, taken together, abnormal neuro-cardiac synchronization in the subcortical targets of cardiac afferents is suggested to trigger altered activity (decrease in the serotonergic system, and increase in the noradrenergic system), which leads to an imbalance between the SMN or SN and the DMN (Fig. 3).

### Abnormal neuro-cardiac synchronization affects emotional processing and interoceptive awareness

Symptoms of AD are congruent with the functions attributed to the affected networks. Increased emotional sensitivity, bodily awareness, and unstable sense-of-self can be attributed to the SN, SMN, and DMN, respectively [114] (Fig. 3). Hence, symptoms and RSFC in AD can be linked to neuro-cardiac synchronization in these regions. Indeed, features of AD such as fear processing and interoception are linked to cardiac function [84, 122]. Garfinkel et al. found that fear processing was more sensitive and intense when the cardiac cycle was in systole (corresponding to the HEP), showing that neuro-cardiac coupling alters emotional processing. Pollatos et al. showed that time perception was positively correlated to phase-locking with cardiac activity and interoceptive sensitivity [84]. These studies suggest that ITC/HEP may be related to emotional and interoceptive sensitivity in AD.

Notably, subjective (sensibility) and objective (sensitivity/accuracy) interoceptive processing may not be correlated in AD. Subjects with autism, who also have anxiety, were found to perceive bodily signals more strongly (higher sensibility) but were worse in interoceptive accuracy (objective measures). The discrepancy between their subjective sense of accuracy (confidence) and the difference between objective and subjective measures of interoception predicted their anxiety symptoms [79, 123].

A few studies have recently investigated neuro-cardiac synchronization with HEP/ITC in AD. In GAD subjects, HEP was abnormally high in the eyes-open condition, but the change in HEP from eyes-open to eyes-closed condition was lower than in controls [124]. Moreover, HEP in the prefrontal cortex was correlated to anxiety symptoms. In another study, false cues of increased heart rate induced larger HEP in healthy subjects with high social anxiety [125]. These studies provide the first evidence for neuro-cardiac mechanisms in AD. Further studies are needed to spatially localize these changes and relate ITC to symptoms.

Finally, we suggest that inter-individual variations in neuro-cardiac synchronization may explain the propensity for anxiety and AD in some individuals. This suggestion is consistent with the view that visceral inputs shape cognitive functions [17, 69]; rather than driven by external inputs, internal (visceral) inputs predispose neural responses to external stimuli. A mis-alignment between the brain and the body may predispose individuals to anxiety.

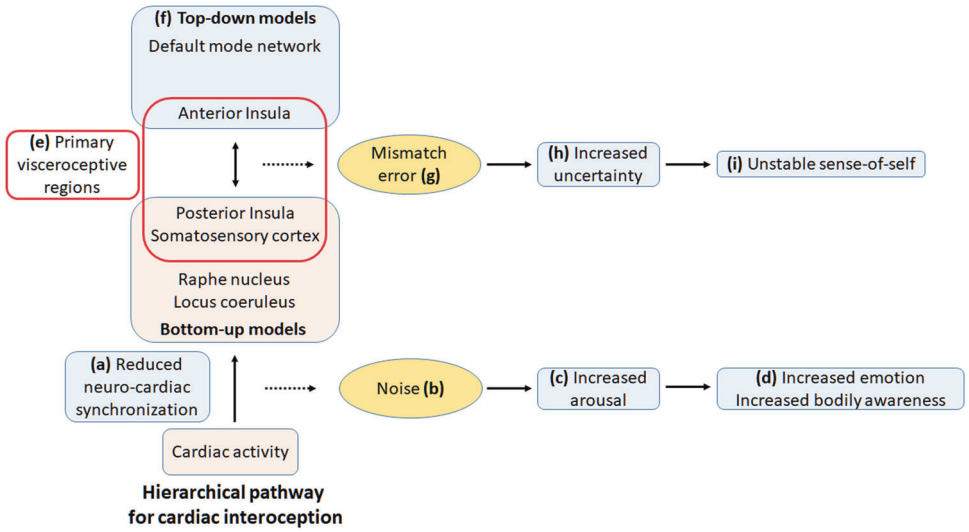


**Fig. 4 Abnormal neuro-cardiac synchronization in an interoceptive predictive coding framework.** Neuro-cardiac synchronization provides a mechanism for the interoceptive predictive processing framework and neurovisceral intergration model. Lower phase synchronization (**a**) leads to bottom-up models being perceived as 'noisy' (**b**) leading to increased arousal (**c**), which manifests in increased emotion and somatic symptoms (**d**). The noisy bottom-up models in the primary viscero-ceptive regions (**e**) do not match predictive models generated in the higher-order cortical regions (**f**), generating persistent somatic errors (**g**) that lead to increased uncertainty (**h**) and at the mental level, to an unstable sense-of-self and worry (**i**).

## Predictive interoceptive processing—noise, desynchronization of functional networks, and symptoms of AD

The insula, along with the somatosensory cortex, is considered to be the primary viscero-ceptive cortical region. We suggest that an abnormal synchronization in the posterior insula may result in a higher degree of neuronal 'noise' (Fig. 4). That is, a lower degree of synchronization reduces certainty about information regarding the bodily state, thereby leading to a mismatch between higher and lower-level models in the neural computational hierarchy. The Embodied Predictive Interoception Coding hypothesis suggests that higher-level predictions are represented in the anterior insula [14]. A mismatch between higher and lower-level models are suggested to trigger corrective viscero-motor signals from the anterior insula to the posterior insula to either correct the mismatch or to adapt signal sampling so that subsequent errors are minimized (Fig. 4).

The neuronal noise may also result in non-neuronal or perceptual noise (Fig. 4). Noisy afferent inputs may reduce certainty of the bodily state in higher-level models. This uncertainty may result in a persistent somatic error and hence, a strong belief of an abnormal bodily state (hyper-precise prior). The persistent error would also lead to context rigidity (i.e., inability to change beliefs despite changing contexts) as bottom-up information would continue to remain noisy in varying contexts, preventing updating of top-down models. Consistent with this suggestion, anxiety symptoms in autism are correlated with higher subjective interoceptive sensibility (own belief that they are accurate) despite lower objective accuracy [123]. The mismatch error triggered corrective signals may reflect functional connectivity, which would be consistent with the increased RSFC in AD in the SN and SMN—networks containing the primary visceral cortex. The uncertainty in top-down models could be related to the decreased RSFC in the DMN, which does not receive direct viscero-ceptive inputs.

Finally, the isolated decrease in DMN RSFC raises the possibility that the degree of neuro-cardiac desynchronization influences the manifested symptoms. A small error may increase neural and psychological uncertainty but not trigger strong top-down corrective signaling. This would manifest as lower RSFC in the DMN without changes in the SN or SMN, and correspondingly lead to persistent anxiety but without overwhelming somatic symptoms, which is characteristic of GAD. Abnormal DMN connectivity across the disorders also indicates a basic deficit in self-related processing [126]. As discussed above, cardiac inputs affect all levels of the neural hierarchy from perception to the meta-cognitive objective self. That is, visceral inputs are part of automatic self-related processing and hence, deficits in this processing would lead to increased self-specificity or self-prioritization. This persistent deficit may contribute to a 'fearful self' that continuously anticipates threats [127].

Together, the abnormal neuro-cardiac phase synchronization in the primary viscero-ceptive regions leads to neuronal and perceptual noise or uncertainty of the bodily state. Higher-order regions trigger corrective visceromotor

signaling to reduce this noise. The desynchronization and top-down signaling may lead to activation of subcortical and cortical regions reflected in increased functional connectivity in the SMN/SN and corresponding decrease in the DMN. This in turn, may manifest in the particular symptom constellation of AD with changes in body awareness, emotion, and sense-of-self.

## Conclusion

In summary, we identified abnormal phase-resetting, which can be experimentally measured by ITC and HEP, as a mechanism for neuro-cardiac desynchronization in AD. This neuro-cardiac desynchronization underlies changes in serotonergic and noradrenergic neurotransmission that lead to opposite modulation of cortical networks like SMN/SN and DMN and the typical AD symptom constellation with increases in bodily awareness and anxiety accompanied by an unstable sense-of-self. We also integrate neuro-cardiac desynchronization in interoceptive predictive processing models as a source of noise and mismatch between bottom-up and top-down models, leading to somatic errors and further to the particular symptom constellation of AD. Together, we propose neuro-cardiac desynchronization as a primarily spatiotemporal basis for the particular symptom constellation of AD, in line with "Spatiotemporal Psychopathology" [6, 7].

Our suggestions also raise further questions. These include—(1) is HRV related to neural variability in visceral regions of the brain? (2) Are these region-specific correlations related to specific symptoms? (3) Subcortical regions also receive visceral inputs [69, 71] and are affected in AD [3]. Are ITC/HEP in these regions abnormal in these disorders, and if so, what is their relation to the implicated cortical regions. (4) We did not consider other visceral inputs—respiration and gastric rhythm, which also affect interoception [128, 129] due to a paucity of studies in AD. The phase coupling of respiratory and gastric activity to neural activity in AD would be of interest as these subjects often show abnormal perception of respiratory and/or gastric activity. (5) Do other oscillatory measures, such as phase amplitude coupling [97] or those from dynamical systems [71] provide additional insight into these disorders? Finally, (6) can interventions be targeted towards serotonergic- and/or noradrenergic-driven neuro-cardiac desynchronization to yield novel therapies for these disorders?

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.



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