

Functional network dysfunction in anxiety and anxiety disorders

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A recent paradigm shift in systems neuroscience is the division of the human brain into functional networks. Functional networks are collections of brain regions with strongly correlated activity both at rest and during cognitive tasks, and each network is believed to implement a different aspect of cognition. We propose here that anxiety disorders and high trait anxiety are associated with a particular pattern of functional network dysfunction: increased functioning of the cingulo-opercular and ventral attention networks as well as decreased functioning of the fronto-parietal and default mode networks. This functional network model can be used to differentiate the pathology of anxiety disorders from other psychiatric illnesses such as major depression and provides targets for novel treatment strategies.

Introduction

A major development in systems neuroscience has been the grouping of human brain regions into functional networks. Functional networks are collections of brain regions with activity that tends to increase or decrease in concert, both at rest and during cognitive tasks. Because different cognitive tasks elicit increases in activity in different functional networks, each network is believed to implement unique aspects of cognition. Many studies define functional networks based on correlations in very low frequency (<0.1 Hz) brain activity as measured by functional magnetic resonance imaging (fMRI) in subjects at rest. Although networks are typically defined by functional connectivity (i.e., activity correlations) at rest, regions within a particular network almost always demonstrate synchronous activity during cognitive tasks; one possibility is that functional connectivity at rest reflects a history of correlated activity changes during goal-directed behavior [1]. Comparisons of known anatomical connections and functional connectivity in macaques suggest close (but not perfect) correspondence of these measures [2,3]. Functional networks in humans include, but are not limited to, the cingulo-opercular, fronto-parietal, dorsal attention, ventral attention, default mode, sensorimotor, visual, and auditory networks (Figure 1) [4,5].

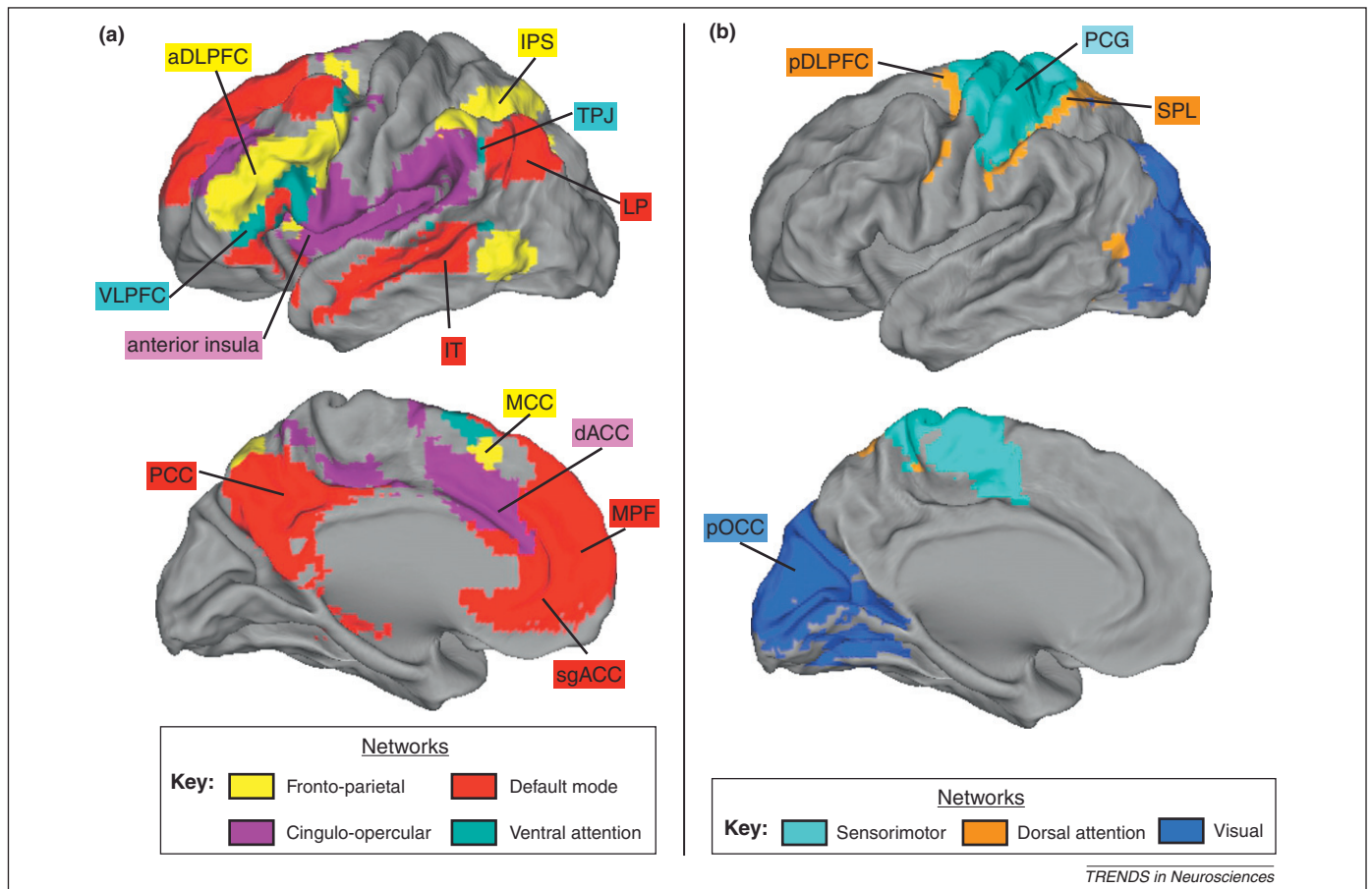
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The organization of brain regions into functional networks may revolutionize our understanding of psychiatric disorders from current symptom-focused classification to network-based schemes. Functional networks can be viewed as dimensions in which the operation of each network ranges from underactive to normal to overactive. Different blends of disturbances along these dimensions could result in different psychiatric disorders, with the phenomenology of the disorder reflecting changes in the cognitive functions performed by the aberrant networks. Although a simplification of functional network operation, this framework allows the development of testable models to capture psychiatric disorders and also provides targets for novel treatments (Figure 2).

Although a functional network model is likely to be robust for understanding and guiding treatment development for many psychiatric disorders, in this Opinion we review the literature and hypothesize a particular pattern of network-level pathology associated with anxiety and anxiety disorders. We propose that anxiety and anxiety disorders are associated with increased or overactive functioning of the cingulo-opercular and ventral attention networks as well as decreased or underactive functioning of the fronto-parietal and default mode networks.

The cingulo-opercular network includes portions of the dorsal anterior cingulate cortex and insula and may be important for detecting the need for changes in cognitive control. Increased functioning of this network may result in a maladaptively low threshold to alter cognitive control. The fronto-parietal network encompasses parts of the dorsolateral prefrontal cortex (PFC) and inferior parietal cortex, and may be responsible for implementing increased cognitive control. Decreased functioning of the fronto-parietal network may result in deficits in implementing cognitive control. The ventral attention network includes parts of the ventrolateral PFC and the temporal-parietal junction and is involved in directing attention to newly appearing stimuli. Increased functioning of the ventral attention network may be linked to increased attention to stimuli that suddenly appear rather than towards stimuli that are currently the focus of the task at hand. Finally, the default mode network includes portions of the subgenual anterior cingulate cortex, medial temporal lobe, and precuneus. The default mode



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Figure 1. The human brain can be divided into functional networks. Seven of these networks are illustrated here, including: (a) the four networks discussed in the main text (cingulo-opercular, ventral attention, fronto-parietal, and default mode), and (b) three other commonly described networks (visual, dorsal attention and sensorimotor). Each functional network is believed to implement unique aspects of cognition. This figure is modified, with permission, from a study of the functional network organization of the human brain [5]. Briefly, the investigators measured very low frequency brain activity (<0.08 Hz) using functional magnetic resonance imaging (fMRI) in healthy subjects lying quietly at rest. Correlations in this low-frequency brain activity were calculated between all voxel pairs (a voxel is the smallest unit of fMRI data, equivalent to a 3D pixel) and each voxel was subsequently categorized into a particular network using graph theory techniques. For visualization purposes, each voxel was color-coded based on network identity and the data were projected onto the cortical surface using CARET software [95] and the population-average, landmark- and surface-based (PALS) atlas [96]. Abbreviations: PFC, prefrontal cortex; aDLPFC, anterior dorsolateral PFC; dACC, dorsal anterior cingulate cortex; IPS, intraparietal sulcus; IT, inferior temporal cortex; LP, lateral parietal cortex; MCC, middle cingulate cortex; PCC, posterior cingulate cortex; PCG, pre/post central gyrus; pDLPFC, posterior dorsolateral PFC; pOCC, posterior occipital cortex; sgACC, subgenual anterior cingulate cortex; SPL, superior parietal lobule; STG, superior temporal gyrus; TPJ, temporal-parietal junction; VLPFC, ventrolateral PFC.

network is hypothesized to implement functions such as emotion regulation, future planning, and self-inspection. Decreased functioning of the default mode network may manifest as difficulty in adaptively regulating emotions based on current goals. Note that decreased (or increased) functioning does not always imply decreased (or increased) activity; functioning of a network is determined by the relation between activity in a network and behavior (i.e., task performance), an important point that is illustrated in detail below.

The vast majority of models and reviews of anxiety and anxiety disorders highlight atypical responses to threatening or fearful stimuli [6–8]. By contrast, we describe a set of changes in generic functional networks that are not related to fear responses *per se* (also [9–11]). This Opinion focuses primarily on studies that use neutral, non-threatening stimuli to probe general network functioning. We explicitly highlight studies that focus on non-emotionally valenced tasks to demonstrate that anxiety disorders include pathology in functional networks involved in cognition (and motivation) in addition to the emotional brain systems typically described. The framework we describe complements fear-response models of anxiety and anxiety

disorders by providing a description of cognitive functions and brain networks that modulate fear responses. Treatments developed to target these more general behaviors and networks may normalize atypical behavioral and neural fear responses classically associated with anxiety and its disorders.

In this Opinion we review four types of data that support our hypothesis for a particular pattern of network-level changes in anxiety and anxiety disorders: (i) changes in behaviors that are believed to rely on particular networks, (ii) changes in brain activity within a network during specific cognitive tasks, (iii) changes in functional connectivity among the brain regions within a particular network, and (iv) changes in functional connectivity between brain regions of different networks. Our hypotheses are generated on the basis of the first two types of data. We review functional connectivity changes (i.e., the latter two categories of data) only to provide supporting evidence. The relation between brain activity during cognitive tasks and functional connectivity changes at rest, in which a subject lies quietly with no overt task, is an area of active investigation. One study reported that repeated practice of a cognitive task is associated with functional connectivity

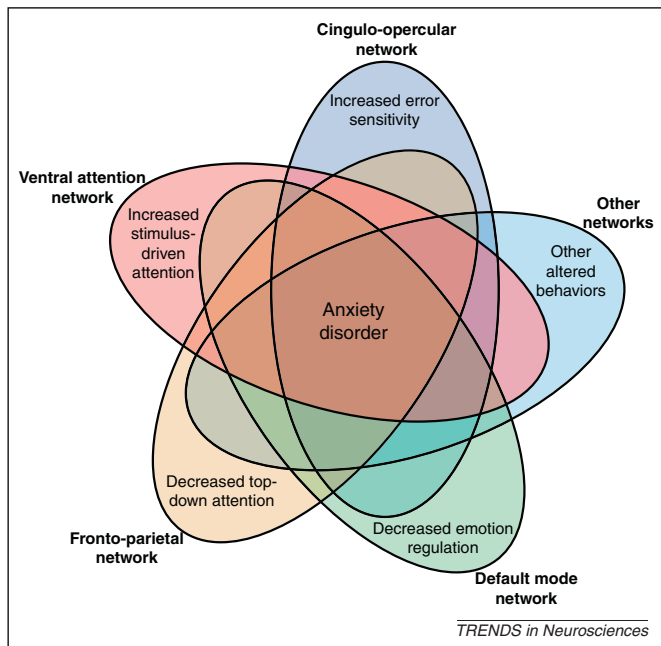


Figure 2. Anxiety disorders may be characterized by a particular pattern of network-level pathology. This Venn diagram highlights changes in behaviors associated with individual networks; anxiety disorders may arise as an interaction between these behaviors. A full description of network-level pathology includes changes in behaviors, task-dependent activity, between-network functional connectivity, and within-network functional connectivity changes associated with each network. Although individuals with all of the network-level changes illustrated above may have the highest probability of developing an anxiety disorder, individuals with most – but not all – of these problematic behaviors may also be at elevated risk. One possibility is that a single network-level alteration triggers a chain of events involving network interactions that eventually results in the full constellation of pathology associated with anxiety disorders. The pathological network-level changes diagrammed above are not intended to be exhaustive. Moreover, there is likely to be heterogeneity even within an individual disorder. Highly comorbid illnesses such as major depression may arise because of a similar but unique pattern of network-level pathology that is not mutually exclusive with the pattern that characterizes anxiety disorders. Background Venn diagram downloaded from http://en.wikipedia.org/wiki/File:Symmetrical_5-set_Venn_diagram.png on June 11, 2011.

changes at rest [1], suggesting that some of the functional connectivity changes measured at rest are related to correlated activity increases during goal-directed behavior. Other factors potentially influencing brain activity at rest include ongoing cognitive processes.

Throughout our discussions we focus on changes in functional networks common to individuals with different anxiety disorders as well as individuals with high trait anxiety. Trait anxiety is often used as an analog for either the presence of, or vulnerability for, an anxiety disorder. This practice is supported by theoretical models and empirical work suggesting that all recognized anxiety disorders share the common factor of high trait anxiety (or the nearly equivalent construct of negative affectivity or neuroticism) [12–14]. Notably, other factors associated with a subset of anxiety disorders, such as autonomic reactivity, fail as analogs for all anxiety disorders because of their observed variation across the disorders [12]. It is likely that important differences exist, at a functional network level, both among different types of anxiety disorders, and between anxiety disorders and high trait anxiety. In the current article, however, we place an emphasis on findings that are consistent across individuals with high trait anxiety as well as those with specific anxiety disorders.

The cingulo-opercular network

The cingulo-opercular network [15] includes portions of the bilateral dorsal anterior cingulate cortex (dACC), anterior insula, anterior PFC, and anterior thalamus (Figure 1; Table 1). This set of regions is sometimes referred to as the salience [16] network and includes regions initially described by Carter, Cohen, and others as being important for detecting errors or conflict (a mismatch between a prepotent response and a correct response) to signal the need for increased cognitive control [17,18]. One hypothesis is that conflict signals generated in the cingulo-opercular network are relayed to the fronto-parietal network that implements increased cognitive control on future trials. Regions in the cingulo-opercular network, especially the dACC, have also been ascribed other functions including processing negative affect, pain, and cognitive control [19].

Several studies demonstrate increased sensitivity to errors or response conflict in tasks involving neutral, non-emotional stimuli in individuals with high anxiety or an anxiety disorder, consistent with increased functioning of the cingulo-opercular network. Error-related negativity is an electroencephalographic (EEG) measure of brain activity that is present in healthy individuals following errors on cognitive tasks. The magnitude of this measure is increased in individuals with generalized anxiety disorder [20], obsessive-compulsive disorder (OCD) [21], and in healthy individuals with high measures of anxiety [22,23] in paradigms that use generic, non-threatening stimuli such as arrows or letters. Subjects with high trait anxiety may make more errors on trials with response conflict relative to healthy controls in tasks that use non-emotional stimuli [24], and individuals with panic disorder have an inappropriately low threshold to change task strategy when the error rate is low, relative to healthy controls [25].

Studies of brain activity during cognitive tasks also support the hypothesis of increased functioning of the cingulo-opercular network in individuals with anxiety and anxiety disorders. The magnitude of the error-related negativity described above, and that is increased in patients with anxiety and anxiety disorders, probably localizes to the dACC, one of the main regions in the cingulo-opercular network [22,26]. fMRI studies of patients with post-traumatic stress disorder indicate increased activity in the dACC or insula during response conflict [27] or while viewing non-emotional salient stimuli [28], relative to control subjects. Although not the focus of this Opinion, there is also a wealth of evidence supporting a similar disruption during the processing of emotionally laden stimuli [6,29–33].

Functional connectivity studies additionally support the hypothesis that the cingulo-opercular network is disrupted in individuals with anxiety and its disorders. Individuals with high trait anxiety demonstrate decreased functional connectivity between regions of the cingulo-opercular network (dACC) and the frontoparietal network (DLPFC) [24], and this could be interpreted as inefficient transmission between the cingulo-opercular network that detects conflict and the fronto-parietal network that implements increased cognitive control to resolve conflict on future trials. There is decreased functional connectivity between regions of the cingulo-opercular network and the amygdala in

Table 1. The cingulo-opercular, fronto-parietal, ventral attention, and default mode networks are altered in anxiety disorders

Functional network	Key brain regions ^a	Supported cognitive function ^b	Suggested task to correct network pathology ^c
Cingulo-opercular	Anterior insula Dorsal anterior cingulate Anterior PFC	Error monitoring	Graded exposure to errors
Fronto-parietal	Dorsolateral PFC Inferior parietal lobe	Top-down attentional control	Top-down attentional control
Ventral attention	Ventrolateral prefrontal Temporal–parietal Junction	Stimulus-driven attention	Irrelevant stimulus-driven cues
Default mode	Subgenual anterior cingulate Lateral parietal cortex Parahippocampal gyrus Precuneus	Emotion regulation	Emotion regulation

^aOnly a subset of brain regions in each network are listed. See text and Figure 1 for further details.

^bEach network performs many related cognitive functions. The cognitive functions listed are those that are dysfunctional in anxiety disorders.

^cThese tasks are described in detail in Figure 3.

patients at rest with generalized anxiety disorder relative to controls [34]. Finally, some studies have revealed altered within-network functional connectivity in the cingulo-opercular network in patients with social anxiety disorder at rest [35] and with OCD during a task involving cognitive control [36].

The fronto-parietal network

The fronto-parietal network [15] includes bilateral anterior portions of the dorsolateral PFC (DLPFC), the inferior parietal lobule, portions of the middle cingulate gyrus, and portions of the precuneus (Figure 1; Table 1). Regions in this network are sometimes referred to as the executive control [16] network. Whereas the cingulo-opercular network is thought to detect errors in behavior, thereby signaling the possible need for strategy adjustment, the fronto-parietal network may incorporate this feedback to make adjustments in processing on later trials [15].

Although the changes in behaviors and brain activity associated with the fronto-parietal network in anxiety and anxiety disorders are not generally agreed upon, an emerging literature suggests decreased functioning of this network. Studies have demonstrated that individuals with high trait anxiety [9,24,37] or post-traumatic stress symptomatology [29] have impaired executive control in tasks that use neutral, non-emotional stimuli, consistent with decreased functioning of the fronto-parietal network (but see [38]). Individuals with high trait anxiety [39] or the similar construct of negative affectivity [40] who also have poor cognitive control are especially prone to distraction by emotional stimuli. Individuals with high state anxiety do not show typical suppression of amygdala response to threatening pictures when attentional focus is engaged elsewhere [41].

Although results are mixed, several fMRI studies support the hypothesis of decreased functioning of the fronto-parietal network in individuals with high trait anxiety in tasks that use exclusively non-emotional stimuli. Several fMRI studies of individuals with high trait anxiety demonstrate decreased activity in regions of the fronto-parietal network during the processing of neutral targets involving some degree of response conflict [9,29,42]. One study reported that individuals with high trait anxiety required higher levels of DLPFC activity to achieve the same degree of cognitive control, consistent with decreased functioning

of this region within the fronto-parietal network [24]. The pattern of results from this study highlights the crucial point that decreased functioning does not always equate to decreased activity; activity in a particular network must be examined in relation to behavior to determine whether the network has increased or decreased functioning.

Individuals with high anxiety or an anxiety disorder also have functional connectivity changes associated with the fronto-parietal network. As previously noted, patients with high trait anxiety demonstrate decreased functional connectivity between regions of the cingulo-opercular and fronto-parietal networks in a Stroop task using neutral stimuli [24]. Another study reported increased functional connectivity between regions of the fronto-parietal network and the amygdala in patients with generalized anxiety disorder at rest [34]. Finally, there are within-network functional connectivity changes at rest in patients with social anxiety disorder relative to healthy controls [35].

The studies reviewed above primarily support decreased functioning of the fronto-parietal network in individuals with high trait anxiety or an anxiety disorder in tasks that use neutral stimuli. Interestingly, some studies report increased activity in portions of the fronto-parietal network in individuals with high anxiety or an anxiety disorder in tasks that use emotionally laden stimuli [29,34,43,44]. One possibility is that individuals with problematic anxiety require additional executive control from the fronto-parietal network to regulate emotions in the presence of emotionally laden stimuli compared to healthy controls [44]. These results highlight the importance of differentiating the function of networks in the presence versus absence of emotionally valenced stimuli.

The ventral attention network

The ventral attention network is largely right-lateralized and includes the ventrolateral PFC (VLPFC), the temporal–parietal junction (TPJ), and portions of the middle and superior temporal gyri (Figure 1; Table 1) [45,46]. Along with the dorsal attention network, the ventral attention network is associated with the orientation of stimulus-driven attention – the automatic orienting to a particular location when a stimulus appears at that location [47]. This section focuses on the ventral, but not the dorsal, attention network because there are no known studies that specifically test whether activity in the dorsal attention

network is implicated in increased stimulus-driven attention in patients with anxiety disorders.

Patients with anxiety disorders may have increased stimulus-driven attention, consistent with an overactive ventral attention network. Subjects with high state anxiety [37], high social anxiety [48], or high trait anxiety (trend-level finding) [49] demonstrate increased behavioral measures of stimulus-driven attention to non-emotional stimuli. The already increased functioning of stimulus-driven attention in patients with high trait anxiety is exaggerated for emotionally laden stimuli [49].

Preliminary evidence is consistent with the hypothesis of increased activity in the ventral attention network during stimulus-driven attention in individuals with anxiety and anxiety disorders. Increased activity in the VLPFC to the onset of non-emotional stimuli has been reported in patients with social phobia [50] and in adolescents with high trait anxiety [43]. In the study of social phobia, the magnitude of VLPFC activity correlated positively with measures of anxiety during a difficult task [50]. The P200 response is a positive event-related potential (ERP) that appears 200 ms following stimulus onset and may be a marker of attention shifts including stimulus-driven shifts; the magnitude of this measure is increased in individuals with high trait anxiety [51,52] or high anxious arousal [53] when they view non-emotional stimuli or a combination of emotional and non-emotional stimuli. Individuals with high anxiety may show a similar increase in activity in the ventral attention network for emotionally laden stimuli as they do for neutral stimuli [33,52,54,55], although this activity has been hypothesized to represent a compensatory response because it was shown to correlate negatively with measures of anxiety in individuals with generalized anxiety disorder [54].

Functional connectivity studies are consistent with an alteration of the ventral attention network in patients with anxiety disorders. There is increased positive functional connectivity between the VLPFC and the amygdala in adolescents with an anxiety disorder during tasks involving both threatening and non-threatening stimuli [56,57]. Increased positive functional connectivity between the ventral attention network and the amygdala could explain, in part, why individuals with high anxiety demonstrate increased anxiety to stimuli that appear suddenly.

The default mode network

The default mode network includes portions of the subgenual anterior cingulate cortex (sgACC), posterior cingulate cortex, the precuneus, lateral parietal cortex, medial PFC, inferior temporal gyrus, parahippocampal gyrus, and the frontal pole/superior frontal cortex (Figure 1; Table 1) [58,59]. Regions in the default mode network demonstrate high rates of metabolism in healthy subjects at rest [59] and decreases in activity across a range of cognitive tasks [58]. Because of this pattern of activity, the default mode network is hypothesized to perform functions such as self-referential activities, future planning, self-inspection, and emotion regulation, the role of which diminishes during traditional cognitive tasks [59].

Key regions of the default mode network, especially the sgACC, seem to be crucial for several emotion regulation strategies including extinction [60] and cognitive regulation

[61]. Extinction refers to diminished fear following repeated presentation of a conditioned stimulus, whereas cognitive regulation refers to explicit mental strategies used to diminish a fear response (such as reappraisal in which an individual consciously reinterprets a threatening stimulus as non-threatening) [62]. The default mode network probably interacts with other brain networks to perform emotion regulation; cognitive regulation of emotion, for example, may rely on an interaction between the default mode network and the fronto-parietal network [61,63].

When not given explicit instructions on how to regulate their emotions, patients with anxiety disorders do not modulate their emotions as well as healthy individuals [64–68], consistent with decreased functioning of the default mode network. Interestingly, however, some studies report that patients with social anxiety disorder can show the same degree of reduction in negative emotion when given explicit instructions on how to regulate their emotions [44,69].

Numerous studies of brain activity report decreased functioning of the default mode network in patients with anxiety disorders under circumstances in which healthy individuals regulate emotion without instruction. Healthy individuals exhibit higher activity across the default mode network as anticipatory anxiety increases [70]. Studies of individuals with high trait anxiety [30,38,71] generalized anxiety disorder [32], panic disorder [72], post-traumatic stress disorder [73], or social anxiety disorder [74], however, report decreased activity in the sgACC in tasks involving emotional stimuli during which healthy subjects would regulate their emotional response without instruction. A similar pattern of results has been demonstrated in other regions of the default mode network in individuals with social anxiety disorder [75] or other anxiety disorders [76]. Of note, however, some studies have reported the opposite pattern in the sgACC [33,77,78] and in other regions of the default mode network [79]. One study reported that individuals with high trait anxiety required higher levels of sgACC activity to achieve the same level of emotion regulation as individuals with low trait anxiety, consistent with impaired functioning of the default mode network during emotion regulation [80].

Functional connectivity studies are also consistent with dysfunction of the default mode network in individuals with high anxiety. At rest, there is decreased functional connectivity between portions of the default mode network and the amygdala in patients with social anxiety disorder [81] and in individuals with high state anxiety [82]. During the processing of emotional stimuli, there have been reports of diminished negative functional connectivity [32] and diminished positive functional connectivity [83] between the sgACC of the default mode network and the amygdala in individuals with high anxiety or an anxiety disorder. Other studies report altered functional connectivity within the default mode network at rest in individuals with social anxiety disorder [81] and in patients with anxious relative to non-anxious late-life depression [84].

Concluding remarks

In this Opinion we propose that anxiety and anxiety disorders are associated with a particular pattern of network-level dysfunction, including increased functioning of the

cingulo-opercular and ventral attention networks as well as decreased functioning of the fronto-parietal and default mode networks. Individuals with high trait anxiety or an anxiety disorder demonstrate alterations in behavior, task-dependent activity, between-network functional connectivity, and within-network functional connectivity associated with each of these four networks; the end result is dysfunction in the components of cognition implemented by each network.

The network-level alterations described may open new avenues for treatments in individuals with anxiety and anxiety disorders. Neurostimulation techniques, including deep brain stimulation and transcranial magnetic stimulation, can directly increase or decrease activity within particular brain regions [85,86]. Psychotherapy may also target the problematic behaviors [87]. Meditation may improve several of the different aspects of cognition identified above and has been correlated with changes in connectivity between brain regions [88,89]. Cognitive training is an appealing prototype of a strategy to correct brain network-level pathology because it is noninvasive and relatively inexpensive. A general approach would be to have subjects with anxiety disorders repeatedly practice cognitive tasks known to increase or decrease activity in particular functional networks with the goal of reversing the changes described here. In Figure 3 we provide examples of cognitive training regimens that could potentially target each of the network-level disruptions associated with anxiety and anxiety disorders.

In the current article we have chosen to highlight evidence that individuals with anxiety and anxiety disorders have general changes in information processing

and brain network function (also [9–11,19]) instead of focusing on changes specific to the processing of threat. Many earlier reviews have discussed the altered processing of emotional stimuli in individuals with high anxiety [6–8], and anxiety disorders are often conceptualized as pathological fear responses such as fear towards stimuli that are no longer or never were threatening [90]. It is unclear whether the primary insult in anxiety disorders involves threat processing or the general cognitive changes described here. One possibility is that a primary deficit in brain systems that detect and appraise threat naturally evolves into general network changes. Alternatively, general network alterations could lead to pathological fear responses by disinhibiting systems involved in threat detection and threat appraisal. At a minimum, the findings we summarize here make it clear that anxiety disorders involve disruption of functional networks supporting not merely emotion but also cognition and motivation.

Relative to adults, less is known about the operation of functional networks in children with anxiety disorders. This gap in the literature is problematic given that mood and anxiety disorders often start in childhood and are increasingly conceptualized as disorders of neurodevelopment [91]. There are some data, reviewed above, to support increased functioning of the ventral attention network in children with anxiety disorders. Furthermore, recent studies examining the development of brain networks [92–94] provide a framework from which to study changes in clinical populations. Longitudinal studies in children, including studies of monozygotic twins discordant for an anxiety disorder, could help to discern whether initial

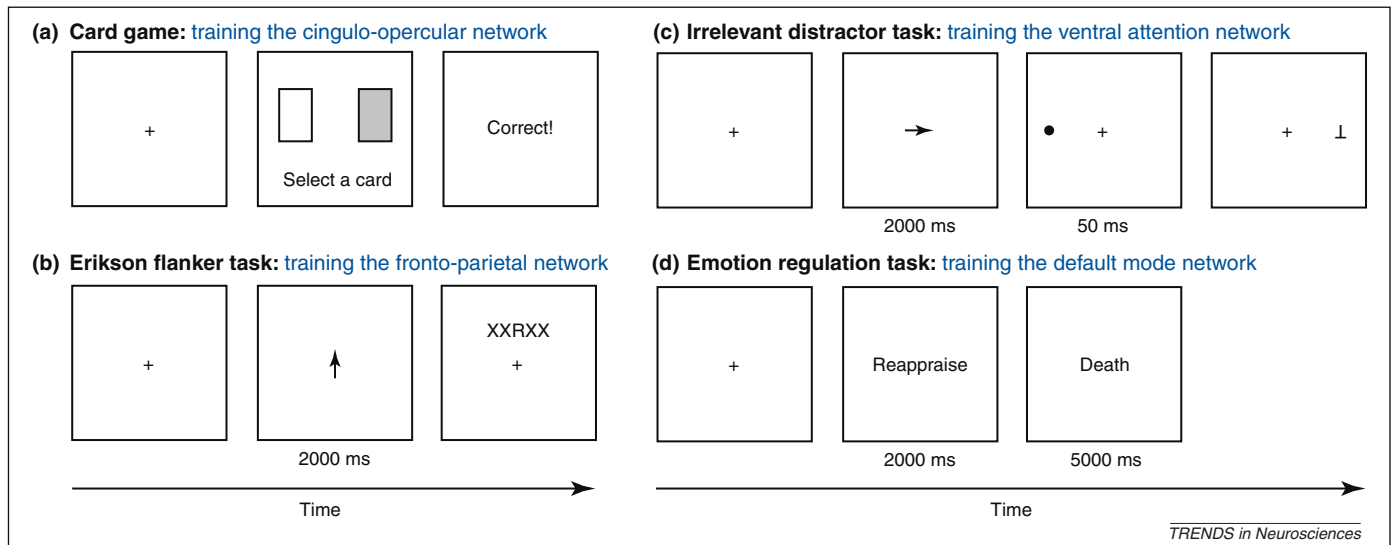


Figure 3. Cognitive training tasks can be designed to correct the network-level pathology of anxiety disorders. **(a)** A task to improve functioning of the cingulo-opercular network during error sensitivity could involve subjects selecting one of two cards on each trial. Error rate is explicitly manipulated by predetermining on each trial whether the response of the subject will be correct or incorrect [25]. Starting with a zero error rate and slowly introducing errors, increased cingulo-opercular activity in response to errors may decrease over many trials through repeated exposure. **(b)** A task to improve functioning of the fronto-parietal network during top-down attentional control could involve repeated practice of a task involving response conflict such as the Erikson flanker task. At the beginning of each trial, a central arrow cues subjects to pay attention to a peripheral location, even as subjects continue to look directly at the central cross. Following a delay, a target appears at the location that had been cued by the central arrow and the task of the subject is to indicate whether the central letter in the target string is an X or an R. By varying the location of the target letter string as well as the congruency between the central letter and the surrounding distracter letters, subjects may learn through practice to develop improved functioning of the fronto-parietal network and top-down attentional control. **(c)** A task to improve functioning of the ventral attention network during stimulus-driven attention could involve directing subjects to attend covertly to a peripheral location with a central arrow. Following a delay, a dot appears briefly at a task-irrelevant location. On the final frame, subjects determine whether a T at the location cued by the central arrow is upright or inverted. Over many trials, subjects may learn to ignore the task-irrelevant dot, decreasing the influence of stimulus-driven attention. **(d)** A task to improve functioning of the default mode network during emotion regulation could involve directing subjects to use a particular emotion regulation strategy before the presentation of a threatening word (task based on [97]).

Box 1. Outstanding Issues

- Our proposed model is based on studies examining regional brain activity. Future studies should define networks *a priori* with resting state functional connectivity and test the tenets of this model with task-based fMRI studies examining activity across entire networks.
- We predict that other psychiatric illnesses will be characterized by different patterns of changes in functional networks. Although not the focus of the current article, major depression, similar to anxiety disorders, may be linked to increased functioning of the cingulo-opercular network [98], decreased functioning of the fronto-parietal network [99,100] and decreased functioning of the default mode network [101]. Whereas anxiety disorders are associated with increased functioning of the ventral attention network, however, major depression may be linked to decreased or normal functioning of this network [102–105]. One study reported decreased magnitude of an electrophysiological signal that may represent stimulus-driven attention in major depression, increased magnitude of this signal in individuals with an anxiety disorder, and an intermediate magnitude in subjects with both disorders [106] (also [107]). These results suggest that functioning of the ventral attention network may define whether an individual develops depression, anxiety, or both disorders.
- Major depression has been linked to increased activity in the default mode network as subjects passively view and reappraise negative pictures [101]. These results have been interpreted as failure to suppress the default mode network during goal-directed activity; the (not mutually exclusive) interpretation offered here is that these results reflect decreased functioning of the default mode network because higher amounts of activity are required to achieve the

same degree of emotion regulation. Future work should determine the relation between psychiatric illnesses, activity in a network during tasks that typically involve that network, and activity in a network when it is typically suppressed.

- An important area for future work is to determine how the model relates to differences among anxiety disorders. One possibility is that most anxiety disorders contain the changes described here and that differences are determined by pathology in other brain regions. Social phobia, for example, is associated with changes in functional connectivity between brain regions involved in face processing and regions in the default mode network [108]. OCD, conversely, has been linked to changes in functional connectivity between the striatum and regions in the default mode and cingulo-opercular networks [109]. Both disorders include changes in the default mode network, but each disorder has additional, unique regional pathology.
- Future studies could target functional brain networks for novel treatment development. Cognitive training regimens based on tasks that increase or decrease activity in a particular functional network could be devised to up- or downregulate disrupted networks. If treatments aimed at correcting functional networks are successful, it would provide evidence that changes functional networks are causative of, rather than effects of, anxiety disorders.
- Future work should examine gender differences in functional brain networks given known differences in the prevalence and expression of anxiety disorders [110].
- The tenets of this model should be tested in anxiety disorders with less available data, such as OCD and PTSD.

defects in anxiety disorders involve systems detecting fear, general cognitive networks, or both.

It is well established that a central feature of the pathophysiology of anxiety disorders is an unusually elevated amygdala response to fear-provoking stimuli [6]. Functional connectivity studies provide initial, although speculative, insights into how the general functional network changes described here could relate to amygdala over-reactivity. Increased functioning of the ventral attention network combined with increased functional connectivity between regions in this network and the amygdala [56,57] could result in larger and potentially maladaptive amygdala responses to suddenly appearing stimuli. Decreased functioning of the fronto-parietal network and changes in connectivity between this network and the amygdala [34] could result in decreased ability of the fronto-parietal network to provide adequate executive control over amygdala activity, thus leading to maladaptive responses. Finally, decreased functioning of the default mode network and decreased functional connectivity between this network and the amygdala [81] could result in decreased ability to use emotion regulation strategies to modify amygdala responses to fearful stimuli. Further studies are needed to clarify the relation between the network changes described here and subcortical changes associated with anxiety disorders (Box 1).

In summary, we provide evidence that anxiety disorders can be conceptualized as dysfunction in brain networks. We propose that anxiety and anxiety disorders are associated with a particular pattern of pathology in the cingulo-opercular, fronto-parietal, ventral attention, and default mode networks. This network-level framework increases our understanding of anxiety disorders, offers a testable model from which to distinguish anxiety disorders from

other illnesses, and provides plausible targets for novel mechanism-based treatments.

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