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].

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 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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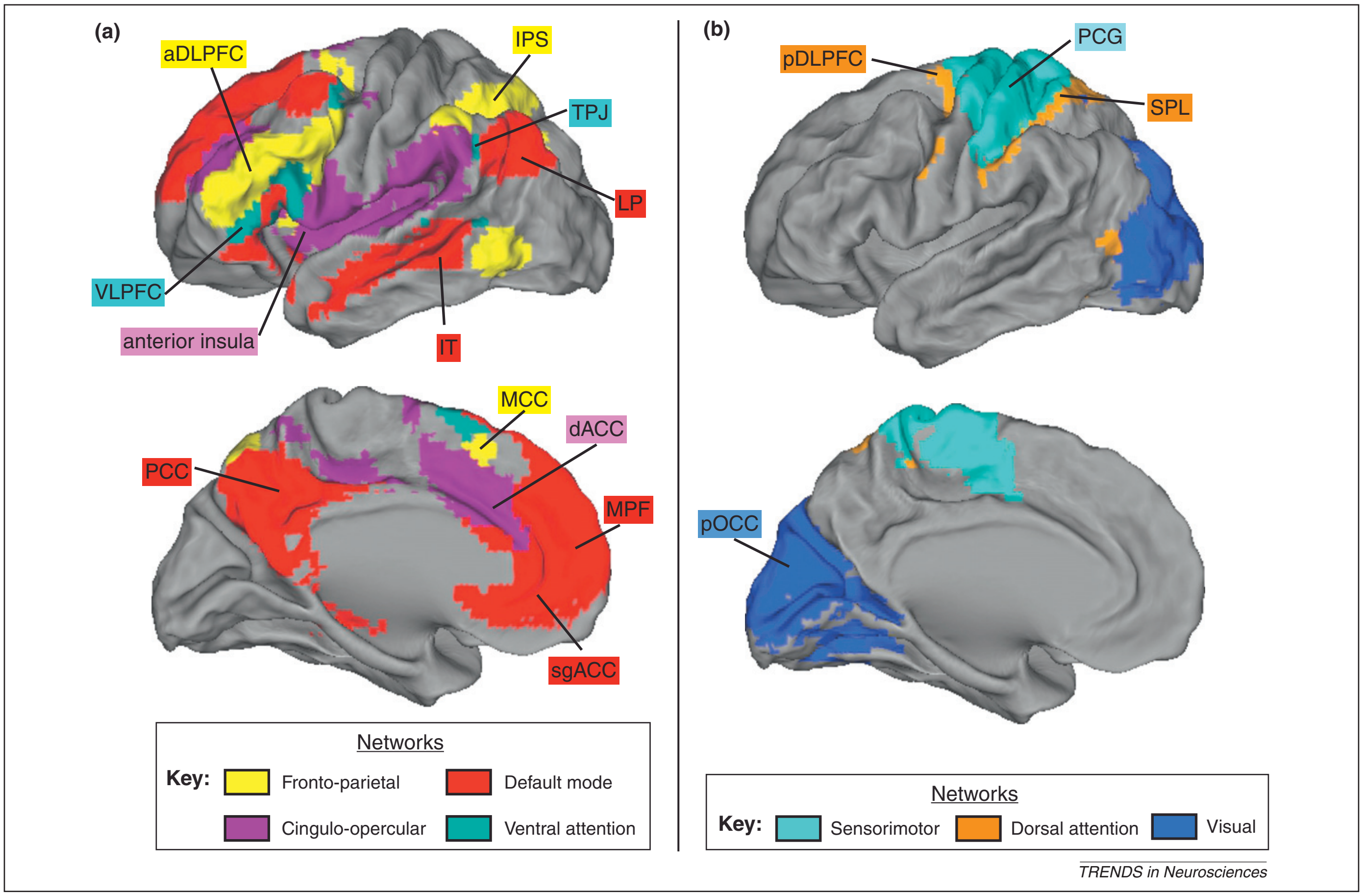

Figure 1. The human brain can be divided into functional networks. Seven of these networks are illustrated here, including: **(a)** the four networks discussed in the main text (cingulo-opercular, ventral attention, fronto-parietal, and default mode), and **(b)** three other commonly described networks (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 cotrex; 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