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Identifying the brain's most globally connected regions

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ABSTRACT

Recent advances in brain connectivity methods have made it possible to identify hubs—the brain's most globally connected regions. Such regions are essential for coordinating brain functions due to their connectivity with numerous regions with a variety of specializations. Current structural and functional connectivity methods generally agree that default mode network (DMN) regions have among the highest global brain connectivity (GBC). We developed two novel statistical approaches using resting state functional connectivity MRI—weighted and unweighted GBC (wGBC and uGBC)—to test the hypothesis that the highest global connectivity also occurs in the cognitive control network (CCN), a network anti-correlated with the DMN across a variety of tasks. High global connectivity was found in both CCN and DMN. The newly developed wGBC approach improves upon existing methods by quantifying inter-subject consistency, quantifying the highest GBC values by percentage, and avoiding arbitrarily connection strength thresholding. The uGBC approach is based on graph theory and includes many of these improvements, but still requires an arbitrary connection threshold. We found high GBC in several subcortical regions (e.g., hippocampus, basal ganglia) only with wGBC despite the regions' extensive anatomical connectivity. These results demonstrate the complementary utility of wGBC and uGBC analyses for the characterization of the most highly connected, and thus most functionally important, regions of the brain. Additionally, the high connectivity of both the CCN and the DMN demonstrates that brain regions outside primary sensory-motor networks are highly involved in coordinating information throughout the brain.

Introduction

The brain is thought to have evolved from simple reflex circuits, bestowing flexibility on behavior by integrating specialized brain regions into coordinated networks. Perhaps reflecting our especially flexible behavioral repertoire, the human brain is estimated to have hundreds of specialized brain regions (Van Essen, 2004). However, it is unknown how these specialized regions are integrated so behavior can be coordinated. Recent research has found that some regions have much higher global brain connectivity (GBC) than others, perhaps reflecting their role in integrating brain activity in order to coordinate cognition and behavior (Achard et al., 2006; Buckner et al., 2009; Hagmann et al., 2008; Heuvel et al., 2008; Salvador et al., 2005a; Sporns et al., 2007).

Existing GBC methods, using both anatomical (Hagmann et al., 2008) and functional (Buckner et al., 2009) connectivity, have identified regions in the default mode network (DMN) as having the highest GBC. This high connectivity may reflect connections necessary to implement the wide variety of cognitive functions the network is involved in. Consistent with this notion, we hypothesized that another large-scale network implementing a variety of cognitive function, the cognitive control network (CCN), also has among the highest GBC.

The CCN has been reported in many studies of cognitive control processes, and is likely involved in coordinating networks of brain regions during novel and non-routine tasks (Cole and Schneider, 2007; Dosenbach et al., 2006). The DMN has been reported in studies of resting state activity, suggesting it is active "by default" (Raichle et al., 2001). However, the DMN is engaged by mind wandering (Mason et al., 2007), prospective and retrospective self-reflection (D'Argembeau et al., 2008), and memory retrieval (Buckner et al., 2005), suggesting that the 'default mode' involves ongoing processing of information for relevance to the self. The CCN is thought to consist of dorsolateral prefrontal cortex (DLPFC), rostrolateral prefrontal cortex (RLPFC), dorsal–caudal anterior cingulate cortex (ACC), pre-supplementary motor area (pre-SMA), inferior frontal junction (IFJ), posterior parietal cortex (PPC), pre-motor cortex (PMC), and anterior insula cortex (AIC). The DMN is thought to consist of posterior cingulate cortex (PCC), rostral anterior cingulate cortex (rACC), anterior temporal lobe (aTL), superior frontal cortex (SFC), and inferior parietal cortex (IPC). Importantly, the CCN and DMN are anti-correlated during task performance and uncorrelated at rest (Fox et al., 2005; Murphy et al., 2008) (Fig. 1A), suggesting they are relatively independent networks. We predicted, given their

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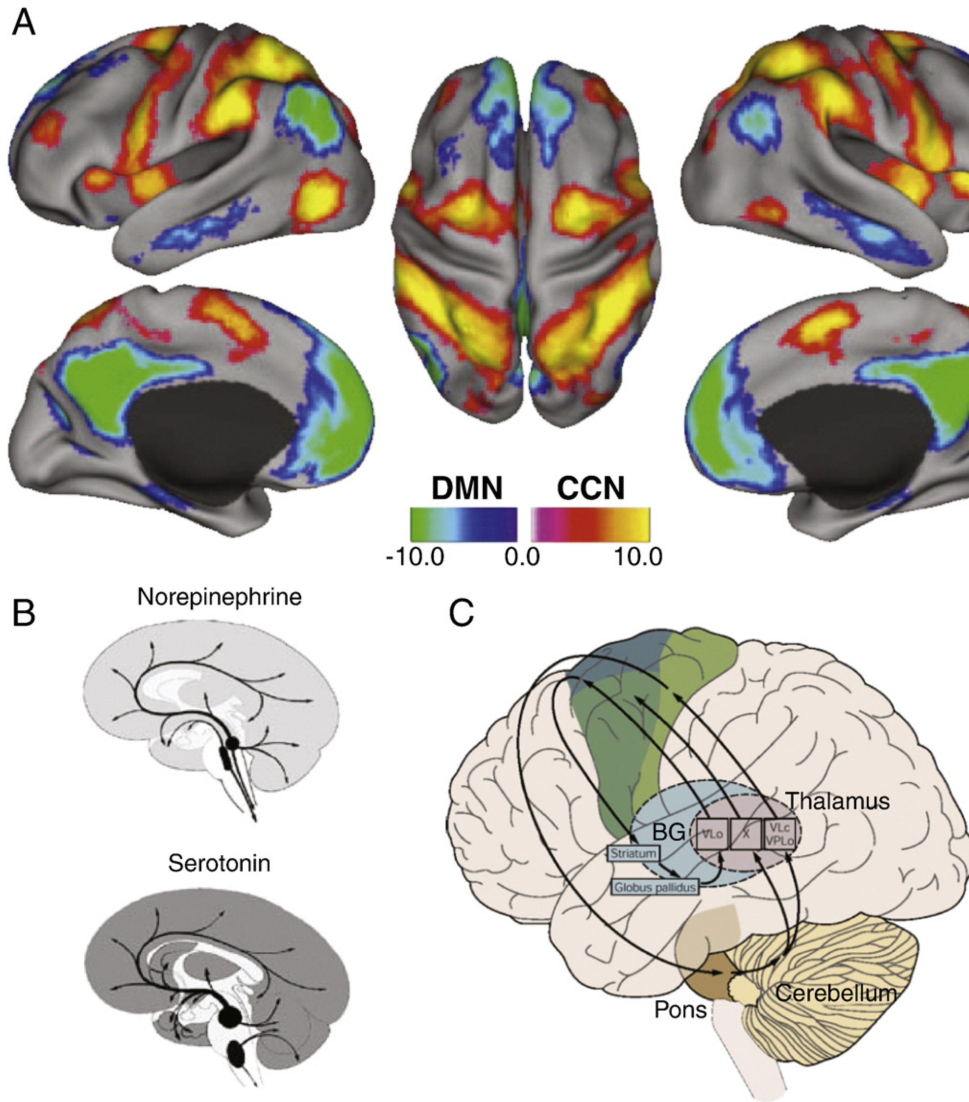

Fig. 1. Hypothesized globally connected circuits. (A) Previous research showed evidence for two large anti-correlated networks in cortex (Fox et al., 2005). Importantly, the functions of these networks suggest that they may have high global brain connectivity (GBC). The cognitive control network (CCN; yellow/red) and default mode network (DMN; blue/green) are thought to be involved in a wide variety of cognitive tasks. The depicted number scales are population *z*-scores (see Fox et al., 2005). Figure adapted from Fox et al. (2005). (B) Extensive work with animal models, and some with humans, has suggested that midbrain neurotransmitter systems project widely throughout the brain (Herlenius and Lagercrantz, 2004), and therefore are likely to have high GBC. Figure adapted from Herlenius and Lagercrantz (2004) and Squire et al. (2003). (C) Evidence from anatomical studies of basal ganglia (BG) shows that loops are formed throughout cortex (not just motor cortex (Middleton and Strick, 1994)), suggesting high GBC for the parts of BG looping with high GBC cortical regions. Anatomical loops have also been found between cerebellum and nearly all of cortex (Middleton and Strick, 1994), via the pons and thalamus, suggesting parts of cerebellum have high GBC as well. Figure adapted from Kandel et al. (2000).

involvement in a wide variety of complex cognitive behaviors that they would both have among the highest GBC in the human brain.

In addition to these two cortical networks, a variety of subcortical brain regions have been found in animal models to have high global connectivity. We predicted that these regions would also show high global connectivity in humans. One such region is amygdala, which is thought to integrate sensory and internal-state information for limbic processing (Barbas, 2000; Jolkkonen and Pitkänen, 1998). Similarly, hippocampal cortex (HC) is thought to integrate information from a wide variety of sources in order to encode entire episodes (Eichenbaum et al., 2007). Also, several midbrain neurotransmitter (MNT) regions such as locus coeruleus and substantia nigra are thought to project to a variety of regions throughout the brain (Fig. 1B) (Herlenius and Lagercrantz, 2004) and are thought to play important roles in motivation and arousal.

Another region, thalamus, includes several nuclei with differing connectivity profiles (Behrens et al., 2003), suggesting that only parts of it might have highly extensive connectivity. Similarly, basal ganglia (BG) and cerebellum connect with cortex via topographic loops (Kelly and Strick, 2003) (Fig. 1C), suggesting that some loops would bestow more wide-spread connectivity on parts of the structures than others. For these reasons, we predicted that amygdala and HC would have high global connectivity, as well as portions of thalamus, BG, and cerebellum.

Functional MRI (fMRI) is an increasingly important method for measuring functional connectivity non-invasively. Among the functional connectivity methods developed with fMRI, the decade-old method of resting state functional connectivity MRI (rs-fcMRI) is unique in its ability to capture functional connectivity largely independent of any particular brain state. Evidence for this comes from a study of anesthetized monkeys (Vincent et al., 2007) that showed rs-fcMRI patterns similar to humans at rest, as well as a study of rs-fcMRI during both task and rest in humans (Fair et al., 2007). Though further research is necessary, rs-fcMRI is thought to be based on very infrequent (~0.01 to 0.1 Hz) bursts of spiking activity in cortex that drive correlated activity through brain networks (Golanov et al., 1994; Kannurpatti et al., 2008).