DEFAULT MODE NETWORK IN DEPRESSION: A PATHWAY TO IMPAIRED AFFECTIVE COGNITION?

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Abstract

Major depressive disorder (MDD) is associated with alterations in multiple brain networks including the default mode network (DMN). The DMN is a set of large-scale connected brain regions that oscillate synchronously and are more active during rest relative to goal-directed tasks. Several functions have been hypothesized for the DMN, including cognitive, self-referential and social functions. Widespread alterations in the core and the subsystems of the DMN as well as in their interplay have been reported in MDD. We will review the evidence supporting DMN alterations in patients with MDD and underscore how they can contribute to social and affective cognitive impairments in this disorder.

Key words: default mode network, cognition, emotion, major depressive disorder, functional magnetic resonance imaging

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Introduction

Major depressive disorder (MDD) is a common (17% lifetime prevalence in the U.S., Andrade et al. 2003) and severe psychiatric disorder with disabling consequences, which make this disorder as the foremost contributor to the global burden of disease (Whiteford et al. 2013). MDD entails a multifaceted pattern of symptoms, which span across multiple domains including mood, cognition, motor and vegetative functions. Consistent with the heterogeneity of symptoms in MDD, studies investigating the neural correlates of this disorder (Vasic et al. 2009) have suggested that brain networks rather than individual regions could underlie the pathogenesis of MDD (Northoff et al. 2011). In particular, recent neuroscientific and clinical interest sparked on the role of the default mode network (DMN). In this paper, we propose that altered DMN can contribute to the development of MDD symptoms, which also include altered affective cognition. To set the stage for this proposal, we will illustrate the anatomical boundaries and the functional characterization of the DMN. Next, the article describes the evidence of altered DMN in MDD. Then, we will illustrate how DMN alterations in MDD could result in impairments of affective cognition.

The Default-mode network: anatomy and function

The DMN is a large-scale interacting brain system, which includes a set of brain regions whose activity is relatively increased during rest and is attenuated during a goal-directed behavior (Raichle et al. 2001). The DMN was originally identified during functional neuroimaging tasks by looking at those brain areas, whose activity increased during rest relative to task performance, so-called "task-induced deactivations", TID (Raichle et al. 2001). Recently, resting state scanning which is an experimental setting where the participant is not required to perform any goal-directed tasks was introduced as more reliable approach to estimate spatial and temporal characteristics of the DMN. Among several techniques, seeded-correlation with the posterior cingulate cortex (PCC) allows the estimation of the network of brain regions whose signal fluctuates synchronously, which includes the DMN. Alternatively, model-free analyses such as independent component analysis can allow the decomposition of the imaging data in spatio-temporal patterns (Sambataro et al. 2010), which could reflect resting state networks including the DMN.

Irrespective of the methodological approach, imaging studies on the DMN converge on a similar
Figure 1. The Default Mode Network (DMN). Axial slices depict the spatial extent of the DMN estimated using seeded connectivity (with the PCC; left) and using independent component analysis (right). Yellow arrows indicate DMN regions. mPFC/ACC, medial Prefrontal Cortex/ anterior cingulare; PreC/PCC, precuneus/ posterior cingulate; TPCx, lateral temporo-parietal cortex

spatial pattern (see figure 1). The DMN is composed by midline areas organized in an anterior “hub”, which is localized in the medial prefrontal cortex (mPFC), and a posterior “hub” encompassing the PCC and the precuneus; laterally, this network includes bilateral inferior temporo-parietal cortexes and ventrally, the medial temporal lobes (Andrews-Hanna et al. 2010). Although all these regions oscillate synchronously, recent studies suggest that the DMN could be decomposed in anatomical-functionally separate subsystems (Andrews-Hanna et al. 2010). Most studies subdivide the DMN in a core, comprising the two midline hubs, and distinct subsystems including anterior, posterior, and ventral regions (Uddin et al. 2009; Andrews-Hanna et al. 2010a, 2010b; Sambataro et al. 2010; Whitfield-Gabrieli et al. 2011; Damoiseaux et al. 2012; Sambataro et al. 2013). Responses in the brain regions within anterior subsystem have been found during tasks tapping on the theory of mind, mentalizing, moral decision making, social narrative understanding, social reasoning and conceptual processing thus suggesting a role in introspection about mental states. The ventral subsystem has been associated with episodic and autobiographical memory, navigation and imagery that are involved in memory-based simulations. The posterior DMN has been implicated in visual processing, motor planning, cognitive functions, memory retrieval, and also self-perception and internal mentation (Sambataro et al. 2010). The core is implicated in emotional, self-referential processing, mentalizing autobiographical memory, moral decision making, anticipation of value, and cognition which can globally contribute to the evaluation of motivationally salient and personally-significant information (Andrews-Hanna et al. 2010).

This overall picture suggests the possibility that the DMN can have a pivotal role in the processing of affective cognition: first, in the attribution of social/personal value to stimuli, then in the planning of social behavioral responses using memory information via prospective simulation of social scenarios (Andrews-Hanna 2012). Also, the DMN could interact with other executive networks thus modulating the allocation of attentional resources for the process at hand (Sambataro et al. 2010).

Affective Cognition

Affective cognition entails those brain processes that lie at the interface between cognition and emotion, including emotion perception and recognition, and social and moral reasoning (Elliott et al. 2011). Classical paradigms used to probe this function investigate emotional processing and its interaction with concurrent cognitive demands: implicit and explicit processing of facial stimuli (Sambataro et al. 2006); emotional stimuli perception and recognition during executive control tasks (Schulz et al. 2009); passive and explicit moral evaluation (Moll et al. 2009). The brain regions usually implicated in the affective/cognition function belong to limbic system, such as amygdala, insula, striatum and the hippocampus, and to the cortical systems such as anterior cingulate (ACC) including subgenual cingulate (sgCC), mPFC/orbitofrontal cortex (OFC) and lateral PFC. Among different multi-compartmental models proposed to explain affective cognition, the model by Philips (Phillips et al. 2003, 2008) modified after Ochsner’s PFC theorization (Ochsner et al. 2005, Ochsner et al. 2007) offers an interesting framework for interpreting affective cognition that distinguishes a ventral and a dorsal system. The ventral system includes amygdala, insula, ventral striatum, ventral ACC and ventral mPFC/OFC and mediates emotional appraisal and the generation of emotional states via bottom-up processing. The dorsal system includes hippocampus, dorsal ACC, and PFC with a role in emotional regulation with a top-down control and more specifically a dorsal part involved in the reappraisal of emotional contexts and the ventral part critical for
Affective cognition impairments in MDD

A number of alterations of affective cognition have been described in MDD, including reduced sensitivity to emotional faces, cognitive dysfunction, and impaired social and moral reasoning. In particular, cognitive biases have been associated with the development, maintenance and relapse of depression (Gotlib and Joormann 2010). Patients with MDD have an increased sensitivity to negative emotional stimuli, increased ability to remember negative items (Bradley et al. 1996), increased overgeneralized autobiographical memory, and pathological sense of guilt. These symptoms have been traditionally included in the seminal Beck’s cognitive triad, which comprises a schema, which is a deep cognitive structures, that biases information processing thus causing negative thoughts about abnormal the self, the world and the future (Beck et al. 1979). Interestingly, altered information processing includes attention, memory and prospecting that are all functions mediated by the DMN.

DMN alterations in MDD

Alterations in the DMN have been associated with several neurological (Wolf et al. 2012, 2013) and psychiatric disorders (Sambataro et al. 2010, Wolf et al. 2011). Studies in MDD have indicated widespread increases of the DMN activity during both tasks and rest: in the anterior DMN including ACC (both subgenual and perigenual portions) and mPFC, in posterior regions including the PCC and the precuneus, and ventrally in the hippocampal formation and parahippocampus (Broyd et al. 2009, Price et al. 2010). Interestingly, these changes were associated with clinical severity. Increased activity in the anterior and posterior DMN in patients during emotional face perception and labeling with MDD predicted depression severity and hopelessness (Grimm et al. 2009). Similarly, Sheline (2009) found a failure to deactivate anterior, posterior and ventral DMN regions during passive viewing and reappraisal of negative emotional pictures. Consistently, increased subgenual cingulate activity in MDD at rest correlates in the dopaminergic system with depressive episode duration (Greicius et al. 2007) as well as with illness severity (Sheline et al. 2010, Hamilton et al. 2011). This region has been implicated in affect and viscero-motor function regulation as well as with negative emotion experience thus suggesting its role in the self, the world and the future (Beck et al. 1979). Interestingly, altered information processing includes attention, memory and prospecting that are all functions mediated by the DMN.

Conclusions

Current evidence amply supports a role of the DMN function and its subsystems in major depression. One of the brain mechanisms through which the DMN could contribute to depressive symptoms could entail the modulation of affective cognition. Interestingly, alterations of affective cognition (Fritzsche et al. 2010) as well as of the DMN (Farb et al. 2011, Elliott et al. 2012) in remitted patients tend to support the view that these are trait rather than state markers of the disorder. Furthermore, another important point to be addressed is whether the DMN alterations at rest can predict altered DMN engagement during the performance of an affective or cognitive task, which may illustrate intrinsic and stable traits for depression (Sambataro et al., personal communication). The modulation of affective cognition by the therapeutic interventions focused on the DMN modulation using psychotherapy (e.g., mindfulness based treatments, see Chiesa et al. 2010), drugs (e.g., selective serotonin reuptake inhibitors, e.g., selective serotonin reuptake inhibitors, Pizzagalli 2011) or deep brain stimulation (Lozano et al. 2008) deserves further investigation. Also, the regions of the DMN (Sambataro et al. 2010, 2013) as well as affective cognition symptoms (Whitmer et al. 2012) in remitted patients tend to support the view that these trait of MDD could open new therapeutic avenues for the treatment of this disorder.

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