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Review

Medial prefrontal cortex and the self in major depression

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ABSTRACT

Self-focus (i.e. the process by which one engages oneself in self-referential processing) is a core issue in the psychopathology of major depression. The cortical midline structures, including the medial prefrontal cortex (MPFC), play a key role in self-referential processing in healthy subjects. Four functional magnetic resonance imaging studies recently found either an increased or a decreased MPFC activation during self-referential processing in depressed patients compared to healthy controls. Building on critical differences in experimental settings, we argue that these conflicting results are indeed consistent with two modes of elevated MPFC activation in major depression. An elevated tonic ventral MPFC activation, as uncovered by an event-related design, may embody automatic aspects of depressive self-focus, such as attracting attention to self-relevant incoming information. An elevated phasic dorsal MPFC activation, as uncovered by a block-based design, may embody more strategic aspects of depressive self-focus, such as comparing the self with inner standards. Additionally, strategic self-focus in depression may recruit the anterior cingulate cortex and more lateral regions of the prefrontal cortex. An aberrant functional connectivity of the dorsal MPFC may underlie this lack of reciprocal inhibition between the cognitive control network and the default mode network. Altogether, these results suggest that self-focus in depression may emerge as a process competing for brain resources due to a lack of inhibition of the default mode network, resulting in detrimental effects on externally-oriented cognitive processes. Follow-up studies are warranted to determine the trait vs. state nature of these biomarkers and their ability to predict treatment outcome.

Contents

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1. Introduction

According to the cognitive theory of depression, depressed patients display systematic errors in the cognitive appraisal of experience that may promote and sustain an unfavorable view of them (Clark and Beck, 1999). These cognitive biases integrate an increased attention to negative stimuli with an increased attention to the self, namely self-focus. Self-focus in depression is not only quantitatively increased (Mor and Winquist, 2002), but also qualitatively distinct (Teasdale, 1999; Watkins, 2008). More specifically, self-focus in depression is characterized by its abstract, evaluative, analytical style (i.e. 'thinking about' experience), rather than being a concrete, intuitive, experiential awareness of experience in the moment. From a philosophical perspective, self-focus in depression is thus more about the 'extended' or 'narrative' aspects of the self (i.e. the self as a continuous object of knowledge), henceforth referred to as 'self', rather than about the so-called 'minimal self' (i.e. the self as the subject of immediate experience) (Gallagher, 2000).

There is clinical evidence suggesting that self-focus may influence the course of depression. Rumination, which is a form of self-focused attention on negative aspects of one's self triggered by negative affect, appears to predict the onset of depression and interacts with negative cognitive styles to predict a more chronic evolution of depression (Nolen-Hoeksema et al., 2008). Furthermore, therapeutic interventions targeting self-focus to reduce its analytic components, such as Mindfulness-Based Cognitive Therapy (MBCT), were found to be efficient in preventing depressive relapse (Ma and Teasdale, 2004; Teasdale et al., 2000; Bondolfi et al., 2010). Although self-focus is a core issue in the psychopathology of major depression as well as an efficient target in psychotherapy, little attention have been paid to its neural underpinnings (Northoff, 2007). In contrast with the neural bases of the increased attention to negative stimuli, which have been extensively studied over the last decade (Leppänen, 2006), those of self-focus have been addressed only recently by clinical neuroscience.

Self-focus may be operationalized in social neuroscience as the process by which one engages him or herself in self-referential processing (Lemogne et al., 2009). This definition is particularly heuristic in that self-referential processing (i.e. the appraisal of stimuli as strongly related to one's own person) is common to the distinct concepts of the self (Northoff et al., 2006). Several studies combining functional neuroimaging with self-referential tasks in healthy subjects have consistently demonstrated the role of three main regions within the cortical midline structures (CMS): two anterior regions, dorsal and ventral, within the medial prefrontal cortex (MPFC) and one posterior region encompassing the posterior cingulate cortex (PCC), the precuneus and the retrosplenial cortex (Northoff et al., 2006). For instance, Fossati et al. (2003) presented healthy subjects with personality traits and asked them to judge whether each trait described them (i.e. a self-referential task) or whether it described a generally desirable trait (i.e. a judgment of social desirability). Activation in the MPFC was unique to the self-referential condition. Mostly based on the same paradigm, four functional magnetic resonance imaging (fMRI) studies addressing the neural bases of self-referential processing in major depression were published by four independent teams in the last two years (Grimm et al., 2009b; Lemogne et al., 2009; Yoshimura et al., 2010; Johnson et al. 2009).

The aim of this article is to provide an updated overview of the available data regarding the neural bases of self-referential processing in major depression. Although one may consider these results as conflicting, we will argue that they indeed provide compelling evidence for the role of an increased MPFC activity in the depressive self-focus. First, we will briefly review the role of the cortical midline structures (CMS), including both dorsal and ventral MPFC, in the neural underpinnings of self-referential processing in healthy subjects. Second, we will outline the importance of self-focus in the psychopathology of major depression, making the case for studying its neural bases. Third, we will summarize the main results of the fMRI studies that addressed this issue, focusing especially on those regarding the MPFC. Finally, building on topographical dissociations and functional peculiarities related to the default mode network, we will try to integrate these results in the wider framework of social cognition.

2. The CMS and the self

Self-referential processing in healthy subjects is associated with more activation or less deactivation within the CMS, whatever the domain of the stimuli that are processed (e.g. words, faces) or their sensory modality (Northoff et al., 2006). From the most anterior regions to the most posterior, these structures include the ventral MPFC, the dorsal MPFC, the anterior cingulate cortex (ACC), the PCC, the precuneus and the retrosplenial cortex. Despite their architectonic heterogeneity, these structures are both anatomically and functionally connected, the later being inferred from high degree of co-activation (or co-deactivation) in various conditions. More specifically, the CMS are part of the so-called 'default mode