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Review

Neural correlates of dysfunctional emotion regulation in major depressive disorder. A systematic review of neuroimaging studies

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ABSTRACT

Abnormal emotion processing is a core feature of major depressive disorder (MDD). Since the emergence of functional neuroimaging techniques, many studies have been conducted in MDD subjects to elucidate the underlying abnormalities in the neural systems involved in emotion regulation. In this systematic review, we discuss this research in the context of the neural model of emotion regulation previously described by Phillips et al. (2008). This model differentiates between automatic and voluntary emotion regulation subprocesses. Automatic regulation subprocesses were shown to involve predominantly medial prefrontal cortical structures, in addition to the hippocampus and parahippocampus, while voluntary regulation processes additionally recruited lateral prefrontal cortical regions. In conclusion, although the available data is limited, findings suggest that MDD subjects demonstrate abnormally reduced activity in lateral prefrontal cortices during explicit voluntary control of emotional experience. During early, automatic stages of emotion regulation, on the other hand, MDD subjects appear to achieve successful emotion regulation by recruiting additional lateral prefrontal neural regions, that may be mediated by medial prefrontal, especially rostral/dorsal anterior cingulate gyrus (ACG) functioning. Dysfunctional automatic regulation may impair successful voluntary emotion regulation, and may present a target for novel therapeutic approaches in MDD.

Contents

Abbreviations: ACG, anterior cingulate gyrus; ant, anterior; BA, Brodmann area; dACG, dorsal ACG; DLPFC, dorsolateral PFC; DMN, default mode network; DMPFC, dorsomedial PFC; LPFC, lateral PFC; MOFC, medial OFC; MPFC, medial PFC; OFC, orbitofrontal cortex; PCG, posterior cingulate gyrus; PFC, prefrontal cortex; rACG, rostral ACG; sgACG, subgenual ACG; TPN, task positive network; vACG, ventral ACG; VLPFC, ventrolateral PFC; VMPFC, ventromedial PFC; VTA, ventral tegmental area.

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1. Introduction

Emotion dysregulation is one of the central features of major depressive disorder (MDD) (Gotlib and Joormann, 2010; Ochsner and Gross, 2007). Insight in this process will aid to better understand the pathophysiology of MDD, which is vital to improve treatment and prevention strategies. Phillips et al. (2003a, 2003b) developed a neural model of emotion regulation to study abnormalities in MDD, bipolar disorder (BD) and schizophrenia. This model distinguished a ventral and a dorsal system; the *ventral* system comprising the amygdala, insula, ventral striatum, ventral anterior cingulate gyrus (vACG), the ventromedial prefrontal cortex (VMPFC)/medial orbitofrontal cortex (OFC); and the *dorsal* system, consisting of the hippocampus, dorsal ACG (dACG) and dorsal prefrontal cortex (PFC). The ventral system is thought to be involved in recognizing emotionally salient stimuli and generating an emotional state (i.e., bottom-up emotional influences), the dorsal system in voluntary regulation of these states (i.e., voluntary top-down control of emotions) (Phillips et al., 2003a, 2003b).

This model was updated in 2008 and used as a framework to further study neural circuitry supporting emotion regulation in BD (Phillips et al., 2008). A major adaptation was the integration with the Ochsner and Gross model, which distinguishes two different top-down cognitive control systems: the dorsomedial prefrontal cortex (DMPFC) and the dorsolateral prefrontal cortex (DLPFC) for reappraisal of emotional contexts, and the ventral PFC for learning of associations between emotionally relevant outcomes and prior choices and events (Ochsner and Gross, 2005, 2007). Furthermore, it was recognized that emotion regulation can be effortful (voluntary) or proceed more or less automatically (Phillips et al., 2008), although it was acknowledged that voluntary and automatic regulatory subprocesses could operate simultaneously with appraisal and generation of emotion. Together, this led to the distinction of six psychological subprocesses of emotion regulation, defined by two factors: type of regulation strategy (behavioral, attentional and cognitive) and the manner in which the strategy is applied (automatically or voluntary) (Phillips et al., 2008).

This conceptual framework allowed for the characterization of the various tasks used in neuroimaging studies on emotion regulation in healthy control subjects (HC) according to the various emotion regulation subprocesses under study. Processes are considered *automatic* when emotional aspects of a given task can be assumed to exert their influence in an implicit way, for example because subjects are not aware of the emotional value of stimuli, or because the emotional meaning of a stimulus is not the explicit focus of the task to be performed. The subject is thought to automatically engage in regulatory processes in order to be successful on the task. These automatic processes were shown to involve predominantly medial prefrontal cortical structures, including the ACG, the OFC and DMPFC, as well as the hippocampus and parahippocampus. *Voluntary* processes comprise effortful attempts to alter emotions of which the subject is consciously aware – for example because these are the focus of the task – and recruited lateral prefrontal cortical regions *in addition to* medial prefrontal cortical structures.

These two systems – automatic and voluntary – were conceptualized as operating in parallel and possibly simultaneously, regulating emotional responses emerging from the amygdala, ventral striatum and thalamus (Phillips et al., 2008). Specifically, in HC, *automatic behavioral control* strategies were found to be associated with medial prefrontal recruitment (subgenual ACG (sgACG) and VMPFC (Etkin et al., 2011; Merz et al., 2011; Phillips et al., 2008); whereas *voluntary behavioral control* strategies involve ventrolateral PFC (VLPFC) in addition to medial prefrontal structures (dACG, and DMPFC and rostral ACG (rACG) (Phillips et al., 2008). Additionally, distancing from aversive pictures was associated with an increase in activity in the DLPFC (Kanske et al., 2011; Vrticka et al., 2011), the frontal pole (BA10) (Koenigsberg et al., 2010), the (inferior) parietal cortex (Kanske et al., 2011), and temporal regions (Kanske et al., 2011; Koenigsberg et al., 2010). *Automatic attentional control* strategies were found to recruit the (rostal) ACG (Amting et al., 2010; Phillips et al., 2008), in addition to the dACG, VMPFC, DMPFC, inferior parietal cortex, and insula (Kanske et al., 2011; Kompus et al., 2009; McRae et al., 2010); *voluntary attentional control* strategies were found to recruit the DLPFC, dACG and probably the right parietal cortex (Butler and James, 2010; Hart et al., 2010; Phillips et al., 2008). For *automatic cognitive change* strategies the hippocampus and parahippocampus were shown to be involved (Phillips et al., 2008), while *voluntary cognitive change* strategies recruited the right DLPFC and ventrolateral PFC (VLPFC), in addition to the ACG and DMPFC (Etkin et al., 2011; Kalisch, 2009; McRae et al., 2010; Phillips et al., 2008; Staudinger et al., 2009). For the sake of consistency, we will further use the term cognitive *control* instead of cognitive change.

The above-described new dual model has been used as a framework for describing altered neural functioning during emotion regulation in bipolar disorder (Phillips et al., 2008). However, this model has not yet been applied to the study of emotion regulation circuitry in MDD. Therefore, in this systematic review we will integrate the existing neuroimaging literature on emotion regulation in MDD within the theoretical framework of the six emotion

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