



Altered functional connectivity between medial prefrontal cortex and the inferior brainstem in major depression during appraisal of subjective emotional responses: A preliminary study



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ABSTRACT

Objective: We tested the hypothesis that reduced rostral anterior cingulate cortex (rACC)-subcortical functional connectivity in depressed subjects might account for depression-related autonomic dysregulation.

Methods: Ten healthy and ten depressed subjects categorized their immediate subjective emotional responses to picture sets while undergoing functional magnetic resonance imaging and electrocardiography. Using an rACC cluster commonly activated in both groups by emotion categorization as a seed region, we then performed voxel-wise functional connectivity analyses to examine rACC connectivity across the brain in depressed and control subjects.

Results: rACC had significantly stronger connectivity with a region of the inferior pons in controls than in depressed subjects. Within-subjects differences in rACC-pons connectivity also significantly correlated with measures of both heart rate variability and depression severity.

Conclusions: These findings support the hypothesis that autonomic dysregulation in depression may be associated with a functional disconnection between rACC and autonomic brainstem nuclei.

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1. Introduction

Major depressive disorder (MDD) is associated with a bias toward negative affective information (Gollan, Pane, McCloskey, & Coccato, 2008), deficits in the regulation of emotions and other related bodily functions such as sleep, appetite, energy and libido (Ehring, Fischer, Schnulle, Bösterling, & Tuschen-Caffier, 2008; Liverant, Brown, Barlow, & Roemer, 2008), as well as a reduction in heart rate variability (Kemp et al., 2010), and increased mortality rates in multiple systemic medical conditions (Frasure-Smith & Lesperance, 2005; Katon et al., 2005; Lane, 2008; Onitilo, Nietert, & Egede, 2006). However, the neural and physiological basis for these features of MDD and their relation to one another remains incompletely understood. Research in this field to date has begun to identify a network of brain structures, including the amygdala, insula, dorsal anterior cingulate cortex (dACC), dorsomedial

(DMPFC) and dorsolateral (DLPFC) prefrontal cortex, as well as the ventromedial PFC (VMPFC), which encompasses both the subgenual (sgACC) and rostral (rACC) portions of the anterior cingulate cortex. Each of these regions has been shown to participate in the processing of emotional information and/or the regulation of subsequent neural and visceral responses (Craig, 2009; Roy, Shohamy, & Wager, 2012; Thayer & Lane, 2009; Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012), and depressed subjects have also been found to have structural and/or functional abnormalities (Fales et al., 2009; Frodl et al., 2002; Kennedy et al., 2007; Koenigs & Grafman, 2009; Lozano et al., 2008; Mayberg et al., 1999; Pizzagalli, 2011; Sheline et al., 2001; Sprengelmeyer et al., 2011) as well as pathological connectivity patterns (De Kwaasteniet et al., 2013; Greicius et al., 2007; Zeng et al., 2012) in several of these same regions.

Substantial evidence suggests that several of these brain regions are organized into a hierarchical regulatory network that evolved to modulate autonomic and visceral activity in response to lower and higher levels of complex information and integration (Thayer & Lane, 2000, 2009; Thayer et al., 2012). Brainstem nuclei are lower in this hierarchy, whereas medial and lateral frontal lobe structures which integrate context, long-term memory, and conscious

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reasoning processes are situated at the top. Currently it is not fully understood, however, whether connections within this hierarchy are associated with the emotion and visceral regulation difficulties observed in depression.

The rACC subregion of VMPFC may be of special significance in relation to the intersection of emotion regulation and peripheral physiology. Converging evidence suggests that this region is associated with multiple functions, including top-down modulation of amygdala-mediated attentional responses to emotional stimuli (Etkin, Egner, & Kalisch, 2011; Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Gyurak, Gross, & Etkin, 2011; Mitchell & Greening, 2011; Mitchell, 2011), the evaluation of costs and benefits in decision-making (Amemori & Graybiel, 2012; Grabenhorst, Rolls, & Parris, 2008), the conscious awareness and appraisal of emotional experience (Gusnard, Akbudak, Shulman, & Raichle, 2001; Lane, Fink, Chua, & Dolan, 1997; Ochsner et al., 2004; Silani et al., 2008), and the integration of context-dependent emotional meaning (Roy et al., 2012) with heart rate variability (HRV) and other brainstem-mediated autonomic and visceral responses (Thayer et al., 2012). In MDD, abnormalities in this region have also been associated with anhedonia (Walter et al., 2009), and greater rACC activity in depressed subjects has been found to predict favorable outcomes to antidepressant treatments (Mayberg et al., 1997; Pizzagalli, 2011; Pizzagalli et al., 2001). At present, however, it is not fully understood which (if any) of these different rACC functions is altered in MDD, or how this may relate to the prognostic utility of its activity. Furthermore, recent work in depressed patients demonstrating evidence for glutamate-mediated alterations in resting-state correlations between rACC and the insula suggests the further possibility that pathological rACC functional connectivity patterns may underlie its significance in depression (Horn et al., 2010).

The “attention to emotion” task developed by Lane et al. (1997) has been shown in several studies using healthy volunteers (Gusnard et al., 2001; Ochsner et al., 2004; Silani et al., 2008) to be a robust probe of changes in rACC activity due to attentional focus on, and appraisal of, conscious emotional responses. As this paradigm involves both attention- and evaluation-related processes, however, it remains unsettled whether rACC activity in this task is best characterized as localizing attended representations of emotions, or instead highlighting the further process of evaluating the meaning of these subjective responses. A recent study using this task (Smith, Fass, & Lane, 2014), however, has also highlighted the possibility that, given the hierarchical nature of the neural control of emotion (Lane, 2008; Thayer & Lane, 2000, 2009; Thayer et al., 2012), this region may simultaneously generate a representation of the conceptual meaning of one’s own emotional state and then use this information to regulate less flexible subcortical responses. Thus emotional representation and subsequent regulatory processes might be usefully carried out within the same structure, providing a means of integrating the apparently distinct roles of rACC in automatic emotion regulation (Phillips, Ladouceur, & Drevets, 2008; Thayer et al., 2012) and representing/evaluating the interoceptive perception of one’s own emotions (Kalisch, Wiech, Critchley, & Dolan, 2006; Lane et al., 1997; Ochsner et al., 2004).

This task may be particularly relevant in depression because depressed individuals, relative to their healthy counterparts, have been shown to display impairments in attention, and are frequently preoccupied with attending to and evaluating their own emotional states (Grimm et al., 2011; Mialet, Pope, & Yurgelun-Todd, 1996). This task thus provides an experimental paradigm for comparison of rACC activity between depressed and healthy subjects during conscious emotional appraisal. Further, because this task is known to reliably activate rACC, it also provides an appropriate context for assessing functional connectivity differences between rACC and the neural structures with which it interacts when it is

engaged in this specific emotion-related attention-and-appraisal function. Selective increases in functional connectivity during these emotion-related attentional/evaluative functions could plausibly reflect either (1) attention-mediated increases in bottom-up information flow toward rACC, or (2) selective increases in regulatory top-down signaling from rACC to subcortical structures lower in the regulatory hierarchy discussed above.

In the present study we therefore sought to extend this task to depressed subjects in order to clarify the role of rACC connectivity in depression. Based on previous work suggesting that the extent to which subjects with MDD attend to their emotions is unrelated to concurrent levels of depressive symptoms (Berenbaum, Bredemeier, Thompson, & Boden, 2010; Neumann, Van Lier, Gratz, & Koot, 2010; Orgeta, 2009; Salovey, Mayer, Goldman, Turvey, & Palfai, 1995; Salovey, Stroud, Woolery, & Epel, 2002), we hypothesized that depressed subjects would be capable of appropriately engaging rACC during attention to, and evaluation of, their own emotional responses. However, as rACC (and surrounding medial prefrontal regions) may subsequently use high-level representations of emotion in context-dependent automatic emotion regulation (Etkin et al., 2006; Kalisch et al., 2006; Mitchell, 2011; Mitchell & Greening, 2011; Ochsner & Gross, 2005; Phillips et al., 2008; Smith, Fass, et al., 2014; Vuilleumier, Armony, Driver, & Dolan, 2001), and given its position at the top of the visceromotor hierarchy (Lane, Reiman, Ahern, & Thayer, 2001; Thayer et al., 2012; Thayer & Lane, 2000, 2009), we hypothesized that emotional and visceral regulation difficulties in depression, and associated bodily dysfunction, could be related to a functional disconnection between medial prefrontal cortex and brainstem autonomic nuclei (Kober et al., 2008). We therefore predicted that the degree of functional connectivity between rACC and brainstem regions during an internal focus of attention would be significantly decreased in depressed subjects relative to healthy controls, and that it would inversely correlate with depression severity.

As a secondary hypothesis, we also predicted that rACC connectivity with insula regions that register bodily feedback from visceral afferents (Craig, 2002, 2009) would be lower in depressed than control participants independent of attentional focus. This prediction was based on previous evidence for rACC–insula connectivity abnormalities in depression (Horn et al., 2010), in conjunction with other work suggesting that autonomic control structures may implement predictive forward models (Critchley, 2005; Seth, 2013; Seth & Critchley, 2013). Predictive forward models (Blakemore, Wolpert, & Frith, 2002; Seth & Critchley, 2013; Seth, 2013) posit that when cognitive and motor control structures issue a command signal, they also send an “efference copy” of this command to sensory structures which monitor bodily responses. In such models, if the predicted body response (conveyed by the efference copy) does not match the actual afferent response signals from the body, a prediction error calculation can be used to adaptively modify the strength of future command signals. Therefore, this last hypothesis was based on our reasoning that if rACC regulation of visceral responsivity is associated with the generation of response predictions that are compared to the actual visceral responses registered in the insula (Paulus & Stein, 2010), and this regulatory ability was diminished in depression due to a functional disconnection, an incongruence should arise between the continuous predicted and actual visceral responses in depressed subjects related to this hypothesized autonomic dysregulation mechanism. Thus, while in controls the predicted visceral response arising out of rACC would match the actual visceral response registered in the insula (leading to high rACC–insula correlations), in depressed subjects rACC–insula correlations would be lower because the actual visceral responses registered in the insula would not match the predicted responses arising out of rACC due to the functional disconnection between rACC and brainstem hypothesized above.

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