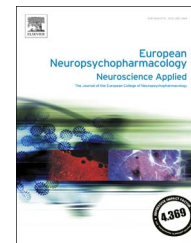




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Anterior cingulate volume predicts response to psychotherapy and functional connectivity with the inferior parietal cortex in major depressive disorder

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Abstract

In major depressive disorder (MDD), the anterior cingulate cortex (ACC) has been associated with clinical outcome as well as with antidepressant treatment response. Nonetheless, the association between individual differences in ACC structure and function and the response to cognitive behavioral therapy (CBT) is still unexplored. For this aim, twenty-five unmedicated patients with MDD were scanned with structural and resting state functional magnetic resonance imaging before the beginning of CBT treatment. ACC morphometry was correlated with clinical changes following psychotherapy. Furthermore, whole-brain resting state

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Functional connectivity

functional connectivity with the ACC was correlated with clinical measures. Greater volume in the left subgenual (subACC), the right pregenual (preACC), and the bilateral supragenual (supACC) predicted depressive symptoms improvement after CBT. Greater subACC volume was related to stronger functional connectivity with the inferior parietal cortex and dorsolateral prefrontal cortex. Stronger subACC-inferior parietal cortex connectivity correlated with greater adaptive rumination. Greater preACC volume was associated with stronger functional connectivity with the inferior parietal cortex and ventrolateral prefrontal cortex. In contrast, greater right supACC volume was related to lower functional connectivity with the inferior parietal cortex. These results suggest that ACC volume and its functional connectivity with the fronto-parietal cortex are associated with CBT response in MDD, and this may be mediated by adaptive forms of rumination. Our findings support the role of the subACC as a potential predictor for CBT response.

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1. Introduction

Major depressive disorder (MDD) is a severe psychiatric illness with a lifetime risk of 10 to 20% in the general population (Kessler et al., 2003). In MDD, reduced volume and functional alterations of the anterior cingulate cortex (ACC), a region important in emotion processing and regulation, are consistently reported (Sacher et al., 2012) and predict poor response to a variety of treatments (Pizzagalli, 2011).

Anatomically, the ACC can be subdivided into three subregions: the subgenual (subACC), the pregenual (preACC) and the supragenual (supACC) ACC. Resting-state functional magnetic resonance imaging (RS-fMRI) studies showed that each ACC subregion is part of a functionally segregated network, with the subACC strongly connected to regions involved in mood regulation, the preACC to regions involved in self-referential processing, and the supACC to regions important in the detection of behaviorally relevant stimuli (Sheline et al., 2010). Additionally, functional imaging studies have identified a feedback circuit between ACC and limbic regions (e.g. the amygdala, hippocampus), which consists of positive afferent amygdala projections to subACC and negative efferent projections from supACC and preACC to the amygdala that is pivotal for emotional processing (Pezawas et al., 2005). Structural imaging studies in MDD showed that greater volume of all three ACC subregions is related to better clinical outcome and, notably, even when structural differences between patients and controls are not found (Frodl et al., 2008). Moreover, functional activity prior to treatment in ACC subregions predicted response to treatment in MDD (Dunlop and Mayberg, 2014; McGrath et al., 2013; Pizzagalli, 2011; Rentzsch et al., 2014). Recently, stronger supACC functional connectivity (FC) with the prefrontal cortex (PFC) has been associated with higher levels of adaptive rumination, known to promote psychotherapy response in MDD (Spati et al., 2015). Notably, clinical response to psychotherapy is associated with reductions in glucose metabolism and blood flow in the PFC (Brody et al., 2001; McGrath et al., 2013). In particular, cognitive behavioral therapy (CBT) response has been associated with reductions of glucose

metabolism in anterior and dorsolateral prefrontal cortex (DLPFC) (Goldapple et al., 2004; Kennedy et al., 2007) along with an increased activity in the hippocampus (Goldapple et al., 2004; Ritchey et al., 2011). These findings are consistent with the view that psychotherapy can reduce dysfunctional thought processes by recruiting PFC that, through its connections with the ACC, can exert a 'top-down' control on limbic regions (DeRubeis et al., 2008; Phillips et al., 2008).

However, the role of individual differences in ACC morphology along with its functional connectivity (FC) with frontal and limbic regions important for CBT response (e.g. PFC, hippocampus) in the response to cognitive behavioral therapy (CBT) in patients with MDD has not been investigated so far. Since mechanisms of action linked to treatment response may be independent of the MDD pathophysiology (Krishnan and Nestler, 2010), rather than merely focusing on differences between patients and healthy controls, the goals of the present study were: First, to investigate whether greater volume of specific ACC subregions was linked to better response to CBT; Second, to identify the association between structural differences and FC strength with other brain regions known to be involved in CBT response in patients with MDD. Furthermore, as rumination and hopelessness have been identified as core processes in the development and maintenance of MDD and as such targets for CBT treatment (Abramson et al., 1989; Watkins, 2009), we also investigated the role of FC in mediating these processes. Since volumetric changes of the ACC could result from differences of cortical thickness and/or surface area that reflect different neurobiological processes (Winkler et al., 2010), we also investigated the association of each measure and CBT response.

2. Experimental procedures

2.1. Procedure

All subjects went through structural and functional scans, and psychometric evaluation (see below) one week prior to CBT treatment. After one week, patients started manualized CBT treatment, consisting of 22 weekly individual sessions. This treatment was performed in the outpatient clinic of the University of

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