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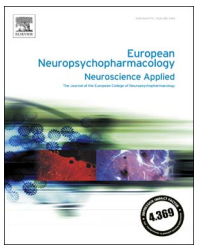

Fronto-limbic effective connectivity as possible predictor of antidepressant response to SSRI administration

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Abstract
The timely selection of the optimal treatment for depressed patients is critical to improve remission rates. The detection of pre-treatment variables able to predict differential treatment response may provide novel approaches for treatment selection. Selective serotonin reuptake inhibitors (SSRIs) modulate the fronto-limbic functional response and connectivity, an effect preceding the overt clinical antidepressant effects. Here we investigated whether the cortico-limbic connectivity associated with emotional bias measured before SSRI administration predicts the efficacy of antidepressant treatment in MDD patients. fMRI and Dynamic Causal Modeling (DCM) were combined to study if effective connectivity might differentiate healthy controls (HC) and patients affected by major depression who later responded (RMDD, n=21), or failed to respond (nRMDD, n=12), to 6 weeks of escitalopram administration. Sixteen DCMs exploring connectivity between anterior cingulate cortex (ACC), ventrolateral prefrontal cortex (VLPFC), Amygdala (Amy), and fusiform gyrus (FG) were constructed. Analyses revealed that nRMDD had reduced endogenous connectivity from Amy to VLPFC and to ACC, with an increased connectivity and modulation of the ACC to Amy connectivity when processing of fearful emotional stimuli compared to HC. RMDD and HC did not significantly differ among themselves. Pre-treatment effective connectivity in fronto-limbic circuitry could be an important factor affecting antidepressant response, and highlight the mechanisms which may be involved in recovery from depression. These results suggest that fronto-limbic connectivity might provide a neural biomarker to predict the clinical outcome to SSRIs administration in major depression.

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1. Introduction

Mood-congruent negative biases in processing emotional information have been suggested as one of the core features which parallel and contribute to the development and maintenance of depressive states (Beck, 2008) by influencing evaluative processes, social judgment, decision making, attention, and memory (Murphy et al., 1999). Previous studies have demonstrated that depressed patients show perception biases in processing negative emotional facial expressions compared to healthy controls (Bouhuys et al., 1995; Gur et al., 1992). Furthermore, the early reversal of these negative emotional biases could mediate the therapeutic effect of antidepressant drugs (Harmer et al., 2009a; Victor et al., 2010, 2013). Several neuroimaging studies helped to define the neural circuitry engaged in emotional processing. The amygdala (Amy) is a critical node in this network, and is necessary in perceiving stimuli with affective salience, mainly for negative environmental stimuli (Amaral and Price, 1984; LeDoux, 2000), and is activated by emotional memories (Cahill et al., 1996; Hamann et al., 1999). This structure is interconnected with other regions, such as the ventrolateral prefrontal cortex (VLPFC) and anterior cingulate cortex (ACC), which are involved in the attribution of emotional salience to stimuli and in active self-regulation of affective states by modulating Amy reactivity (Beauregard et al., 2001; Ochsner et al., 2004; Phan et al., 2005; Phillips et al., 2003a; Schaefer et al., 2002; Urry et al., 2006). Both these frontal regions are recruited and interact in facial expression processing, these stimuli are initially elaborated by the visual cortex and fusiform gyrus (FG) (Fusar-Poli et al., 2009).

In depression, abnormalities in this functional network have been consistently demonstrated. The most replicated findings reveal increased activation of the Amy and medial prefrontal cortex, and a reduced connectivity between these regions in response to negative emotional stimuli (Davey et al., 2011; Delvecchio et al., 2012; Hamilton et al., 2012; Victor et al., 2012). These findings could reflect a dysfunctional regulation of subcortical limbic activity by cortical areas, which may contribute to the mood-congruent bias in MDD pathophysiology (Rive et al., 2013). This hypothesis is in line with several MRI studies which demonstrated abnormal functional and structural connectivity between frontal and limbic regions in depressed patients compared to controls (Dichter et al., 2014; Shizukuishi et al., 2013).

The regulation of the fronto-limbic circuitry is modulated by serotoninergic transmission: previous studies showed that the activity and functional connectivity in this circuitry was influenced by polymorphisms of the serotonin transporter gene (Dannlowski et al., 2010; Hariri et al., 2002; Klucken et al., 2013; Volman et al., 2013) and by challenges with serotonin reuptake inhibitors (SSRIs) (Grady et al., 2013; Harmer et al., 2006; McCabe et al., 2010; Murphy et al., 2009a; Norbury et al., 2007; Outhred et al., 2013; Phillips et al., 2015; Windischberger et al., 2010). Moreover, depression recovery has been consistently associated with functional activity in fronto-limbic structures such as the ACC, medial prefrontal cortex, DLPFC and Amy (Canli et al., 2004; Hamann, 2005; Maddock et al., 2003): before treatment, higher metabolic rates/functional response during passive emotional processing or response inhibition tasks in ACC and Amy were able to predict antidepressant response and remission (Chen et al., 2007; Langenecker et al., 2007; Mayberg et al., 1997; Seminowicz et al., 2004), whereas a lower pre-treatment activity in the ventrolateral prefrontal cortex during the down-regulation of positive emotion was associated with better response to SSRI in depressed patients (Light et al., 2011). Furthermore, a higher connectivity within cortico-limbic networks both, in unipolar and in bipolar depressed patients, was induced by treatment (Anand et al., 2007; Anand et al., 2005; Vai et al., 2015a) and a higher functional resting state connectivity predicted antidepressant response in unipolar depressed patients (Kozel et al., 2011).

The timely selection of the optimal treatment for depressed patients is critical to improving remission rates. The identification of reliable biomarkers, especially the detection of pre-treatment variables that predict differential treatment response, may provide novel approaches for treatment selection (Phillips et al., 2015). However, the prediction offered by cortico-limbic effective connectivity has not been examined despite the hypothesis that depression and response to treatment may best be considered as a network disorder (Vai et al., 2014).

Differences at the baseline neural functional response between depressed patients support the hypothesis that responders or not to antidepressant treatment may differ in terms of neurobiological characteristics (Chen et al., 2007; Gillin et al., 2001; Langenecker et al., 2007; Mayberg et al., 1997; Seminowicz et al., 2004; Wu et al., 1999; Wu et al., 2001).

Therefore, the aim of the present study was to assess whether cortico-limbic connectivity associated with emotional bias predicted the efficacy of antidepressant SSRI treatment in major depressed patients.

Connectivity was explored by combining conventional fMRI with a technique that allows the investigation of causal relationships between regions (Dynamic Causal Modeling, DCM) (Friston et al., 2003). DCM offers a deep comprehension of the connectivity, thanks to the possibility of modeling causality between regions (this aspect mainly differs the effective connectivity from functional one, which does not allow to infer direction). Moreover, DCM estimates how a region causes dynamics in another area via synaptic connections, independently by the experimental condition (intrinsic/endogenous connections), and how these connection change under the influence of external perturbations (i.e. emotional processing of fearful faces, named as modulatory effects) (Stephan et al., 2010).

Specifically, we hypothesized that an increased bottom-up connectivity from Amy and prefrontal cortex could contribute to a better response in terms to depressive recovery. This effect could underlie to a higher pre-treatment recruitment of cortical control on subcortical activity in responders, resulting into a more efficient top-down regulation. This was suggested by previous studies which showed a higher connectivity within cortico-limbic networks as pre-treatment neurobiological underpinnings of response during resting state (Kozel et al., 2011) and as neural correlate of antidepressant efficacy (Anand et al., 2007; Anand et al., 2005; Vai et al., 2015a).

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