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Research report

Brain effects of antidepressants in major depression: A meta-analysis of emotional processing studies

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ABSTRACT

Background: A consistent brain activity pattern has been identified in major depression across many resting positron emission tomography (PET) studies. This dysfunctional pattern seems to be normalized by antidepressant treatment. The aim of this meta-analysis was to identify more clearly the pattern associated with clinical improvement of depression following an antidepressant drug treatment, in emotional activation studies using functional magnetic resonance imaging (fMRI).
Methods: A quantitative Activation Likelihood Estimation (ALE) meta-analysis was performed across 9 emotional activation fMRI and PET studies (126 patients) using the Activation Likelihood Estimation technique.
Results: Following the antidepressant drug treatment, the activation of dorsolateral, dorsomedial and ventrolateral prefrontal cortices was increased whereas the activation of the amygdala, hippocampus, parahippocampal region, ventral anterior cingulate cortex, orbitofrontal cortex, and insula was decreased. Additionally, there was a decreased activation in the anterior (BA 32) and posterior cingulate cortices, as well as in the precuneus and inferior parietal lobule, which could reflect a restored deactivation of the default mode network.
Limitations: The small number of emotional activation studies, using heterogeneous tasks, included in the ALE analysis.
Conclusions: The activation of several brain regions involved in major depression, in response to emotional stimuli, was normalized after antidepressant treatment. To refine our knowledge of antidepressants' effect on the neural bases of emotional processing in major depression, neuroimaging studies should use consistent emotional tasks related to depressive symptoms and that involve the default mode network, such as self-referential processing tasks.

1. Introduction

Functional brain imaging investigations in acutely depressed patients revealed a consistent pattern of brain activation, characterized by an abnormal cooperation between cortical, limbic, and subcortical regions. Major Depressive Disorder (MDD) has been associated with a decreased

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activity in prefrontal areas, including the dorsolateral prefrontal cortex (DLPFC) [i.e. Brodmann Area (BA) 9] and the ventrolateral prefrontal cortex (VLPFC), as well as in other cortical regions, such as the inferior parietal lobule (BA 40) and the dorsal anterior and posterior cingulate cortices. Conversely, increased activity has been demonstrated in limbic and paralimbic regions, such as the ventral part of the anterior cingulate cortex (i.e. subgenual cingulate, BA 25), hippocampus, hypothalamus, amygdala, and insula in MDD. This pattern is frequently observed in studies using positron emission tomography (PET) (Bench et al., 1992; Drevets et al., 1992; Mayberg, 2003) or functional magnetic resonance imaging (fMRI) (Rose et al., 2006; Siegle et al., 2007).

Compared with the results of resting PET studies, those of fMRI and PET studies using activation tasks are easier to interpret, as they are usually based on a controlled design comparing at least two psychological tasks. For instance, fMRI and PET activation studies allow for modelling psychopathological processes such as emotional or cognitive biases associated with MDD. However, as a drawback, the results of fMRI and PET activation studies are also more difficult to generalize due to the different tasks used. For instance, whereas the hypofrontality of depressed patients is well known at rest, fMRI studies yielded mixed results, such as prefrontal hyperactivity during working memory processes when controlling for task performance (Harvey et al., 2005; Fitzgerald et al., 2008a).

Several resting state PET studies highlighted that antidepressant treatments, especially antidepressant drugs, tend to restore a normal brain function (see for review Mayberg, 2003; Mayberg et al., 2000) while improving depressive symptoms. These findings were recently confirmed in a meta-analytic study. Normalization of hypometabolism in neocortical regions (prefrontal and parietal cortex) and of hypermetabolism in limbic and paralimbic areas has been reported (Fitzgerald et al., 2008b). Some fMRI activation studies showed similar effects of antidepressants in acutely depressed patients (e.g. Robertson et al., 2007; Fales et al., 2009). However these findings were more heterogeneous than those of resting state studies. For example, both increased (Davidson et al., 2003) and decreased (Fu et al., 2004) activation in the dorsal anterior cingulate cortex have been reported. These discrepancies may have been caused by differences across activation studies in cognitive and emotional tasks which may have probed different parts of the cortico-limbic network implicated in the pathophysiology of MDD and clinical treatment response.

The main goal of the present study was to identify more clearly the regions targeted by antidepressants in relation to the neural underpinnings of emotional processing as such knowledge may ultimately inform therapeutic strategy. Therefore, we examined the pattern of changes in brain activation during emotional processing associated with a clinical improvement of depression. Note that the fMRI activation studies dealing with the antidepressants effects on cognitive (non-emotional) processing in MDD patients were too few to allow a meta-analysis. We employed a recent quantitative meta-analysis method, using Activation Likelihood Estimation (ALE), which allows the integration of neuroimaging results across studies (Turkeltaub et al., 2002).

2. Materials and methods

2.1. Data sources and inclusion criteria

Studies of antidepressant drug effects on brain activation during emotional processing in acute MDD were identified by a systematic literature search in large databases (Medline, Embase, PsychInfo, and Web of sciences) for English-language manuscripts of neuroimaging studies published prior to December 2009. The search keywords were “depressive disorder”, “depression”, “brain imaging”, “fMRI”, “PET”, and “antidepressant”. In addition, we examined the references of the selected papers.

All studies included met the following criteria:

1) they involved MDD patients (i.e. excluding seasonal affective disorder, or bipolar disorder);
2) they measured regional cerebral blood flow (PET), glucose metabolism (PET), or blood oxygenation (fMRI) (i.e. excluding receptor binding studies);
3) both at baseline (without treatment) and after the administration of the antidepressant (at least 6 weeks); the data from the non-responder subgroup were excluded when they were distinct from those of responder patients;
4) they assessed brain activation by using an emotional task that engages the subject to process explicitly or implicitly emotional stimuli (in order to limit the data variability between studies due to divergent tasks, one fMRI study using exclusively a cognitive task was excluded); and
5) they provided standard Talairach or Montreal Neurologic Institute (MNI) coordinates, allowing for comparison of findings across studies and across laboratories.

Since the studies adopted different analysis methods and significance criteria, all foci were accepted when reported as significant by the criteria designated in the individual studies. Usually studies reported p values that were not corrected for multiple comparisons.

2.2. Meta-analysis procedure

Presentation of results has been limited to regional activation changes (as revealed by task and antidepressant versus baseline comparisons). Studies that focused on functional connectivity, structural data, or brain–behaviour correlations were not included.

The technique of ALE analysis has been recently described (Turkeltaub et al., 2002; Laird et al., 2005). The ALE algorithm has been modified in the current version (GingerALE 2.0) (Eickhoff et al., 2009). In short, all reported foci (coordinates of maximum activation) for a given study are modelled as the peaks of 3D Gaussian probability distribution. A “modelled activation” (MA) map is computed, representing a summary of the results of that specific study. ALE scores are then calculated on a voxel-by-voxel basis by taking the union of these individual MA maps. This revised analysis tests for convergence between studies (random-effects) rather than foci (fixed-effects). All ALE data processing was performed using the BrainMap Search and View software (http://brainmap.org). Any coordinates of maximum activation were modelled by a 3D Gaussian distribution (all were