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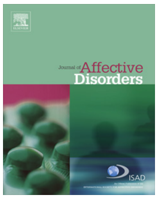

Review

Meta-analytic evidence for neuroimaging models of depression: State or trait?

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ABSTRACT

Background: Major Depressive Disorder (MDD) is a leading cause of disease burden worldwide. With the rapid growth of neuroimaging research on relatively small samples, meta-analytic techniques are becoming increasingly important. Here, we aim to clarify the support in fMRI literature for three leading neurobiological models of MDD: limbic–cortical, cortico–striatal and the default mode network.

Methods: Searches of PubMed and Web of Knowledge, and manual searches, were undertaken in early 2011. Data from 34 case-control comparisons ($n=1165$) and 6 treatment studies ($n=105$) were analysed separately with two meta-analytic methods for imaging data: Activation Likelihood Estimation and Gaussian-Process Regression.

Results: There was broad support for limbic–cortical and cortico–striatal models in the case-control data. Evidence for the role of the default mode network was weaker. Treatment-sensitive regions were primarily in lateral frontal areas.

Limitations: In any meta-analysis, the increase in the statistical power of the inference comes with the risk of aggregating heterogeneous study pools. While we believe that this wide range of paradigms allows identification of key regions of dysfunction in MDD (regardless of task), we attempted to minimise such risks by employing GPR, which models such heterogeneity.

Conclusions: The focus of treatment effects in frontal areas indicates that dysregulation here may represent a biomarker of treatment response. Since the dysregulation in many subcortical regions in the case-control comparisons appeared insensitive to treatment, we propose that these act as trait vulnerability markers, or perhaps treatment insensitivity. Our findings allow these models of MDD to be applied to fMRI literature with some confidence.

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1. Introduction

Major Depressive Disorder (MDD) is a leading cause of disease burden worldwide (Murray et al., 2013). The study of MDD with functional neuroimaging techniques has increased year on year for over a decade but despite many findings of brain differences in MDD, we still do not have a clear idea of the neural aetiology. Various candidate networks have been identified as neuroimaging models of MDD. Each has strengths and limitations, either offering only a partial explanation for the symptoms that patients experience, or using data generated from Positron Emission Tomography (PET) evidence (e.g. Mayberg, 1997) with an associated lack of spatial and temporal resolution. With the multiple neuroimaging models proposed, summarising the evidence for and against each model in a coherent manner with a meta-analysis may provide a greater understanding of the relative merits of each.

The purpose of neuroimaging meta-analysis is to localize the brain regions that are activated consistently (across a range of related studies) in response to a certain intervention or in a certain clinical condition. Meta-analysis imbues greater statistical power due to the increased number of subjects included and can provide a more heterogeneous data pool from which to draw conclusions (Costafreda, 2009). In a recent review, Marchand (2010) notes that it is unclear whether particular brain changes in depression are a consequence of symptoms or due to underlying neural vulnerabilities. Meta-analytic techniques may aid the identification of both state and trait markers. Characterising consistent state markers may reveal which patients are likely to be sensitive to treatment. In contrast, describing trait markers would support the determination of neural vulnerabilities that are associated with aetiological pathways.

Mayberg's classic neurobiological model (Drevets, 2001; Mayberg, 2003; Seminowicz et al., 2004) considers MDD in the context of seven key areas of cortical and limbic dysfunction: lateral prefrontal cortex, medial prefrontal cortex, orbitofrontal cortex, subgenual anterior cingulate cortex, rostral anterior cingulate cortex, hippocampus and anterior thalamus (Seminowicz et al., 2004). In this limbic–cortical model, over-activity in limbic areas (including the hippocampus) is not adequately controlled by prefrontal areas, with an associated depressed mood (Mayberg et al., 1999). The rostral and subgenual regions of the anterior cingulate cortex are believed to play a key mediatory role in this network (Disner et al., 2011; Seminowicz et al., 2004) which is also employed during emotion processing in healthy volunteers (Phillips et al., 2003; Stevens and Hamann, 2012).

An alternative model places greater emphasis on the role of subcortical structures in the aetiology of depression. The concept of parallel, overlapping, cortico–striato–pallidal–thalamic loops was introduced by Alexander et al. (1986). Circuits extend from the striatum to prefrontal and limbic regions and are involved in separable functions including cognitive and emotional processing and motor control. Striatal dysfunction in particular has been associated with symptoms of MDD including anhedonia and psychomotor retardation and grey-matter volume reductions have been shown throughout regions of this network in MDD (Bora et al., 2012).

Patients with current MDD frequently score highly on scales of negative mood valent rumination (Mor and Winquist, 2002), with associated heightened depressive symptom load and hyperactivity in the default mode network (Pizzagalli, 2011). This dispersed network includes medial prefrontal regions, precuneus, lateral parietal cortex and the lateral temporal cortex (Raichle et al., 2001). These areas show increased activity at rest in current MDD (Greicius et al., 2007) along with a failure to deactivate normally during task conditions (Shulman et al., 1997). This model, based on a cognitive rumination process, is thought to best represent a state-dependent feature and may, in part, account for maintenance of an episode.

There are two main approaches to meta-analysis of functional imaging studies: image-based and coordinate-based. Image-based meta-analysis uses the voxel-wise estimates of effect size from each contributing study. However, although less accurate (Salimi-Khorshidi et al., 2009), coordinate-based meta-analysis methods have become the standard approach since they require only the locations of peak activations as reported in the literature. In this study we employed both Activation Likelihood Estimation (ALE) (Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2002) and Gaussian-process regression (GPR) (Salimi-Khorshidi et al., 2011) coordinate-based meta-analyses. ALE models peak activations as probability distributions with widths that estimate the spatial uncertainty due to the between-subject and between-template variability. GPR enables a coordinate-based meta-analysis to incorporate coordinates and their (both positive and negative) effect sizes, modelling the intervening regions between the reported peak activations to produce an estimate of the combined effect-size at every intracerebal voxel.

In previous meta-analyses of MDD data with ALE, there was broad support for all of the regions in the aforementioned three models implicated in MDD, although the direction of effects was unclear. These previous analyses have variously used a mixture of PET, SPECT and fMRI data (Delaveau et al., 2011; Diener et al., 2012; Fitzgerald et al., 2008a, 2006; Fu et al., 2012; Sacher et al., 2012; Steele et al., 2007) and focused on specific paradigms (Delaveau et al., 2011; Diener et al., 2012; Fitzgerald et al., 2008a; Hamilton et al., 2012) or brain regions (Fitzgerald et al., 2006; Steele et al., 2007). This methodology excludes many otherwise eligible studies which are ruled out and their data lost. More importantly, although PET and fMRI can give similar results, the two methods measure fundamentally different phenomena and it is clear that one cannot always predict the other (Kinahan and Noll, 1999).

The meta-analytic study reported here seeks to clarify the support for each model specifically in the fMRI literature, and to investigate the possible interplay between them, using case-control comparisons and treatment studies with a broad range of study designs. It is hypothesised that support will be shown for all models described. We consider that the default mode network in particular will show a decrease in activity with treatment, indicating that regions of this network are a putative state marker for depression and may index differential treatment response.