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Predictive neural biomarkers of clinical response in depression: A meta-analysis of functional and structural neuroimaging studies of pharmacological and psychological therapies

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ABSTRACT

We performed a systematic review and meta-analysis of neural predictors of response to the most commonly used, evidence based treatments in clinical practice, namely pharmacological and psychological therapies. Investigations of medication-free subjects suffering from a current major depressive episode who underwent positron emission tomography (PET) or functional or structural magnetic resonance imaging (MRI) scans prior to the initiation of treatment were reviewed. Results of 20 studies from 15 independent samples were included in the functional imaging meta-analysis and 9 studies from 6 independent samples in the structural neuroimaging meta-analysis. Regional activations with prognostic value include the well replicated finding that increased baseline activity in the anterior cingulate is predictive of a higher likelihood of improvement. As well, increased baseline activation in the insula and striatum is associated with higher likelihood of a poorer clinical response. Structural neuroimaging studies indicated that a decrease in right hippocampal volume is a statistically significant predictor of poorer treatment response. Overall, the predictive information that is measurable with brain imaging techniques is both multimodal and regionally distributed as it contains functional as well as structural correlates which encompass several brain regions within a frontostriatal–limbic network. To develop clinically relevant, prognostic markers will require high predictive accuracy at the level of the individual. Predicting clinical response will help to stratify patients and to identify at an early stage those patients who may require more intensive or combined therapies. We propose that structural and functional neuroimaging show significant potential for the development of prognostic markers of clinical response in the treatment of depression.

Introduction

No biomarkers for predicting treatment response in depression are currently used in clinical practice. Treatment is usually chosen on an empirical basis, informed by the clinical characteristics; such as, depression severity and subtype, previous history of response, and comorbid disorders (Fava et al., 1997; Thase et al., 1997; Trivedi et al., 2006). Once treatment has begun, an improvement in clinical symptoms early in the course of therapy generally points towards an eventual good treatment response (Nierenberg et al., 2000). However, in most cases, efficacy needs to be evaluated after 6 to 12 weeks of treatment, and a large proportion of patients have persistent symptoms despite a full treatment trial (Wisniewski et al., 2009). For an individual patient, it is still not possible to predict his or her clinical response before the initiation of treatment.

Previous work has suggested that neuroimaging measures may be useful to predict response before treatment onset. Early studies of the antidepressant treatment effects of sleep deprivation observed greater baseline anterior cingulate and amygdala metabolism in subsequent responders relative to nonresponders and healthy controls (Ebert et al., 1991; Wu et al., 1992). In a treatment study of antidepressant medication, Mayberg et al. (1997) reported that responders to treatment showed increased anterior cingulate metabolism at baseline relative to non-responders and to healthy controls. A well-replicated finding since has been an association of anterior cingulate activity with treatment response to standard pharmacological therapies as well as to short term sleep deprivation and the more experimental treatment of transcranial magnetic stimulation (Fu et al., 2003; Pizzagalli, 2011). Furthermore, structural neuroimaging studies suggest that the volume of regional structures, for example the anterior cingulate and hippocampus, may predict clinical response (Costafreda et al., 2009a; Vakili et al., 2000). Structural and functional neuroimaging thus has the potential to stratify patients into subgroups according to their underlying biological abnormalities to determine specific patterns of response to treatment (Trusheim et al.,

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2007). Whether this strategy is clinically useful will depend on the extent that the neuroimaging markers are predictive at the level of the individual patient (Fu et al., 2008a).

In the present review, we sought to examine the extent to which the results from over a decade of neuroimaging treatment studies in depression support the notion of neural predictors of response to the most commonly used evidence-based treatments in clinical practice, namely pharmacological and psychological therapies. Moreover, we sought to identify regions throughout the brain which may predict clinical response, rather than limiting effects to a single region. We conducted a systematic review and quantitative analysis of functional and structural neuroimaging treatment studies in unipolar depression that employed either of the evidence-based treatments of antidepressant medication and psychological therapy, thus excluding short term and investigational treatments, such as sleep deprivation, transcranial magnetic stimulation, ketamine, and vagal nerve stimulation. In order to optimise spatial resolution and mapping, we focused on the neuroimaging paradigms of positron emission tomography and functional and structural magnetic resonance imaging. We employed voxel-based meta-analysis to ascertain the brain regions with significant evidence across studies on their prognostic potential (Costafreda et al., 2009b) and extended this method to incorporate both whole-brain, coordinate-based findings and outcomes from region of interest ROI studies, which are highly prevalent in the literature.

Methods

Literature search

A literature search was conducted to identify studies using functional or structural neuroimaging measurements to predict treatment response in depressed adult patients. To identify relevant studies, we performed a search of the MEDLINE database, covering the period from January 1990 to September 2011 using the following search terms: ("major depression" or "depression" or "depressed") and ("PET" or "positron" or "MR" or "MRI" or "fMRI" or "sMRI"). The reference lists of studies meeting the selection criteria and pertinent review articles were also searched manually for relevant articles.

To be considered for inclusion, a study had to employ functional or structural magnetic resonance imaging (fMRI/sMRI) or positron-emission tomography (PET) before treatment initiation; ascertain patients through recognised diagnostic criteria such as DSM-IV (APA, 2000) or ICD-10 (Isaac et al., 1996) for a major depression, unipolar subtype, with the exclusion of geriatric depression; and use pharmacological or psychological treatment validated through randomised clinical trial evidence, excluding electro-convulsive therapy (ECT) and short term and investigational treatments, such as sleep deprivation, transcranial magnetic stimulation (TMS), ketamine, vagal nerve stimulation and deep-brain stimulation. For functional studies, we only included studies in which scanning had been performed in unmedicated subjects (i.e. before treatment initiation), as there is evidence that treatment can have acute effects on brain activation (Norbury et al., 2007). For structural studies, we decided to relax this requirement to include studies in which scanning was performed before or up to 4 weeks after treatment initiation.

From the selected studies, we included those contrasts that compared the baseline measurements of those individuals who subsequently responded and did not respond to treatment (responder vs non-responder analysis), those that correlated baseline measurements to continuous measures of subsequent response (such as change in depression scale rating score between baseline and endpoint), and studies that employed newly developed pattern recognition approaches to predict the treatment outcome of individual patients based on their baseline imaging measures.

These criteria identified 30 studies aiming at predicting treatment response based on neurofunctional or neuroanatomical imaging measurements. Of these, 21 were functional neuroimaging papers (Brannan et al., 2000; Brody et al., 1999; Chen et al., 2007; Costafreda et al., 2009c; Davidson et al., 2003; Frodl et al., 2011; Fu et al., 2008a, 2008b; Konarski et al., 2009; Langenecker et al., 2007; Little et al., 1996, 2005; Marquand et al., 2008; Milak et al., 2009; Ritchey et al., 2011; Roy et al., 2010; Samson et al., 2011; Saxena et al., 2003; Siegle et al., 2006; Wagner et al., 2010; Walsh et al., 2007). Two studies were excluded because antidepressant medication was initiated before scanning (Canli et al., 2005; Keedwell et al., 2010). The papers identified in the search were scrutinised to determine whether they reported data from independent samples. One publication was excluded (Little et al., 1996) as it was a preliminary report of a subsample of the patients of a later paper (Little et al., 2005). Several publications were also identified as reporting on overlapping samples (overlapping sample #1: (Frodl et al., 2011; Samson et al., 2011); overlapping sample #2 (Chen et al., 2007; Fu et al., 2008a; Marquand et al., 2008; Walsh et al., 2007); overlapping sample #3 (Costafreda et al., 2009c; Fu et al., 2008b). The findings from overlapping papers were pooled across publications into a single summary result prior to analysis to ensure that their repeated inclusion did not bias the overall analysis: in summary, results from 15 independent patient samples were included in the functional imaging meta-analysis.

For the structural neuroimaging analysis, the literature search identified 9 studies meeting our inclusion criteria. Of these, 5 publications used whole-brain voxel-based morphometry to predict treatment response (Chen et al., 2007; Costafreda et al., 2009a; Gong et al., 2011; Li et al., 2010; Nouretdinov et al., 2011), reporting results from 3 independent patient samples. We also identified 3 independent publications on the prognostic value of hippocampal volume to predict treatment response (Frodl et al., 2004; MacQueen et al., 2008; Vakili et al., 2000) and 1 study on the predictive value of caudate and lenticular nucleus volume on treatment response (Pillay et al., 1998).

Statistical analysis

We employed two approaches to the quantitative analysis of the data: 1) a modified version of parametric voxel-based meta-analysis (PVM) (Costafreda, 2009; Costafreda et al., 2009b) allowing the pooling of both ROI-based and coordinate-based findings from individual studies and 2) an effect size meta-analysis of the association between hippocampal volume and treatment response. These methods are summarised in the following paragraphs, and further details can be found in our previous publications (Cole et al., 2011; Costafreda, 2009; Costafreda et al., 2009b).

From the studies included in the functional meta-analysis, we extracted the coordinates of activation, their associated effect size, the statistical threshold below which findings were considered non-significant in that study (e.g. $P<0.001$) and the anatomical labels as provided in the paper, for both whole-brain and ROI contrasts. When appropriate, coordinates were transformed from Talairach to the Montreal Neurological Institute coordinate system by using a non-linear transformation (Brett et al., 2002). Effect sizes were also converted from *Z*, *T* or *P* values to *Z*-scores, using as appropriate the cumulative probability function for the *T* distribution and the cumulative distribution function for the standard normal distribution. Three fMRI studies (Costafreda et al., 2009c; Fu et al., 2008a; Marquand et al., 2008) employed pattern recognition approaches exclusively which did not produce classical effect sizes estimates, and were therefore not used in this meta-analysis. For ROI studies, anatomical locations as described by the study's authors were transformed to the coordinates of the centroid of the anatomical area, as determined in the standard automated anatomical labelling (AAL) scheme described by Tzourio-Mazoyer et al. (2002). Summary maps for each study were then created by convolving the effect sizes for each