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Review

Imaging predictors of remission to anti-depressant medications in major depressive disorder

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ABSTRACT

Background: We review what is currently known about neuroimaging predictors of remission in major depressive disorder (MDD) after antidepressant medication (ADM) treatment.
Methods: A systematic literature search found a total of twenty-seven studies comparing baseline neuroimaging findings in depressed patients who achieved remission with non-remitters following treatment with ADMs.
Results: Eighteen of these studies utilised structural magnetic resonance imaging (MRI). These studies associated larger hippocampal (four studies) and cingulate volume (two studies) with remission. Two diffusion MRI studies identified a positive relationship between the fractional anisotropy of the cingulum bundle and remission. White matter signal hyperintensities were quantified in two papers – both observing decreased remission rates with increasing lesion burden. Nine studies on functional imaging met inclusion criteria – three using functional MRI, one with single photon emission computed tomography (SPECT), and five which evaluated patients with positron emission tomography (PET). These findings were not convergent, with different regions of interest interrogated.
Limitations: The studies were generally underpowered. Overall these data were heterogeneous with only a small number identifying concordant findings.
Conclusions: At present, the data remains inconsistent. The more promising biomarker of remission to ADMs appears to be hippocampal size, although this marker also has conflicting reports. Given remission should be the primary end-point of treatment, and that ADMs are the front-line treatment type for MDD, more focussed research is required to focus specifically on the imaging correlates of remission to ADMs.

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1. Background

Anti-depressant medications (ADM) are the front-line treatment for major depressive disorder (MDD), however less than two thirds of patients respond to the initial treatment, and even fewer achieve remission (Rush et al., 2008). Neuroimaging does not have a current role in either the diagnosis or clinical management of MDD. Multiple imaging studies have shown both structural and functional disturbances in the brains of MDD patients, some of which are modulated by treatment with ADMs and other forms of therapy. Research has uncovered a variety of potential biomarker predictors of treatment outcome across a variety of modalities including genetics, endocrinology, electrophysiology and imaging, however none have yet been translated into routine clinical practise (Breitenstein et al., 2014). These biomarkers may enable clinicians to more precisely match patients to treatment types, and therefore represent an important potential means for personalising and improving care. Imaging has been highlighted as a potentially critical means to understand and predict the effects of treatment. However, the majority of imaging studies of treatment outcome in depression have used *response* as the outcome measure, while a much more modest number of studies addressing possible imaging predictors for *remission*. While response may reflect an immediate relief of symptoms, achieving remission is the ultimate goal of treatment. Hence imaging the neural correlates of remission is a critical step toward the practical use of imaging in clinical psychiatry. Here, we review the existing data pertaining to imaging tests that predict remission to ADMs.

Although other treatment options are available, ADMs are the dominant treatment for MDD and the use of this class of treatment is on the rise. Between 1987 and 1997, the percentage of depressed patients in the US receiving antidepressants doubled from 37.3% to 74.5% (Olfson et al., 2002). ADM treatment response rates range from 50% to 65% (Papakostas and Fava, 2009; Thase et al., 2005), however the rate of remission is much lower at approximately 30–40%, with the probability of remission to ADM decreasing with each unsuccessful trial (Gartlehner et al., 2012; Hansen et al., 2008). There are currently no objective measures to guide the treatment decisions in MDD, and the clinical standard of care essentially involves trial and error of different agents (Rush et al., 2008). These iterative cycles of different medications represent an enormous burden of direct healthcare costs, are associated with indirect economic losses and cause a substantial increase in the total healthcare burden associated with MDD. A consequence of this suboptimal treatment cycle is that a significant proportion of patients will not only fail to improve, but are also at risk of clinical deterioration. If effective imaging predictors of antidepressant remission were available, not only would remitters be steered more quickly to effective medications, but the subgroup of patients most unlikely to remit with ADMs could also be directed toward other treatment options earlier.

Neuroimaging of MDD can be subdivided into structural and functional measures. Structural measures include magnetic resonance imaging (MRI) measurements of grey matter (GM) using T1-weighted volumetric data; white matter (WM) tractography using diffusion tensor imaging (DTI) and WM lesion determination using FLAIR or T2-weighted imaging. GM volume is typically assessed using voxel-based morphometry (VBM), which involves a voxel-by-voxel comparison of GM partitions in the brain (Ashburner and Friston, 2000; Mechelli et al., 2005). The integrity of WM tracts can be assessed with diffusion tensor imaging (DTI) by evaluating the fractional anisotropy (FA) of water molecule diffusion along axonal fibres, either directly or assessing connectivity using various forms of WM tractography (Jones and Leemans, 2011; Stieltjes et al., 2001). White matter hyperintensities (WMH) can be quantified with automated software or manual delineations and have been more relevant in studies of late-life depression (LLD), given the relatively higher burden of these lesions seen in this patient group (Wu et al., 2006).

Functional studies comprise both nuclear imaging and MRI. Regional cerebral blood flow (CBF) can be evaluated with either positron emission tomography (PET), MR perfusion or single photon emission computed tomography (SPECT) (Ito et al., 2006). Metabolism can be measured using 18-fluordeoxyglucose (FDG) PET, which accounts for the majority of PET studies in this area (Su et al., 2014). In addition, PET and SPECT radioligands can be used to estimate the degree of binding of a wide variety of neuroreceptors implicated in depression (Smith and Jakobsen, 2013). Assessment of intracranial metabolite levels can also be achieved with magnetic resonance spectroscopy (MRS), however little work has been performed using these tools to specifically evaluate remission to ADM treatment.

Functional MRI (fMRI) is the dominant method for the evaluation of functional brain features in MDD. The basis of fMRI is blood-oxygenation level dependent (BOLD) contrast, which is dependent on the increases in MRI signal that result from alterations in the ratio of oxygenated (paramagnetic) and deoxygenated (diamagnetic) blood in areas of high metabolic activity (Logothetis and Wandell, 2004) during performance of specific tasks. Functional MRI can also be conducted with subjects in the resting state i.e. in the absence of performance tasks. Task-based fMRI evaluates neural activity in depressed patients using a variety of cognitive and emotional paradigms. Tasks used to probe emotion function using facial expressions have been widely studied and have revealed abnormal activations in a number of cortico-limbic structures in MDD, notably the amygdala, where hyperactivity in