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Mood Disorders (AH Young, Section Editor)

# Recent Advances in Neuroimaging of Mood Disorders: Structural and Functional Neural Correlates of Depression, Changes with Therapy, and Potential for Clinical Biomarkers

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## Opinion Statement

Major depressive disorder (MDD) is associated with key regions of the brain involved in emotional processing. The present meta-analysis revealed widespread structural reductions in limbic and prefrontal regions that occur in MDD, with no regions of increased grey matter volume. Functional impairments involve many of the same regions with dysregulated interactions between limbic and cortical structures. Longitudinal treatment studies have predominantly investigated pharmacological therapies, and there have been fewer studies of psychological treatments. Reports of increased hippocampal

volume and reductions in amygdala activation following treatment suggest implications for the course of illness and the impact of pharmacological as well as psychological therapies. Measures of regional brain volume and activity during an acute depressive episode prior to or early in the course of treatment offer the potential to develop predictors of clinical response. High predictive accuracy at the level of the individual is essential for translation of these findings to clinical use. Development of such biomarkers may help to guide treatment strategies, particularly for individuals who may not benefit from current first-line therapeutic options, in order to preclude a potential series of ineffective treatment trials.

## Introduction

Major depression is one of the top contributors to the global burden of disease [1, 2]. It is an often debilitating disorder that typically follows a recurring and relapsing course of illness. At present, the diagnostic criteria of depression include an assessment of mood as well as cognitive and somatic symptoms, and treatment decisions are based on clinical characteristics such as severity and course of the illness as well as past treatment response. Evidence-based treatments for depression include antidepressant medications and psychological therapies, individually or in combination, but remission rates have been relatively modest [3]. To date, there are no biological markers that are used in clinical practice to diagnose the disorder or to predict treatment response [4••, 5•].

Structural and functional magnetic resonance imaging (MRI) studies have sought to delineate the brain abnormalities associated with depression and to examine the effects of treatment. Understanding the neurobiological mechanisms that contribute to the pathogenesis of the disorder may also provide models in the development of biomarkers for diagnosis, prognosis, and response prediction [5•]. Often, fMRI studies in depression have used experimental paradigms such as tasks of affective and cognitive processing to engage the regions that may be impaired. Connectivity analyses provide an additional understanding of the interactions among brain regions. Longitudinal treatment studies have predominantly focussed on antidepressant treatment, and selective serotonin reuptake inhibitors (SSRIs) in particular, while there have been fewer studies of psychological treatments [6••]. Identifying neurobiological correlates of treatment response and establishing biological markers of diagnosis and response prediction will require high predictive accuracy at the individual level as well as a measure of the confidence of the prediction [7]. In this way, treatment strategies could be personalised, in particular to identify patients with more severe forms of the disorder early in the course of their illness in order to prevent a potential series of ineffective treatment trials.

# Structural and Functional Neural Correlates of Depression

MRI studies have revealed structural and functional brain abnormalities associated with MDD in limbic and prefrontal regions, key areas involved in emotional processing and regulation. In our meta-analysis of grey matter abnormalities in MDD, we retrieved 34 studies from a systematic literature search of five databases (PubMed, Scopus, Ovid MEDLINE, PsycINFO, and Ovid EMBASE) between January 1995 and June 2012 [8](Table 1). The subjects included a total of 1,341 MDD patients and 1,364 healthy controls. The patient group comprised adults who were both on medication and not taking medication. Neuroimaging studies utilizing region-of-interest (ROI) as well as voxel-based morphometry (VBM) methods were included in order to determine to what extent the methods used in individual studies may have

influenced the results of the meta-analysis. Studies that reported no significant difference in grey matter volume (GMV) or density between patients and control subjects were also included.

The whole-brain analysis revealed volumetric reductions of grey matter in 10 clusters across the brain comprising the right anterior cingulate cortex (ACC), right medial superior frontal gyrus, right dorsolateral prefrontal cortex (DLPFC), bilateral orbitomedial prefrontal cortex, right inferior frontal gyrus opercular part and triangular part, bilateral insula, right claustrum, and the right putamen.

The combined whole-brain and ROI analysis revealed more extensive grey matter reductions across 18 clusters, including the bilateral anterior cingulate, bilateral medial superior frontal gyrus, right DLPFC, left superior frontal gyrus, right inferior frontal gyrus opercular part, bilateral inferior frontal gyrus triangular part, bilateral insula, right claustrum, and right rectus gyrus, in MDD patients compared to controls. In addition to the whole-brain findings, grey matter reductions were also significant in the bilateral parahippocampal gyrus, left thalamus, and left postcentral gyrus. Notably, there was no increased grey matter volume found in any region in either the whole-brain or combined whole-brain and ROI analyses.

The ACC is a region consistently implicated throughout the course of MDD. Structural magnetic resonance imaging (sMRI) studies have demonstrated total volume reductions present in the ACC in never-treated MDD patients [9, 10]. Studies of medication-naïve and medication-free samples may provide further elucidation of brain abnormalities more directly related to MDD itself, without potentially confounding effects of medication. Voxel-based morphometry (VBM) analysis of sMRI data have shown that ACC grey matter density is significantly reduced in medication-free and medication-naïve patients [11–13]. Reduced white matter volumes have also been reported in the right ACC [14].

There is evidence that such structural abnormalities have functional consequences likely related to impairments in emotional processing [15]. For example, increased activity of the ACC as well as in the amygdala, anteromedial prefrontal cortex, parahippocampus, and insula regions in response to negative images has been observed in unmedicated depressed patients [16], and altered functional connectivity has been reported in subgenual ACC networks of medication-naïve MDD adolescents when evaluating negative emotional stimuli [17]. MDD is associated with dysregulated interconnections within limbic–cortical structures, particularly between the ACC and amygdala [18, 19].

In the amygdala, reduced volumes have been reported in both region-of-interest [20] and VBM [11, 21] studies. Functional activation tasks have demonstrated abnormal and greater amygdala response to negative emotion in MDD patients at baseline prior to antidepressant treatment as compared to controls [4••, 16, 22–24]. Studies have revealed decreased functional connectivity between the amygdala and PFC, including the ACC, in response to negative emotional stimuli [19, 25], and the amygdala and left anterior insula networks in whole-brain resting-state studies of medication-naïve MDD [26]. It is clear that MDD modulates amygdala responsivity and widespread functional connectivity to prefrontal cortical regions [19].

**Table 1. Demographic summary of studies included in meta-analysis [8]**

| Study | Patients | | Healthy controls | | Depression rating scale (score) | Medication status | Illness duration | Anxiety disorder | Matching | Tesla |
|---|---|---|---|---|---|---|---|---|---|---|
| | N (m/f) | Age mean±SD | N (m/f) | Age mean ±SD | | | | | | |
| Abe et al. (2010) [93] | 21 (11/10) | 48.1 (13.5) | 42 (22/20) | 48 (13.2) | 17-HDRS =9.2 | 19/21 on AD; 2/21 Medication-free | - | Not excluded | Age, gender | 1.5 |
| Amico et al. (2011) [14] | 33 (19/14) | 32 (8) | 94 (53/41) | 30.55 (8.15) | 21-HDRS =23 | 27/33 on AD; 6/33 Medication-free | 3.4 years | Excluded | - | 1.5 |
| Avila et al. (2011) [94] | 48 (14/34) | 70.04 (6.67) | 31 (8/23) | 70.29 (7.24 | HDRS =18.58 | 8/48 on AD | - | Not excluded | Age | 1.5 |
| Bergouignan et al. (2009) [95] | 21 (4/17) | 33.16 (9.58) | 21 (7/14) | 28.21 (5.5) | MADRS= 28.71 / BDI= 19.36 | 21/21 on AD | 8.45 years | Not excluded | Age, level of education | 1.5 |
| Cheng et al. (2010) [96] | 68 (21/47) | 29.91 (7.92) | 68 (21/47) | 30.54 (7.3) | 17-HDRS= 22.32 | 68/68 Medication-free | 10.98 months | Excluded | Sex, age, education | 1.5 |
| Egger et al. (2008) [97] | 14 (4/10) | 71.4 (7.49) | 20 (7/13) | 72.3 (7.77) | GDS=21.14 | 10/14 on AD | - | - | Sex, age, education | 1.5 |
| Frodl et al. (2008) [98] | 77 (42/35) | 46.1 (11.3) | 77 (42/35) | 43.6 (11.3) | 21-HDRS= 22.8 | 61/77 on AD; 16/77 Medication-free | 5.4 years | Excluded | Age, gender, handedness | 1.5 |
| Hwang et al. (2010) [99] | 70 (70/0) | 79.4 (5.3) | 26 (26/0) | 79.5 (4.3) | HDRS=29.2 | - | Suicidal depressive 6.5 months Non-suicidal depressive 9.5 months | - | Age and education | 2 |
| Inkster et al. (2010) [100] | 145 (51/94) | 49 (13.3) | 183 (73/ 110) | 48 (13.3) | SCAN=5.5 | 119/145 on AD, last 6 months | 14.3 months | Not excluded | Age, gender, ethnicity | 1.5 |
| Kim et al. (2008) [101] | 22 (0/22) | 38.5 (9.7) | 25 (0/25) | 35.3 (11.25) | BDI=22.3 | 10/22 on AD; 12/22 Medication-free | - | Excluded | Age, education | 1.5 |
| Koolschijn et al. (2010) [102] | 28 (0/28) | 64.04 (10.9) | 38 (0/38) | 61.89 (11.03) | MADRS =18.3 | 17/28 on AD | 31 years | Excluded | Age, gender, handedness, education, health status | 1.5 |
| Lai et al. (2010) [12] | 16 (5/11) | 37.91 (8.76) | 15 (4/11) | 34.3 (9.87) | HDRS =35.91 | 16/16 Medication-naïve | 17.5 weeks | Not excluded | Age, sex, handedness | 3 |
| Lee et al. (2011) [103] | 47 (5/42) | 46 (9.1) | 51 (5/46) | 45.7 (8.04) | 17-HDRS =20.1 | 29/47 on AD 18/47 Medication-naïve | 46.7 months | Excluded | - | 1.5 |
| Leung et al. (2009) [104] | 17 (0/17) | 45.5 (8.5) | 17 (0/17) | 45.8 (9.8) | BDI=29.7 | 17/17 on AD | 7 years | Excluded | Age, intelligence | 1.5 |
| Li et al. (2010) [105] | 44 (11/33) | 44.5 (11.7) | 25 (6/19) | 40.6 (12.7) | 17-HDRS =21.9 | 44/44 on AD | Non-Remitting MDD 9.4 years; Remitting MDD 9 years | Not excluded | Age, gender, handedness | 1.5 |

**Table 1.** (Continued)

| Study | Patients N (m/f) | Age mean ± SD | Healthy controls N (m/f) | Age mean ± SD | Depression rating scale (score) | Medication status | Illness duration | Anxiety disorder | Matching | Tesla |
|---|---|---|---|---|---|---|---|---|---|---|
| Mak et al. (2009) [106] | 17 (0/17) | 45.5 (8.5) | 17 (0/17) | 45.8 (9.8) | BDI=29.7 | 17/17 on AD | - | Excluded | Age, intelligence | 1.5 |
| Mwangi et al. (2012) [107] | 30 (11/19) | 45.4 (11.25) | 32 (14/18) | 41.8 (11.75) | BDI=30.45 / HDRS= 25.54 | 25/30 on AD 5/30 Medication-free | >3 months | Not excluded | Age, gender, intelligence | 1.5 |
| Peng et al. (2011) [28] | 22 (8/14) | 46.7 (8.9) | 30 (11/19) | 45.9 (9) | 17-HDRS= 18.5 | 5/22 on AD | 8.6 months | Excluded | Age, gender, education | 3 |
| Pizzagalli et al. (2004) [108] | 38 (15/23) | 34.8 (10.85) | 18 (8/10) | 38.1 (13.6) | HDRS=19.15 | 38/38 Medication-free, 2 months | - | Not excluded | - | 1.5 |
| Ries et al. (2009) [109] | 15 (5/10) | 66.3 (5.3) | 32 (14/18) | 68.4 (7.4) | CES-D = >10 | - | - | Excluded | Age, gender | 3 |
| Salvadore 2et al. (2011) [29] | Currently depressed 58 (21/37) Remitted 27 (6/21) | Currently depressed 38.8 (11.1) Remitted 40.2 (12.2) | 107 (47/60) | 36.2 (10.3) | MADRS Currently depressed = 26 | 58/58 Medication-free | Currently depressed 18.4 years Currently remitted 15.1 years | Excluded | - | 3 |
| Scheuerecker et al. (2010) [35] | 13 (10/3) | 37.9 (10.1) | 15 (10/5) | 35.5 (10.9) | HDRS =20.5 | 13/13 Medication free | 52.3 months | Excluded | Age, sex, handedness | 3 |
| Shah et al. (1998) [110] | TRD 20 (13/7) Remitted 20 (13/7) | TRD 48.9 (9.8) Remitted 47.7 (9.9) | 20 (13/7) | 49.3 (11.8) | 17-HDRS TRD=20.6 | 20/20 on AD | TRD 263 weeks Remitted 76 weeks | Excluded | Age, gender, intelligence, education | 1 |
| Soriano-Mas et al. (2011) [111] | 70 (29/41) | 61.56 (9.68) | 40 (17/23) | 59.23 (7.09) | 17-HDRS =28.6 | 50/70 on AD 20/70 Medication-free | 10.45 years | Excluded | - | 1.5 |
| Tang et al. (2007) [11] | 14 (0/14) | 29.5 (6.84) | 13 (0/13) | 29.46 (6.86) | 17-HDRS = >18 | 14/14 Medication-free | - | Not excluded | Age, education, family history | 1.5 |
| Treadway et al. (2009 ) [112] | 19 (9/10) | 35.2 (10.5) | 19 (9/10) | 30.3 (8.6) | HDRS =21.5 | 19/19 Medication-free | 12.9 years | Not excluded | Age and gender | 3 |
| Taki et al. (2005) [113] | 34 (13/21) | 72.37 (1.7) | 109 (55/54) | 72.17 (1.73) | GDS=18.6 | 34/34 Medication-free | - | Not excluded | Age | 0.5 |
| VanTol et al. (2010) [114] | 68 (24/44) | 37.16 (10.24) | 65 (24/41) | 40.54 (9.71) | MADRS =13.1 | 58/156 on AD | 13 months | Not excluded | Age, sex, handedness | 3 |
| Vasic et al. (2008) [115] | 15 (9/6) | 37.4 (8.5) | 14 (8/6) | 31.4 (9.6) | 21-HDRS= 16.9 | 15/15 on AD | 43.4 months | Excluded | Age, handedness, education and intelligence | 1.5 |
| Wagner et al. (2008) [27] | 15 (0/15) | 41.4 (9.2) | 16 (0/16) | 38.8 (9.1) | HDRS=23.5 | 15/15 Medication-free, 1 week prior | 7.5 months | Excluded | Age and education | 1.5 |
| Wagner et al. | 30 (5/25) | 37.55 (11.5) | 30 (5/25) | 35.1 (10.4) | 21-HDRS High | - | High risk suicide | Excluded | Gender, age and | 1.5 |

**Table 1.** (Continued)

| Study | Patients N (m/f) | Age mean±SD | Healthy controls N (m/f) | Age mean ±SD | Depression rating scale (score) | Medication status | Illness duration | Anxiety disorder | Matching | Tesla |
|---|---|---|---|---|---|---|---|---|---|---|
| (2011) [116] | | | | | risk suicide = 23.9 Non-high-risk suicide = 25.7 | | 8.9 years Non-high risk suicide 3 years | | education | |
| Yuan et al. (2008) [117] | 19 (9/10) | 67.1 (7.2) | 16 (8/8) | 67.7 (3.8) | HDRS =3.1 | 19/19 Medication-free, 3 months prior | 3.7 years | Excluded | Age | 1.5 |
| Zhang et al. (2009) [118] | 15 (10/5) | 33.5 (10.2) | 15 (10/5) | 33.4 (10.2) | 17-HDRS =21.1 | 15/15 on AD | 10.3 years | Excluded | Age, sex, handedness and education | 3 |
| Zhou et al. (2010) [119] | 23 (10/13) | 31.1 (10.4) | 23 (10/13) | 36.6 (12.9) | 17-HDRS = >18 | 23/23 Medication-naïve | 7.6 months | Excluded | - | 3 |

AD = Antidepressants, TRD = Treatment-Resistant Depression, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery–Asberg Depression Rating Scale, GDS = Geriatric Depression Scale, SCAN = Schedules for Clinical Assessment in Neuropsychiatry, BDI = Beck Depression Inventory

The DLPFC has been consistently implicated in MDD, with reduced volume observed in the majority of studies [27–31], including in medication-naïve and medication-free MDD patients [32]. In a study of medication-naïve subjects, Wu et al. [33] reported abnormalities in white matter fibres compromising the connectivity within dorsolateral–prefrontal circuits. Healthy controls with a family history of MDD have also been shown to exhibit smaller volumes of white matter in the DLPFC [14]. As the DLPFC plays an important role in working memory and executive functions, disruptions of the DLPFC, in connection with other cortical and subcortical regions as part of the limbic–cortical dysregulation model, contribute to diminished cognitive ability and disturbances in social behaviour and emotional regulation [34].

Reductions in orbitofrontal cortex (OFC) volume in MDD are thought to be associated with functional alterations in the network of emotion regulation [35]. In a study that combined fMRI and VBM methods, unmedicated patients performing a Stroop task demonstrated hyperactivation of the ACC that was inversely correlated with GMV reduction in the OFC [27]. Frodl et al. [36] reported decreased connectivity between the OFC and the ACC, thought to be associated with a deficit in regulating self-schemas, and increased connectivity between the OFC and the DLPFC, demonstrating greater neural response to negative stimuli in drug-free patients with MDD. In resting-state fMRI, Zhang et al. [37] reported a decrease in functional activity in an affective network between the amygdala and OFC in first-episode medication-naïve MDD adolescents.

One of the most replicated findings in MDD is decreased hippocampal volume [38, 32], which is evident at the first episode of depression [39]. Recurrent episodes can lead to further volume reductions in the hippocampus over the course of the disorder, which may also contribute to symptoms of cognitive decline in MDD [40].

MDD is also associated with increased GMV in the thalamus [31, 32, 41] and the right insula [31] of medication-naïve first-episode MDD individuals. Decreased grey matter density in the thalamus has been proven to be a significant diagnostic marker of depression in medication-free MDD [42]. The thalamus has extensive connections with cortical and limbic structures and is believed to be involved in consciousness, awareness, and arousal. Abnormal functioning of the thalamus may contribute to symptoms such as disturbed sleep patterns. The insula is a structure that has been implicated in interoceptive awareness [43]. During an interoceptive attention task, the dorsal mid-insula exhibited decreased activity in unmedicated MDD subjects compared to controls [44]. Decreased activity has also been associated with severity of depression and somatic symptoms in depressed subjects.

## Structural Changes with Antidepressant Treatment

Antidepressants such as selective serotonin reuptake inhibitors (SSRIs), which are widely used in the treatment of depression, have been reported

to alter the structure of frontal-subcortical circuits involved in the pathophysiology of depression [31, 45, 46•, 47, 48].

Increases in hippocampal volume have been reported following eight weeks of treatment with citalopram [46•] as well as following three years of treatment with various antidepressant medications [47]. Volume increases have also been reported in the dorsolateral and orbitofrontal cortices following treatment with fluoxetine [31]. The hippocampus is involved in declarative or explicit memory function [49, 50], and these findings may be consistent with the amelioration of memory impairments in depressed patients [51] following antidepressant treatment [52, 53].

However, not all studies have found alterations in brain volume of depressed patients following antidepressant treatment [54, 55]). In addition, a decrease in volume in the dorsolateral prefrontal cortex has been reported [56]. More research is needed to delineate volume change and direction of volume change associated with antidepressant treatment and improved mood and function.

## Functional Changes with Antidepressant Treatment

The effects of antidepressant treatment on affective processing networks have been more widely studied, as there is a mood-congruent processing bias evident in patients with depression. This negative bias is evident in the processing of facial expressions [57], and MDD patients show both implicit and explicit attentional biases toward negative stimuli and away from positive stimuli [58]. fMRI studies often use implicit emotional processing paradigms such as a gender decision task, as these tasks are more likely to elicit activations in subcortical and extrastriate cortical regions [59].

Implicit processing of sad facial expressions has revealed abnormal activations in corticolimbic regions such as the amygdala [24, 60], insula and anterior cingulate [24] at baseline, followed by significant decreases in the amygdala following treatment with antidepressants [24, 62]. Happy facial expressions, on the other hand, tend to be associated with decreased corticolimbic activations in patients compared to controls, and which normalize following antidepressant treatment [63]. Moreover, amygdala activations are also observed during passive viewing of negative stimuli [16, 64] which attenuate with treatment [64]. Conversely, explicit labelling of emotions is likely to decrease the probability of amygdala activation compared to passive viewing or implicit processing [59]. There is also some evidence of a lateralization of amygdala activations in which the left rather than the right amygdala is more likely to be activated during processing of evident unmasked emotional stimuli [65–67], and therefore may be more functionally inclined to modulation by antidepressants [67].

The fusiform gyrus is important in face processing [65], and is typically engaged during explicit processing of emotional stimuli. Similar to amygdalar responses, fusiform gyrus activations are seen in patients versus controls during negative emotional processing, while decreased activations have been observed in patients during processing of positive emotional stimuli [68]. Normalization of the fusiform gyrus activity after antidepressant

treatment is seen during both positive [69] and negative [61] emotional stimuli, suggesting that antidepressants modulate regions that are associated with emotion dysregulation in depression.

In addition to biases in emotional processing, depression is associated with cognitive impairments leading to difficulties in memory and attention. The anterior cingulate is more likely to be activated during tasks of cognitive demand [24, 70], and fMRI studies of cognitive processing have shown increased rostral anterior cingulate activity during Stroop tasks [71, 72] and tasks of cognitive control [73]. Subregions of the anterior cingulate cortex – namely the pregenual and the subgenual ACC – are important targets for antidepressant action [74], and normalization of the frontocingulate activity has been observed with antidepressant treatment [73].

It has been proposed that depression results from abnormal connections between the limbic regions, such as the amygdala, and other parts of the brain. Therefore, in addition to investigating regional brain activations, studies have also looked at the interaction between brain regions that are impaired in depression. Patients with depression show reduced functional connectivity between the frontocortical and limbic regions [16, 19, 67], which is improved following treatment with antidepressants [67].

Activation in the anterior cingulate and orbitofrontal cortex during an acute depressive episode is predictive of subsequent clinical response [6••]. In addition, differences in functional orbitofrontal cortex connectivity prior to treatment have been shown to distinguish responders from non-responders [75]. The anterior cingulate and orbitofrontal cortices play an important role in emotional processing, and the orbitofrontal cortex is particularly associated with reward and hedonic experience [76]. Greater pre-treatment activity in these regions may suggest better ability to process emotions and greater responsivity to hedonic stimuli, and therefore predictive of a clinical response [6••].

## Functional Changes with Cognitive Behavioural Therapy

Fewer studies have investigated the neural correlates of emotional processing following psychotherapy. Most studies have investigated cognitive behavioural therapy (CBT), an effective treatment for major depressive disorder, with rates of efficacy comparable to antidepressant medication [77], and which focuses on modifying dysfunctional thinking and behaviour that are common in depression [78].

Elevated baseline amygdala-hippocampal activity has been identified in depressed patients in comparison to healthy controls during implicit processing of sad facial expressions which ameliorates following a course of cognitive behaviour therapy [60]. Other reported changes in depressed patients following cognitive behavioural therapy have included decreased activation in the medial prefrontal cortex (mPFC) and ventral anterior cingulate cortex (vACC) in response to an emotional processing task [79] and during self-referential processing of negative words [80]. The medial prefrontal cortex is thought to play an important role in self-referential processing of negative stimuli [81], which is a central feature of rumination and depression [82]. These functional changes in activity following CBT treatment may reflect an increased engagement of processes involved in modulating responses to

affect-laden stimuli compatible with a "top-down" mechanism of action [83].

This cortical top-down model of cognitive therapy focuses on altering memory and attention processes that are involved in the mediation of cognitive biases and maladaptive processing of information [84]. There is evidence to suggest that antidepressants may have a mechanism of action similar to cognitive therapy in modulating negative biases and memory impairments in depression, occurring very early in the course of treatment, even before patients report any change in their mood or anxiety [85••, 86]. As such, these treatments may have similar neurobiological mechanisms on common underlying processes, leading to improvement in depression.

## Clinical Neuroimaging Biomarkers in Depression

In addition to examining treatment effects in major depression, identifying biomarkers of clinical response may aid in treatment recommendations as well as in the development of novel strategies to augment existing treatment methods. Our meta-analysis of both pharmacological and psychological treatment studies revealed that higher pre-treatment anterior cingulate activity was a consistent predictor of clinical response, while reduced baseline hippocampal volume and increased insula and striatum activity were indicative of a poorer clinical response [6••]. Anterior cingulate activity as a predictor of clinical response has been widely reported across different antidepressant treatment studies using a variety of tasks, including resting-state [87, 88], emotion processing [23, 74, 89], and cognitive [90] tasks. The predictive function of the anterior cingulate is usually observed in response to negative rather than positive emotional stimuli [23, 74, 89]. Whilst there is strong evidence for increased baseline activation in the anterior cingulate as a predictor for antidepressant response, the evidence for CBT has been more mixed [6••], in part due to the limited number of studies. Further investigation is warranted.

To translate these findings into clinical application, it is important to identify clinical biomarkers with high predictive accuracy at the individual level [5•]. Using neuroimaging measures, it has been possible to identify biomarkers of clinical response even before the start of treatment. To date, there are no biological markers that are used to diagnose the disorder or to predict clinical response. Methods of analyses based on machine learning algorithms have been applied to neuroimaging measures such as structural and functional data to predict diagnosis, course of illness, and treatment prognosis [7]. The pattern of baseline neural activity during sad facial expression accurately classified 84 % of MDD patients and 89 % of healthy controls [4••], while neural correlates of verbal working memory showed reduced accuracy [90]. Baseline neural activity during sad facial processing predicted remission to CBT with a sensitivity of 71 % and specificity of 86 % [91], while remission to antidepressants showed a trend towards significance [4••]. Evidence from structural data, on the other hand, revealed that grey matter density predicted clinical response to antidepressant medication, in particular in the anterior cingulate [42, 92]. Further investigation of neuroimaging as well as other biological measures is required to develop clinically useful biomarkers. This would help optimize treatment strategies, especially for

those who may not benefit from current first-line treatment options that are available for depression.

## Compliance with Ethics Guidelines

**Conflict of Interest**
Lauren Atkinson, Anjali Sankar, Tracey Adams, and Cynthia H.Y. Fu each declare no conflict of interest.

**Human and Animal Rights and Informed Consent**
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance


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