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

*Lauren Atkinson*¹

*Anjali Sankar*²

*Tracey M. Adams*³

Cynthia H. Y. Fu^{2,4*}

Address

¹Department of Psychiatry, University of Oxford, Oxford, UK

²Department of Psychological Medicine, Institute of Psychiatry, King's College London, London, UK

³Psychological Services, Warneford Hospital, Oxford, UK

⁴School of Psychology, University of East London, Water Lane, London, E15 4LZ, UK

Email: c.fu@uel.ac.uk

Published online: 2 July 2014

© Springer International Publishing AG 2014

Keywords Depressive disorder · Emotions · Biological markers · Magnetic resonance imaging · Antidepressive agents · Cognitive behavioural treatment

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 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
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 exclud- ed	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 exclud- ed	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 exclud- ed	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 exclud- ed	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 exclud- ed	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 exclud- ed	Age, gender, handedness	1.5

Table 1. (Continued)

Study	Patients		Healthy controls		Age mean $\pm$ 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)	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)	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)	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)	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)	CES-D = >10	-	-	Excluded	Age, gender	3
Salvadore et al. (2011) [29]	Currently depressed 58 (21/37) Remitted 27 (6/21) 13 (10/3)		Currently depressed 38.8 (11.1) Remitted 40.2 (12.2) 37.9 (10.1)	107 (47/60)		MADRS Currently depressed = 26	58/58 Medication-free	Currently depressed 18.4 years Currently remitted 15.1 years	Excluded	-	3
Scheuercker et al. (2010) [35]	TRD 20 (13/7) Remitted 20 (13/7)		TRD 48.9 (9.8) Remitted 47.7 (9.9) 61.56 (9.68)	40 (17/23)		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) 61.56 (9.68)	20 (13/7)		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)		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)		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)		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)		GDS=18.6	34/34 Medication-free	-	Not excluded	Age	0.5
Van Tol et al. (2010) [114]	68 (24/44)		37.16 (10.24)	65 (24/41)		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)		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)		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)		21-HDRS High	-	High risk suicide	Excluded	Gender, age and	1.5

Table 1. (Continued)

Study	Patients		Healthy controls		Age mean $\pm$ SD	Depression rating scale (score)	Medication status	Illness duration	Anxiety disorder	Matching	Testa
	N (m/f)		N (m/f)								
(2011) [116]						risk suicide = 23.9 Non-high-risk suicide = 25.7 HDRS = 3.1		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)		19/19 Medication-free, prior 3 months	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.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Murray CJ, Lopez AD. Measuring the global burden of disease. *N Engl J Med*. 2013;369(5):448–57.

2. The World Health Report 2000: Health Systems: Improving Performance. World Health Organization, 2000.

3. Ruhe HG, Booij J, Veltman DJ, Michel MC, Schene AH. Successful pharmacologic treatment of major depressive disorder attenuates amygdala activation to negative facial expressions: a functional magnetic resonance imaging study. *J Clin Psychiatry*. 2012;73(4):451–9.

4. •• Fu CH, Mourao-Miranda J, Costafreda SG, Khanna A, Marquand AF, Williams SC, et al. Pattern classification of sad facial processing: toward the development of neurobiological markers in depression. *Biol Psychiatry*. 2008;63(7):656–62.

First publication to identify potential of neural correlates for diagnosis and prognosis in depression with the application of machine learning methods to develop markers with high accuracy at the level of the individual.

5. • Fu CH, Costafreda SG. In Review Neuroimaging-Based Biomarkers in Psychiatry: Clinical Opportunities of a Paradigm Shift. *Can J Psychiat*. 2013;58(9):499–508.

[Class IV] This article examines recent findings on neural biomarkers in psychiatry and its potential clinical applications. This review focusses on machine learning-based approaches to identifying clinical biomarkers; and discusses the clinical opportunities and challenges in developing biomarkers for psychiatric disorders in the absence of a diagnostic gold standard.

6. •• Fu CH, Steiner H, Costafreda SG. Predictive neural biomarkers of clinical response in depression: a meta-analysis of functional and structural neuroimaging

studies of pharmacological and psychological therapies. *Neurobiol Dis*. 2013;52:75–83.

[Class I] This is the only comprehensive meta-analysis performed to date that has examined both structural and functional neuroimaging based biomarkers of clinical response to psychotherapy and antidepressant medication in depression

7. Nouretdinov I, Costafreda SG, Gammernan A, Chervonenkis A, Vovk V, Vapnik V, et al. Machine learning classification with confidence: application of transductive conformal predictors to MRI-based diagnostic and prognostic markers in depression. *Neuroimage*. 2011;56(2):809–13.

8. Atkinson L. Grey matter abnormalities in Major Depressive Disorder: An updated meta-analysis of voxel-based morphometry studies. Unpublished master's thesis, Institute of Psychiatry. Kings College London, London, United Kingdom, 2012.

9. Caetano SC, Kaur S, Brambilla P, Nicoletti M, Hatch JP, et al. Smaller cingulate volumes in unipolar depressed patients. *Biol Psychiatry*. 2006;59:702–6.

10. Yucel K, McKinnon MC, Chahal R, Taylor VH, Macdonald K, et al. Anterior Cingulate Volumes in Never Treated Patients with Major Depressive Disorder. *Neuropsychopharmacol*. 2008;33:3157–63.

11. Tang Y, Wang F, Xie G, Liu J, Li L, et al. Reduced ventral anterior cingulate and amygdala volumes in medication-naïve females with major depressive disorder: A voxel-based morphometric magnetic resonance imaging study. *Psychiat Res*. 2007;156:83–6.

12. Lai CH, Hsu YY, Wu YT. First episode drug-naïve major depressive disorder with panic disorder: Gray matter deficits in limbic and default network structures. *Eur Neuropsychopharmacol*. 2010;20:676–82.
13. Bora E, Fornito A, Pantelis C, Yücel M. Gray matter abnormalities in Major Depressive Disorder: A meta-analysis of voxel-based morphometry studies. *J Affect Disord*. 2012;138:9–18.
14. Amico F, Meisenzahl E, Koutsouleris N, Reiser M, Möller HJ, et al. Structural MRI correlates for vulnerability and resilience to major depressive disorder. *J Psychiatry Neurosci*. 2011;36(1):15–22.
15. Lai CH. Gray matter volume in major depressive disorder: a meta-analysis of voxel-based morphometry studies. *Psychiatry Res*. 2013;211(1):37–46.
16. Anand A, Li Y, Wang Y, Wu J, Gao S, et al. Antidepressant effect on connectivity of the mood-regulating circuit: an fMRI study. *Neuropsychopharmacol*. 2005;30(7):1334–44.
17. Ho TC, Yang G, Wu J, Cassey P, Brown SD, et al. Functional connectivity of negative emotional processing in adolescent depression. *J Affect Disord*. 2014;155:65–74.
18. Matthews SC, Strigo IA, Simmons AN, Yang TT, Paulus MP. Decreased functional coupling of the amygdala and supragenual cingulate is related to increased depression in unmedicated individuals with current major depressive disorder. *J Affect Disord*. 2008;111(1):13–20.
19. Costafreda SG, McCann P, Saker P, Cole J, Cohen-Woods S, et al. Modulation of amygdala response and connectivity in depression by serotonin transporter polymorphism and diagnosis. *J Affect Disord*. 2013;150:96–103.
20. Hamilton JP, Siemer M, Gotlib IH. Amygdala volume in Major Depressive Disorder: A meta-analysis of magnetic resonance imaging studies. *Mol Psychiatr*. 2008;13:993–1000.
21. Kong L, Chen K, Womer F, Jiang W, Luo X, et al. Sex differences of gray matter morphology in cortico-limbic-striatal neural system in major depressive disorder. *J Psychiatr Res*. 2013;47(6):733–9.
22. Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, et al. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol Psychiatry*. 2001;50(9):651–8.
23. Davidson RJ, Irwin W, Anderle MJ, Kalin NH. The neural substrates of affective processing in depressed patients treated with venlafaxine. *Am J Psychiatry*. 2003;160:64–75.
24. Fu CH, Williams SC, Cleare AJ, Brammer MJ, Walsh ND, et al. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. *Arch Gen Psychiatr*. 2004;61(9):877–89.
25. Kong L, Chen K, Tang Y, Wu F, Driesen N, et al. Functional connectivity between the amygdala and prefrontal cortex in medication-naïve individuals with major depressive disorder. *J Psychiatry Neurosci*. 2013;38(6):417–22.
26. Veer IM, Beckmann CF, van Tol MJ, Ferrari L, Milles J, et al. Whole brain resting-state analysis reveals decreased functional connectivity in major depression. *Front Syst Neurosci*. 2010;4:41.
27. Wagner G, Koch K, Schachtzabel C, Reichenbach JR, Sauer H, et al. Enhanced rostral anterior cingulate cortex activation during cognitive control is related to orbitofrontal volume reduction in unipolar depression. *J Psychiatry Neurosci*. 2008;33(3):199–208.
28. Peng J, Liu J, Nie B, Li Y, Shan B, et al. Cerebral and cerebellar gray matter reduction in first-episode patients with major depressive disorder: A voxel-based morphometry study. *Eur J Radiol*. 2011;80:395–9.
29. Salvatore G, Nugent AC, Lemaitre H, Luckenbaugh DA, Tinsley R, et al. Prefrontal cortical abnormalities in currently depressed versus currently remitted patients with major depressive disorder. *Neuroimage*. 2011;54:2643–51.
30. Lai CH, Wu YT. Frontal-insula gray matter deficits in first-episode medication-naïve patients with major depressive disorder. *J Affect Disord*. 2014;160:74–9.
31. Kong L, Wu F, Tang Y, Ren L, Kong D, et al. Frontal-Subcortical Volumetric Deficits in Single Episode, Medication-Naïve Depressed Patients and the Effects of 8 Weeks Fluoxetine Treatment: A VBM-DARTEL Study. *PLoS ONE*. 2014;9(1):e79055.
32. Zhao YJ, Du MY, Huang XQ, Lui S, Chen ZQ, et al. Brain grey matter abnormalities in medication-free patients with major depressive disorder: a meta-analysis. *Psychol Med*. 2014. doi:10.1017/S0033291714000518.
33. Wu F, Tang Y, Xu K, Kong L, Sun W, et al. White matter abnormalities in medication-naïve subjects with a single short-duration episode of major depressive disorder. *Psychiatry Res*. 2011;191:80–3.
34. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biol Psychiatry*. 2003;54(5):515–28.
35. Scheuerecker J, Meisenzahl EM, Koutsouleris N, Roesner M, Schöpf V, et al. Orbitofrontal volume reductions during emotion recognition in patients with major depression. *J Psychiatry Neurosci*. 2010;35(5):311–20.
36. Frodl T, Bokde AL, Scheuerecker J, Lisiecka D, Schöpf V, et al. Functional connectivity bias of the orbitofrontal cortex in drug-free patients with major depression. *Biol Psychiatry*. 2010;67:161–7.

37. Zhang X, Zhu X, Wang X, Zhu X, Zhong M, et al. First-episode medication-naïve major depressive disorder is associated with altered resting brain function in the affective network. *PLoS ONE*. 2014;9(1):e85241. doi:[10.1371/journal.pone.0085241](https://doi.org/10.1371/journal.pone.0085241).
 38. Kempton MJ, Salvador Z, Munafò MR, Geddes JR, Simmons A, et al. Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. *Arch Gen Psychiatr*. 2011;68(7):675–90.
 39. Cole J, Costafreda SG, McGuffin P, Fu CH. Hippocampal atrophy in first episode depression: A meta-analysis of magnetic resonance imaging studies. *J Affect Disord*. 2011;134:483–7.
 40. aan het Rot M, Mathew SJ, Charney DS. Neurobiological mechanisms in major depressive disorder. *Can Med Assoc J*. 2009;180:305–13.
 41. Zhang X, Yao S, Zhu X, Wang X, Zhong M. Gray matter volume abnormalities in individuals with cognitive vulnerability to depression: a voxel based morphometry study. *J Affect Disord*. 2012;136:443–52.
 42. Costafreda SG, Chu C, Ashburner J, Fu CHY. Prognostic and diagnostic potential of the structural neuroanatomy of depression. *PLoS ONE*. 2009;44(7):e6353.
 43. Sliz D, Hayley S. Major depressive disorder and alterations in insular cortical activity: a review of current functional magnetic imaging research. *Front Hum Neurosci*. 2012;6:323.
 44. Avery JA, Drevets WC, Moseman SE, Bodurka J, Barcalow JC, et al. Major Depressive Disorder Is Associated with Abnormal Interoceptive Activity and Functional Connectivity in the Insula. *Biol Psychiatry*. 2013. doi:[10.1016/j.biopsych.2013.11.027](https://doi.org/10.1016/j.biopsych.2013.11.027).
 45. Malykhin NV, Carter R, Seres P, Coupland NJ. Structural changes in the hippocampus in major depressive disorder: contributions of disease and treatment. *J Psychiatry Neurosci*. 2010;35:337–43.
 46. Arnone D, McKie S, Elliott R, Juhasz G, Thomas EJ, Downey D, et al. State-dependent changes in hippocampal grey matter in depression. *Mol Psychiatry*. 2013;18(12):1265–72. doi:[10.1038/mp.2012.150](https://doi.org/10.1038/mp.2012.150).
- This is a recent article suggesting that reduced hippocampal grey matter volume may be involved in the aetiology of depression and risk of relapse
47. Frodl T, Jäger M, Smajstrlova I, Born C, Bottlender R, Palladino T, et al. Effect of hippocampal and amygdala volumes on clinical outcomes in major depression: a 3-year prospective magnetic resonance imaging study. *J Psychiatry Neurosci*. 2008;33(5):423–30.
 48. Kraus C, Ganger S, Losak J, Hahn A, Savli M, Kranz GS, et al. Gray matter and intrinsic network changes in the posterior cingulate cortex after selective serotonin reuptake inhibitor intake. *Neuroimage*. 2014;84:236–44. doi:[10.1016/j.neuroimage.2013.08.036](https://doi.org/10.1016/j.neuroimage.2013.08.036).
 49. Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. *J Neuropsychiatry Clin Neurosci*. 2000;12:103–13.
 50. Zola SM, Squire LR, Teng E, Stefanacci L, Buffalo EA, Clark RE. Impaired recognition memory in monkeys after damage limited to the hippocampal region. *J Neurosci*. 2000;20:451–63.
 51. Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci*. 1999;19:5034–43.
 52. Cassano GB, Puca F, Scapicchio PL, Trabucchi M. Paroxetine and fluoxetine effects on mood and cognitive functions in depressed non-demented elderly patients. *J Clin Psychiatry*. 2002;63:396–402.
 53. Levkovitz Y, Caftori R, Avital A, Richter-Levin G. The SSRI drug Fluoxetine but not the noradrenergic tricyclic drug Desipramine, improves memory performance during acute major depression. *Brain Res Bull*. 2002;58:345–50.
 54. Vythilingam M, Vermetten E, Anderson GM, et al. Hippocampal volume, memory, and cortisol status in major depressive disorder: effects of treatment. *Biol Psychiatry*. 2004;56:101–12.
 55. Janssen J, Hulshoff Pol HE, Schnack HG, Kok RM, Lampe IK, et al. Cerebral volume measurements and subcortical white matter lesions and short term treatment response in late life depression. *Int J Geriatr Psychiatry*. 2007;22:468–74.
 56. Smith R, Chen K, Baxter L, Fort C, Lane RD. Corrigendum to “Antidepressant effects of sertraline associated with volume increases in dorsolateral prefrontal cortex”. *J Affect Disord*. 2013;162:114–5.
 57. Persad SM, Polivy J. Differences between depressed and nondepressed individuals in the recognition of and response to facial emotional cues. *J Abnorm Psychol*. 1993;102(3):358.
 58. Surguladze S, Brammer MJ, Keedwell P, Giampietro V, Young AW, Travis MJ, et al. A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. *Biol Psychiatry*. 2005;57(3):201–9.
 59. Costafreda SG, Brammer MJ, David AS, Fu CH. Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 PET and fMRI studies. *Brain Res Rev*. 2008;58(1):57–70.
 60. Fu CH, Williams SC, Cleare AJ, Scott J, Mitterschiffthaler MT, Walsh ND, et al. Neural responses to sad facial expressions in major depression

- following cognitive behavioral therapy. *Biol Psychiatry*. 2008;64(6):505–12.
61. Frodl T, Scheuerecker J, Schoepf V, Linn J, Koutsouleris N, Bokde AL, et al. Different effects of mirtazapine and venlafaxine on brain activation: an open randomized controlled fMRI study. *J Clin Psychiat*. 2011;72(4):448.
 62. Arnone D, McKie S, Elliott R, Thomas EJ, Downey D, Juhasz G, et al. Increased amygdala responses to sad but not fearful faces in major depression: relation to mood state and pharmacological treatment. *Am J Psychiatry*. 2012;169(8):841–50.
 63. Fu C, Williams S, Brammer M, Suckling J, Kim J, Cleare A, et al. Neural responses to happy facial expressions in major depression following antidepressant treatment. *Am J Psychiatry*. 2007;164(4):599–607.
 64. Anand A, Li Y, Wang Y, Gardner K, Lowe M. Reciprocal effects of antidepressant treatment on activity and connectivity of the mood regulating circuit: an FMRI study. *J Neuropsychiatry Clin Neurosci*. 2007;19(3):274–82.
 65. Iidaka T, Omori M, Murata T, Kosaka H, Yonekura Y, Okada T, et al. Neural interaction of the amygdala with the prefrontal and temporal cortices in the processing of facial expressions as revealed by fMRI. *J Cognitive Neurosci*. 2001;13(8):1035.
 66. Adolphs R. Neural systems for recognizing emotion. *Curr Opin Neurobiol*. 2002;12(2):169–77.
 67. Chen CH, Suckling J, Ooi C, Fu CH, Williams SC, Walsh ND, et al. Functional coupling of the amygdala in depressed patients treated with antidepressant medication. *Neuropsychopharmacol*. 2007;33(8):1909–18.
 68. Groenewold NA, Opmeer EM, de Jonge P, Aleman A, Costafreda SG. Emotional valence modulates brain functional abnormalities in depression: evidence from a meta-analysis of fMRI studies. *Neurosci Biobehav Rev*. 2013;37(2):152–63.
 69. Jiang W, Yin Z, Pang Y, Wu F, Kong L, Xu K. Brain functional changes in facial expression recognition in patients with major depressive disorder before and after antidepressant treatment A functional magnetic resonance imaging study. *Neural Regen Res*. 2012;7(15):1151–7.
 70. Duncan J, Owen AM. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci*. 2000;23(10):475–83.
 71. Wagner G, Sinsel E, Sobanski T, Köhler S, Marinou V, Mentzel HJ, et al. Cortical inefficiency in patients with unipolar depression: an event-related FMRI study with the Stroop task. *Biol Psychiatry*. 2006;59(10):958–65.
 72. Mitterschiffthaler M, Williams S, Walsh N, Cleare A, Donaldson C, Scott J, et al. Neural basis of the emotional Stroop interference effect in major depression. *Psychol Med*. 2008;38(2):247.
 73. Wagner G, Koch K, Schachtzabel C, Sobanski T, Reichenbach JR, Sauer H, et al. Differential effects of serotonergic and noradrenergic antidepressants on brain activity during a cognitive control task and neurofunctional prediction of treatment outcome in patients with depression. *J Psychiatry Neurosci JPN*. 2010;35(4):247.
 74. Chen CH, Ridler K, Suckling J, Williams S, Fu CH, Merlo-Pich E, et al. Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. *Biol Psychiatry*. 2007;62(5):407–14.
 75. Lisiecka D, Meisenzahl E, Scheuerecker J, Schoepf V, Whitty P, Chaney A, et al. Neural correlates of treatment outcome in major depression. *Int J Neuropsychopharmacol*. 2011;14(4):521.
 76. Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience. *Nat Rev Neurosci*. 2005;6(9):691–702.
 77. DeRubeis RJ, Hollon SD, Amsterdam JD, Shelton RC, Young PR, Salomon RM, et al. Cognitive therapy vs medications in the treatment of moderate to severe depression. *Arch Gen Psychiat*. 2005;62:409–16.
 78. Beck AT, Shaw B, Rush J, Emery G. *Cognitive Therapy for Depression*. New York: Guilford Press; 1979.
 79. Ritchey M, Dolcos F, Eddington KM, Strauman TJ, Cabeza R. Neural correlates of emotional processing in depression: changes with cognitive behavioral therapy and predictors of treatment response. *J Psychiat Res*. 2011;45(5):577–87.
 80. Yoshimura S, Okamoto Y, Onoda K, Matsunaga M, Okada G, Kunisato Y, et al. Cognitive behavioral therapy for depression changes medial prefrontal and ventral anterior cingulate cortex activity associated with self-referential processing. *Soc Cogn Affect Neurosci*. 2014;9(4):487–93. doi:10.1093/scan/nst009.
 81. Kelley WM, Macrae CN, Wyland CL, Caglar S, Inati S, Heatherton TF. Finding the self? An event-related fMRI study. *J Cognitive Neurosci*. 2002;14(5):785–94.
 82. Nolen-Hoeksema S, Wisco BE, Lyubomirsky S. Rethinking rumination. *Perspect Psychol Sci*. 2008;3(5):400–24.
 83. Goldapple K, Segal Z, Garson C, et al. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. *Arch Gen Psychiat*. 2004;61(1):34–41.
 84. Clark DA, Beck AT. Cognitive theory and therapy of anxiety and depression: Convergence with neurobiological findings. *Trends Cogn Sci*. 2010;14:418–24.
 85. Harmer C, O'Sullivan U, Favaron E, Massey-Chase R, Ayres R, Reineck A, et al. Effect of acute antidepressant administration on negative affective bias in depressed patients. *Am J Psychiatry*. 2009;166:1178–84.
- Findings have important implications for early effects of antidepressant treatment on neural correlates of depression.

86. Harmer C, Heinzen J, O'Sullivan U, Ayres R, Cowen P. Dissociable effects of acute antidepressant drug administration on subjective and emotional processing measures in healthy volunteers. *J Psychopharmacol*. 2008;199:495–502.
87. Kennedy S, Konarski J, Segal Z, Lau M, Bieling P, McIntyre R, et al. Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. *Am J Psychiatry*. 2007;164(5):778–88.
88. Konarski JZ, Kennedy SH, Segal ZV, Lau MA, Bieling PJ, McIntyre RS, et al. Predictors of non-response to cognitive behavioural therapy or venlafaxine using glucose metabolism in major depressive disorder. *J Psychiatry Neurosci: JPN*. 2009;34(3):175.
89. Keedwell PA, Drapier D, Surguladze S, Giampietro V, Brammer M, Phillips M. Subgenual cingulate and visual cortex responses to sad faces predict clinical outcome during antidepressant treatment for depression. *J Affect Disord*. 2010;120(1):120–5.
90. Marquand AF, Mourão-Miranda J, Brammer MJ, Cleare AJ, Fu CH. Neuroanatomy of verbal working memory as a diagnostic biomarker for depression. *Neuroreport*. 2008;19(15):1507–11.
91. Costafreda SG, Khanna A, Mourao-Miranda J, Fu CH. Neural correlates of sad faces predict clinical remission to cognitive behavioural therapy in depression. *Neuroreport*. 2009;20(7):637–41.
92. Gong Q, Wu Q, Scarpazza C, Lui S, Jia Z, Marquand A, et al. Prognostic prediction of therapeutic response in depression using high-field MR imaging. *Neuroimage*. 2011;55(4):1497–503.
93. Abe O, Yamasue H, Kasai K, Yamada H, Aoki S, et al. Voxel-based analyses of gray/white matter and diffusion tensor data in major depression. *Psychiatry Res*. 2010;181:64–70.
94. Avila R, Ribeiz S, Duran FLS, Arrais JPI, Moscoso MAA, et al. Effect of temporal lobe structure volume on memory in elderly depressed patients. *Neurobiol Aging*. 2011;32:1857–67.
95. Bergouignan L, Chupin M, Czechowska Y, Kinkingnéhun S, Lemogne C, Le Bastard G, et al. Can voxel-based morphometry, manual segmentation, and automated segmentation equally detect hippocampal volume differences in acute depression? *Neuroimage*. 2009;45:29–37.
96. Cheng Y, Xu J, Chai P, Li H, Luo C, Yang T, et al. Brain volume alteration and the correlations with the clinical characteristics in drug-naïve first-episode MDD patients: A voxel-based morphometry study. *Neurosci Lett*. 2010;480:30–4.
97. Egger K, Schocke M, Weiss E, Auffinger S, Esterhammer R, Goebel G, et al. Pattern of brain atrophy in elderly patients with depression revealed by voxel-based morphometry. *Psychiatry Res*. 2008;164:237–44.
98. Frodl T, Koutsouleris N, Bottlender R, Born C, Jäger M, Mörgenthaler M, et al. Reduced gray matter brain volumes are associated with variants of the serotonin transporter gene in major depression. *Mol Psychiatry*. 2008;13:1093–101.
99. Hwang J, Lee T, Tsai S, Chen T, Yang C, Limg J, et al. Cortical and subcortical abnormalities in late-onset depression with history of suicide attempts investigated with MRI and voxel-based morphometry. *J Geriatr Psychiatry Neurol*. 2010;23(3):171–84.
100. Inkster B, Rao AW, Ridler K, Nichols TE, Saemann PG, Auer D, et al. Structural brain changes in patients with recurrent major depressive disorder presenting with anxiety symptoms. *J Neuroimaging*. 2011;21(4):375–82.
101. Kim MJ, Hamilton JP, Gotlib IH. Reduced caudate gray matter volume in women with major depressive disorder. *Psychiatry Res*. 2008;164:114–22.
102. Koolschijn PC, van Haren NE, Schnack HG, Janssen J, Hulshoff Pol HE, Kahn RS. Cortical thickness and voxel-based morphometry in depressed elderly. *Eur Neuropsychopharmacol*. 2010;20:398–404.
103. Lee KH, Tae WS, Yoon H, Lee B, Paik J, Son K, et al. Demonstration of decreased gray matter concentration in the midbrain encompassing the dorsal raphe nucleus and the limbic subcortical regions in major depressive disorder: An optimized voxel-based morphometry study. *J Affect Disord*. 2011;133:128–36.
104. Leung KK, Lee TM, Wong MM, Li LS, Yip PS, Khong PL. Neural correlates of attention biases of people with major depressive disorder: a voxel-based morphometric study. *Psychol Med*. 2009;39:1097–106.
105. Li CT, Lin CP, Chou KH, Chen IY, Hsieh JC, Wu CL, et al. Structural and cognitive deficits in remitting and non-remitting recurrent depression: A voxel-based morphometric study. *Neuroimage*. 2010;50:347–56.
106. Mak AKY, Wong MMC, Han SH, Lee TMC. Gray matter reduction associated with emotion regulation in female outpatients with major depressive disorder: A voxel-based morphometry study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33:1184–90.
107. Mwangi B, Ebmeier KP, Matthews K, Steele D. Multi-centre diagnostic classification of individual structural neuroimaging scans from patients with major depressive disorder. *Brain*. 2012;135:1508–21.
108. Pizzagalli DA, Oakes TR, Fox AS, Chung MK, Larson CL, Abercrombie HC, et al. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. *Mol Psychiatry*. 2004;9:393–405.
109. Ries ML, Wichmann A, Bendlin BB, Johnson SC. Posterior cingulate and lateral parietal gray matter volume in older adults with depressive symptoms. *Brain Imaging Behav*. 2009;3:233–9.

110. Shah PJ, Ebmeier KP, Glabus MF, Goodwin GM. Cortical grey matter reductions associated with treatment-resistant chronic unipolar depression. Controlled magnetic resonance imaging study. *Br J Psychiatry*. 1998;172:527–32.
111. Soriano-Mas C, Hernández-Ribas R, Pujol J, Urretavizcaya M, Deus J, Harrison BJ. Cross-sectional and longitudinal assessment of structural brain alterations in melancholic depression. *Biol Psychiatry*. 2011;69:318–25.
112. Treadway MT, Grant MM, Ding Z, Hollon SD, Gore JC, Shelton RC. Early Adverse Events, HPA Activity and Rostral Anterior Cingulate Volume in MDD. *PLoS ONE*. 2009;4(3):e4887.
113. Taki Y, Kinomura S, Awata S, Inoue K, Sato K, Ito H, et al. Male elderly subthreshold depression patients have smaller volume of medial part of prefrontal cortex and precentral gyrus compared with age-matched normal subjects: A voxel-based morphometry. *J Affect Disord*. 2005;88(3):313–20.
114. van Tol M, van der Wee N, van den Heuvel O, Nielen M, Demenescu L, Aleman A, et al. Regional brain volume in depression and anxiety disorders. *Arch Gen Psychiatry*. 2010;67(10):1002–11.
115. Vasic N, Walter H, Höse A, Wolf RC. Gray matter reduction associated with psychopathology and cognitive dysfunction in unipolar depression: A voxel-based morphometry study. *J Affect Disord*. 2008;109:107–16.
116. Wagner G, Koch K, Schachtzabel C, Schultz CC, Sauer H, Schlösser RGM. Structural brain alterations in patients with major depressive disorder and high risk for suicide: Evidence for a distinct neurobiological entity? *Neuroimage*. 2011;54:1607–14.
117. Yuan Y, Zhu W, Zhang Z, Bai F, Yu H, Shi Y, et al. Regional gray matter changes are associated with cognitive deficits in remitted geriatric depression: An optimized voxel-based morphometry study. *Biol Psychiatry*. 2008;64:541–4.
118. Zhang TJ, Wu QZ, Huang X-Q, Sun XL, Zou K, Lui S, et al. Magnetization transfer imaging reveals the brain deficit in patients with treatment-refractory depression. *J Affect Disord*. 2009;117:157–61.
119. Zou K, Deng W, Li T, Zhang B, Jiang L, Huang C, et al. Changes of brain morphometry in first-episode, drug-naïve, non-late-life adult patients with major depression: An optimized voxel-based morphometry study. *Biol Psychiatry*. 2010;67:186–8.