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466 *Current Neuropharmacology,* **2015**, *13,* **466-479**

Brain Functional Effects of Psychopharmacological Treatment in Major Depression: A Focus on Neural Circuitry of Affective Processing

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Abstract: In the last two decades, neuroimaging research has reached a much deeper understanding of the neurobiological underpinnings of major depression (MD) and has converged on functional alterations in limbic and prefrontal neural networks, which are mainly linked to altered emotional processing observed in MD patients. To date, a considerable number of studies have sought to investigate how these neural networks change with pharmacological antidepressant treatment. In the current review, we therefore discuss results from a) pharmacological functional magnetic resonance imaging (fMRI) studies investigating the effects of selective serotonin or noradrenalin reuptake inhibitors on neural activation patterns in relation to emotional processing in healthy individuals, b) treatment studies in patients with unipolar depression assessing changes in neural activation patterns before and after antidepressant pharmacotherapy, and c) predictive neural biomarkers of clinical response in depression. Comparing results from pharmacological fMRI studies in healthy individuals and treatment studies in depressed patients nicely showed parallel findings, mainly for a reduction of limbic activation in response to negative stimuli. A thorough investigation of the empirical findings highlights the importance of the specific paradigm employed in every study which may account for some of the discrepant findings reported in treatment studies in depressed patients.

Keywords: Antidepressants, brain activity, major depression.

INTRODUCTION

Extensive functional magnetic resonance imaging (fMRI) research over the last 25 years has revealed abnormal brain activation patterns in major depression. Evidence from numerous imaging studies converges on an imbalance between a hypoactive prefrontal network and a hyperactive limbic network [1, 2]. This imbalance is proposed to underlie altered emotional and cognitive processing, such as increased reactivity as well as increased attentional and cognitive bias towards negative stimuli in major depressive disorder [3, 4].

The hypoactive cortical circuit mainly comprises the dorsolateral prefrontal cortex (dlPFC), the ventrolateral prefrontal cortex (vlPFC), the dorsal cingulate cortex (dACC) and the inferior parietal cortex [5]. The limbic network is mainly comprised of the ventral or subgenual anterior cingulate cortex (vACC), the hippocampus, the hypothalamus, the amygdala and the insula [5]. Interestingly, this neural activation pattern seems, at least partly, reversed by the intake of psychopharmacological substances, *e.g.*, antidepressants. In the last ten years, substantial research has been undertaken to identify the effects of antidepressant treatment (*e.g.*, selective serotonin reuptake inhibitors (SSRI), noradrenalin reuptake inhibitors (NRI)) on neural circuitry functioning in major depression. A considerable part of this research has dealt with the short-term effects of antidepressant treatment on neural activation patterns in healthy subjects, using the so-called pharmacological fMRI design. Most of this research – in patients and healthy subjects – has been devoted to the pharmacological effects on the processing of emotions and on their underlying neural correlates. In the following review, we briefly summarize studies on short-term effects of antidepressant medication on brain activation patterns in healthy individuals. Then, we investigate the antidepressant treatment effects on brain activation patterns in patients with (major) depression and we conclude with studies exploring potential predictive neural markers of successful clinical response during the depressive state. Moreover, as an attempt to account for some discrepant findings reported mainly in studies in depressed patients, we discuss the potential role of the specific paradigm employed in each study as a factor that could have a crucial impact on brain activation patterns and may interact with treatment effects. Such an attempt to take into account potential confounding effects of the specific paradigm has not been made in previous reviews and has not been formally tested (mainly due to insufficient number of studies) by meta-analyses on the topic.

PHARMACOLOGICAL FUNCTIONAL MAGNETIC RESONANCE IMAGING IN HEALTHY SUBJECTS

In healthy subjects, most studies investigated the single-dose effects of selective serotonin reuptake inhibitors (SSRIs) or (selective) noradrenalin reuptake inhibitors (NRIs) on

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1570-159X/15 $58.00+.00

blood oxygenation level dependent (BOLD) responses to different kind of emotional stimuli (pictures, words, faces) or emotional tasks. For clarity, we grouped findings from these studies based on the substance under investigation.

Selective Serotonin Reuptake Inhibitors

In a series of studies, investigating the effect of SSRI intake on BOLD responses to emotional and neutral stimuli in healthy, never-depressed participants, decreased amygdala activity in response to aversive stimuli has been observed relatively consistently [6-12]. This effect has been shown in studies using single dose treatment [6, 8, 10, 11] as well as those applying a 7 to 21 days treatment [7, 9, 12] with an SSRI (*e.g*., citalopram, escitalopram, fluvoxamine). Further, attenuation of limbic (mainly amygdala) activation to aversive stimuli after SSRI treatment was reported during overt and covert stimulus presentation as well as for different stimulus types (faces, pictures). Interestingly, no such dampening effect of pharmacological treatment was observed for positive pictures [9]. Norbury and colleagues [13] even showed increased amygdala responses to happy faces following 7 to 10 days SSRI treatment.

In addition to the described changes in task-related neural activation after SSRI administration, pharmacological intervention also appears to modify healthy individual's resting-state neural activity. Recently, Kraus and colleagues [14] observed enhanced resting-state connectivity within ventral precuneus and PCC (DMN) in healthy study participants after 10 days SSRI treatment and this enhanced connectivity was associated with gray matter volume increases in the PCC and ventral precuneus. Furthermore, following a 2-weeks duloxetine treatment, functional connectivity between the default mode network (DMN) and task-positive network (TPN) was decreased, showing reduced connectivity between medial PFC and lateral parietal cortex and decoupling between medial PFC and dorsolateral PFC [15]. This effect may reflect less self-referential processing after antidepressant treatment, leading to less negatively biased self-perception and rumination. In line with this finding, depressed patientsexhibited increased dominance of the DMN over the TPN at rest compared to healthy subjects and this DMN dominance over TPN was associated with higher levels of rumination [16].

Noradrenaline Reuptake Inhibitors

Studies investigating the effects of noradrenaline reuptake inhibitors on neural response patterns to emotional stimuli in healthy individuals are more sparse. After single dose reboxetine administration, Norbury and colleagues [17] showed similar dampening effects on amygdala responses to fearful faces and increased amygdala response to happy faces. Further, in a task where participants are instructed to categorize and subsequently recognize self-referent positive and negative personality trait words, single-dose reboxetine administration had no effect on neural response patterns during categorizing personality traits, but in the following recognition test participants receiving reboxetine showed reduced activation in fronto-parietal brain circuits during the correct recognition of positive target vs. distractor words, accompanied by an increased speed to recognize positive vs. negative self-referential words [18]. This finding suggests facilitated memory retrieval for positive self-referential stimuli after single-dose reboxetine intake. These effects were partially replicated in a second study of that group [19] which applied a 7 days reboxetine treatment. In this study, reboxetine also changed neural response patterns during the categorization of self-referent positive personality characteristics by increasing activation in the precuneus and inferior frontal gyrus. Reversely, decreased neural activation in the precuneus, ACC and medial frontal gyrus was observed during the recognition of positive words. This reversal of neural activation patterns has been proposed to underlie increased positive bias following successful treatment in depressive patients. This is in line with results from Papadatou-Pastou and colleagues [20] who showed that, after single dose reboxetine treatment, brain activation differences in the processing of positive versus negative autobiographical memories were accompanied by increased memory speed for positive memories in healthy individuals.

Few studies have investigated the differential effects of serotonin and noradrenalin reuptake inhibitors on neural activation patterns. Comparing the neural responses to rewarding and aversive stimuli before and after SSRI and NRI treatment in healthy individuals demonstrated decreased activation of ventral striatum and ventral medial OFC to rewarding stimuli after SSRI treatment, but increased activation in medial OFC and no suppression of ventral striatal activity to reward after NRI treatment [21]. This result nicely mimics clinical observations and patient reports of emotional blunting during SSRI treatment. Both substances had beneficial effects for the processing of aversive stimuli, reflected by decreased activation of lateral OFC to aversive stimuli.

Taken together, results of pharmacological fMRI studies in healthy individuals present a pattern of decreased limbic (mainly amygdala) activation in response to aversive stimuli and either unchanged or increased neural activity to positive stimuli after SSRI treatment. Unfortunately, only few studies included positive stimuli in their experimental paradigms or they collapsed stimuli of different valence in the respective data analyses. Interestingly, NRI treatment seems to facilitate processing of positive information (*e.g*. memory for positive events; categorization or recognition of positive personality traits) and reward, whereas at least for rewarding stimuli, SSRI appears to have an opposite effect.

BRAIN EFFECTS OF ANTIDEPRESSANT TREATMENT IN MAJOR DEPRESSION

In this part of the review, we summarize evidence from 31 imaging studies that have examined the effects of antidepressant medication on brain activation patterns during active tasks or resting-state in depressed patients (for details on these studies please refer to Table **1** for study design and clinical aspects and to Table **2** for paradigm, analysis and results). The majority of these studies (30 out of 31) employed a longitudinal design and examined the effects of antidepressant medication for a period of 6-12 weeks [22-52]. Despite the common design, there is huge variation in the type of antidepressant administered, the dose, and the dose adjustment regime. Moreover, the specific paradigm

Table 1. Demographics and clinical characteristics of the studies on antidepressant effects on brain activation in depressed patients.

Reference	Study Participants (males/females)	Mean Age (SD)	Study Design	Depression Score (HAM-D) at T1	Antidepressant Treatment	Duration of Treatment	Clinical Response
Sheline *et al.* 2001 [44]	n = 11 MDD, m/f:5/6 n=11 CON, m/f: 5/6	MDD=40.3 (18-55) CON=39.8 (20-55)	open-label study, longitudinal design	HAM-D=23.3	Sertraline[a]	Scan 1: Baseline Scan 2: 8 weeks	Only 1 non-responder, 2 partial responders and 8 responders. HAM-D=9.7
Davidson *et al.* 2003 [27]	n = 12 MDD, m/f:4/8 n=5 CON, m/f: 4/1,	MDD=38.2(9.3) CON=27.8 (10.4)	open-label study, longitudinal design	HAM-D=25	Venlafaxine[b]	Scan 1: Baseline Scan 2: 2 weeks Scan 3: 8 weeks	70% reduction in HAM-D scores from baseline to 8 weeks treatment HAM-D=16 after 2 weeks HAM-D=8 after 8 weeks
Fu *et al.* 2004 [30]	n = 19 MDD, m/f:8/11 n = 19 CON, m/f:6/13	MDD=42.8 (6.7) CON=43.2 (8.8)	open-label study, longitudinal design	HAM-D=21.1 (2.3)	Fluoxetine[a]	Scan 1: Baseline Scan 2: 8 weeks	10/12 responders HAM-D=8.5 ± 4.8
Anand *et al.* 2005 [23]	n = 12 MDD, m/f:3/9 n = 11 CON, m/f:3/8	MDD=30 (9) CON=29 (8)	open-label study, longitudinal design	HAM-D=32 (8)	Sertraline[a]	Scan 1: Baseline Scan 2: 6 weeks	10/12 responders. HAM-D=6 ± 6
Schaefer *et al.* 2006 [43]	n = 9 MDD, m/f:3/6 n=14 CON, m/f: 4/10	MDD=35.9 CON=28.2	open-label study, longitudinal design	HAM-D=23.4 (7.2)	Venlafaxine[b]	Scan 1: Baseline Scan 2: 21.8 weeks (range=15–32 weeks)	68% reduction in HAM-D scores. 6/9 patients achieved remission. Decrease in HAM-D scores in all patients
Anand *et al.* 2007 [22]	n = 12 MDD, m/f:3/9 n = 11 CON, m/f:3/8	MDD=30 (9) CON=29 (8)	open-label study, longitudinal design	HAM-D=32 (8)	Sertraline[a]	Scan 1: Baseline Scan 2: 6 weeks	10/12 responders. HAM-D=6 ± 6
Walsh *et al.* 2007 [49]	n = 20 MDD, m/f:6/14 n=20 CON, m/f: 7/13	MDD=43.7 (8.3) CON=43.7 (8.6)	open-label study, longitudinal design	HAM-D=21.2 (2.4)	Fluoxetine[a]	Scan 1: Baseline Scan 2: 2 weeks Scan 3: 8 weeks	HAM-D=16(6) after 2 weeks HAM-D=9 (6) after 8 weeks
Robertson *et al.* 2007 [39]	n = 10 MDD, m/f:3/7	MDD=41.4 (7)	open-label study, longitudinal design	HAM-D=21 (4)	Bupropion[e]	Scan 1: Baseline Scan 2: 7 weeks	HAM-D=9.8 (6)
Fu *et al.* 2007 [29]	n = 19 MDD, m/f:6/13 n=19 CON, m/f: 8/11	MDD=43.2 (8.8) CON=42.8 (6.7)	open-label study, longitudinal design	HAM-D=21.1 (2.3)	Fluoxetine[a]	Scan 1: Baseline Scan 2: 2 weeks Scan 3: 8 weeks	-
Chen *et al.* 2008 [26]	n = 19 MDD, m/f:6/13 n = 19 CON, m/f:8/11	MDD=43.3 (8.6) CON=42.8 (6.7)	open-label study, longitudinal design	HAM-D=21.3 (2.4)	Fluoxetine[a]	Scan 1: Baseline Scan 2: 8 weeks	56% reduction in HAM-D scores. HAM-D =9.3 (5.8)
Benedetti *et al.* 2009 [25]	n = 8 MDD, m/f:1/7	MDD=46.3 (12.4)	open-label study, longitudinal design	HAM-D=25.88 (4.4)	Venlafaxine[b] and light therapy	Scan 1: Baseline Scan 2: 4 weeks	4/8 patients achieved remission. HAM-D=17.62 (7.96) at week 1; 12.75 (7.48) at week 2; 13.25 (7.48) at week 3; and 10.62 (5.37) at week 4
Keedwell *et al.* 2009 [33]	n = 12 MDD, m/f:6/6	MDD=49	open-label study, longitudinal design	HAM-D=25 (0.7)	Naturalistic study: variety of different antidepressant treatments	Scan 1: Baseline Scan 2: 12 weeks (range 8–16 weeks).	HAM-D = 11 (10.4) range = 2–24

Table 1. contd….

Reference	Study Participants (males/females)	Mean Age (SD)	Study Design	Depression Score (HAM-D) at T1	Antidepressant Treatment	Duration of Treatment	Clinical Response
Fales *et al.* 2009 [28]	n = 23 MDD, m/f:10/13 n=18 CON, m/f: 9/9	MDD=36.4 9.4) CON=33.4 (8.2)	open-label study, longitudinal design	HAM-D=20 (2.3)	Escitalopram[a] (n=18) Sertraline[a] (n=4) Paroxetine[a] (n=2)	Scan 1: Baseline Scan 2: 8 weeks	14/23 patients achieved at least 89% reduction in HAM-D scores, 7/23 showed 50-88% improvement, and 2/23 showed 43-49% reduction
Lemogne *et al.* 2010 [34]	n = 8 MDD, m/f:0/8 n=8 CON, m/f:3/5	MDD=33.1 (9) CON=28.4 (6.1)	open-label study, longitudinal design	MADRS= 29.5 BDI=18.5	Selective serotonin-reuptake inhibitor (n=4), serotonin–norepinephrine reuptake inhibitor (n=2), tricyclic antidepressant (n=2)	Scan 1: Baseline Scan 2: 8.9 weeks (range=6-14 weeks)	3/8 responders (i.e. a score reduction ≥ 50%) and 2/8 achieved remission (score < 10). MADRS=19 (12)
Lopez-Sola *et al.* 2010 [36]	n = 13 MDD, m/f:2/11 n = 20 CON, m/f:5/15	MDD=44.6 (8.3) CON=47.2 (7.7)	open-label study, longitudinal design	HAM-D=21.3 (2.6)	Duloxetine[b]	Scan 1: Baseline Scan 2: 1 week Scan 3: 8 weeks	9/13 responders and 6/13 achieved remission. HAM-D = 16.7 (3.9) after 1 week. HAM-D = 9.6 (5.9) after 8 weeks
Wagner *et al.* 2010 [48]	n = 8 MDD reboxetine, m/f:1/7 n = 12 MDD citalopram, m/f:1/11 n = 20 CON, m/f:2/18	MDD rebe=36.1 (10.8) MDD cital=42.4 (12.8) CON=37.6 (10.8)	open-label study, longitudinal design, nonrandomized controlled clinical treatment with either the NRI reboxetine or the SSRI citalopram	HAM-D reb=24.4 (4.7) HAM-D cital=23.4 (4.4)	Reboxetine[f] (n=8), Citalopram[a] (n=12)	Scan 1: Baseline Scan 2: 6 weeks	16/20 responders and 10/20 of 20 patients achieved remission. HAM-D reb=8.8 (5.8) HAM-D cital=8.3 (6.3)
Lisiecka *et al.* 2011 [35]	n = 23 MDD, m/f:15/8	MDD_ven=38.9 (9.6) MDD_mir=37.7 (8.5)	open-label study, longitudinal design	HAM-D_ven=29.5 (3.9) HAM-D_mir=21.6 (5.9)	Mirtazapine[d] (n=10) Venlafaxine[b] (n=13)	Scan 1: Baseline Scan 2: 4 weeks	12/23 responders. Mean HAM-D_ven=11.5 ± 5.5 Mean HAM-D_mir=8.5 ± 4.9
Samson *et al.* 2011 [42]	n = 21 MDD, m/f:14/7 n = 12 CON, m/f:8/4	MDD=41.5 (9.8) CON=35.8 (11.4)	open-label study, longitudinal design	HAM-D=21.3 (5.4)	Mirtazapine[d] (n=9) Venlafaxine[b] (n=12)	Scan 1: Baseline Scan 2: 4 weeks	10/21 responders (HAM-D = −62.50%, SD = 11.77). For non-responders (n= 11, HAM-D = −31.90%, SD = 16.20)
Arnone *et al.* 2012 [24]	n =32 MDD n=15 CON	-	open-label study, longitudinal design	MADRS=27 (4.2)	Citalopram[a]	Scan 1: Baseline Scan 2: 8 weeks	25/32 achieved remission. MADRS score: 3.84 SD=2.8
Jiang *et al.* 2012 [53]	n = 21 MDD, m/f:9/12	MDD=29.5 (7.7)	open-label study, longitudinal design	HAM-D=24.6 (5.1)	Escitalopram[a]	Scan 1: Baseline Scan 2: 10 weeks (range=8-12 weeks)	all 21 responders. HAM-D= 5.7 ± 4.0
Stoy *et al.* 2012 [45]	n = 15 MDD, m/f:10/5 n = 15 CON, m/f:10/5	MDD=41.9 (12.2) CON=39.5 (11.9)	open-label study, longitudinal design	HAM-D=18.7 (2.9)	Escitalopram[a]	Scan 1: Baseline Scan 2: 6 weeks	11/15 responders. HAM-D = 8.1 (4)

Table 1. contd….

Reference	Study Participants (males/females)	Mean Age (SD)	Study Design	Depression Score (HAM-D) at T1	Antidepressant Treatment	Duration of Treatment	Clinical Response
Godlewska *et al.* 2012 [31]	n = 21 MDD escitalopram, m/f:10/11 n = 12 MDD placebo, m/f:9/12 n = 17 CON, m/f:4/13	MDD escitalopram=32 (10.7) MDD placebo=31.1 (12.1) CON=33.7 (12.3)	double-blind, placebo-controlled, parallel group study	HAM-D_escital=24.2 (5.7) HAM-D_placebo= 23.3 (4.5)	Escitalopram[a] or placebo	Scan 1: Baseline Scan 2: 1 week	HAM-D_escital=19.8 ± 7.8 HAM-D_placebo= 20 ± 4.3
Rosenblau *et al.* 2012 [40]	n = 12 MDD, m/f:7/5 n = 12 CON, m/f:7/5	MDD=43.5 (11.5) CON=45.8 (11.9)	open-label study, longitudinal design	HAM-D=21.2 (4.2)	Escitalopram[a]	Scan 1: Baseline Scan 2: 59 days (SD=13 days)	9/12 responders and 6/12 patients achieved remission. 3/12 non-responders. HAM-D= 8.3 (4)
Wang *et al.* 2012 [51]	n = 18 MDD, m/f:7/11 n = 18 CON, m/f:7/11	MDD=31.6 (7.8) CON=31.6 (6.8)	open-label study, longitudinal design	-	Fluoxetine[a]	Scan 1: Baseline Scan 2: 8 weeks	All 18 patients achived remission.
Tao *et al.* 2012 [46]	Completed both sessions: n = 15 MDD n = 17 CON	MDD=14.2 (1.9) CON=14.9 (2.5)	open-label study, longitudinal design	Children's Depression Rating Scale–Revised: 51.9 (7.6)	Fluoxetine[a]	Scan 1: Baseline Scan 2: 8 weeks	9/15 responders
Ruhe *et al.* 2012 [41]	n = 15 MDD, m/f:9/6	MDD=42.1 (8.6)	First 6 weeks: open-label study, longitudinal design Last 6 weeks: double-blind placebo-controlled study	HAM-D=23.4 (4)	Paroxetine[a]	Scan 1: Baseline Scan 2: 6 weeks Scan 3: 12 weeks	4/15 and 9/15 responders at 6 and 12 weeks, respectively at 6 weeks: HAM-D= 16.1 (6.6) at 12 weeks: HAM-D=11.9 (6.4)
Rizvi *et al.* 2013 [38]	Completed all 3 sessions: n= 17 MDD n=11 CON	MDDnon_res=37.3 (12.8) MDD_res=40.2 (10.7)	open-label study, longitudinal design	HAM-D non_res=22.3 (1.9) HAM-D res=21.1 (1.1)	Olanzapine[c]/Fluoxetine[a] combination treatment	Scan 1: Baseline Scan 2: 1 week Scan 3: 6 weeks	57% responders and 48% achieved remission (HAM-D<7)
Heller *et al.* 2013 [32]	Completed both sessions: n= 21 MDD n=14 CON	-	open-label study, longitudinal design	HAM-D=21	Fluoxetine[a] (n=9), Venlafaxine[b] (n=12)	Scan 1: Baseline Scan 2: 8 weeks	9/21 patients achieved remission. 6/21 responders and 6/21 nonresponders. HAM-D=9
Miller *et al.* 2013 [37]	n = 17 MDD, m/f:7/10	MDD=35.6 (13.3)	open-label study, longitudinal design	HAM-D=25.5 (6.9)	Escitalopram[a]	Scan 1: Baseline Scan 2: 8 weeks	52% responders and also achived remission HAM-D=12.2 (7.1)
Victor *et al.* 2013 [47]	n = 10 MDD, m/f:4/6 n = 10 CON, m/f:3/7	MDD=33.3 (5) CON=28.4 (5.7)	open-label study, longitudinal design	HAM-D=24.5 (5.8)	Sertraline[a]	Scan 1: Baseline Scan 2: 8 weeks	9/10 responders. 7/10 patients achieved remission. HAM-D= 6.4 (6.0)
Wang *et al.* 2014 [49]	n = 14 MDD, m/f:9/5 n = 14 CON, m/f:9/5	MDD=32.9 (13.9) CON=34.1 (12.6)	open-label study, longitudinal design	HAM-D=26.7 (3.3)	Escitalopram [a]	Scan 1: Baseline Scan 2: 8 weeks	All 14 responders. HAM-D= 5.9 (4)

MDD: Major depressive disorder; CON: Healthy controls; HAM-D: Hamilton Depression rating scale; MADRS: Montgomery–Åsberg Depression Rating Scale; BDI: Beck Depression Inventory

*Same sample for Anand *et al*. 2005 and Anand *et al*. 2007

[a] Selective serotonin reuptake inhibitor

[b] Serotonin-norepinephrine reuptake inhibitor

[c] Atypical antipsychotic

[d] Noradrenergic and specific serotonin antidepressant

[e] Atypical antidepressant

[f] Norepinephrine reuptake inhibitor

Treatment response defined as 50% reduction in HAM-D scores

Remission defined as HAM-D scores lower than 7

Table 2. Characteristics of the experimental design, the analysis, and the main findings of the studies on antidepressant effects on brain activation in depressed patients.

Reference	MRI Assessment	fMRI Task Design	Analysis	Findings
Sheline *et al*. 2001 [44]	1.5T Siemens VISION system (Erlanger, Germany	Masked emotional faces paradigm	**ROI analysis:** right and left amygdala	Depressed patients demonstrated a significant reduction in right and left amygdala activation following treatment. Depressed patients and control subjects no longer differed in either left or right amygdala following treatment. Time by group interaction was not tested
Davidson *et al*. 2003 [27]	General Electric (Waukesha, Wis.) EchoSpeed 1.5 Tesla scanner	Passive viewing of emotional pictures	**Whole brain analysis**	Group by time interactions in response to the negative versus neutral stimuli were found in the left insular cortex and the left anterior cingulate. Patients had significantly less relative activation in these regions in response to negative versus neutral stimuli at baseline. After 8 weeks of treatment, this difference was completely eliminated (increase in activation).
Fu *et al*. 2004 [30]	neuro-optimized 1.5-T IGE LX System (General Electric, Milwaukee, Wis	Implicit processing of sad faces	**Whole brain analysis**	Group by time interaction in the following regions of the left brain: the amygdala, ventralstriatum (putamen/globus pallidus), insula, caudate nucleus, thalamus, anterior,dorsal and posterior cingulate cortex, precentral gyrus, postcentral gyrus, inferior parietal lobule and in the right ventral striatum and thalamus and right inferior parietal lobule. Post hoc analysis showed that amplitude of response to sad faces in these brain areas was significantly increased in patients compared with healthy volunteers at baseline and reduced significantly in patients during the course of 8 weeks of treatment.
Anand *et al*. 2005 [23]	General Electric (Waukesha, Wisc.) 1.5 T MRI scanner	Passive viewing or permit of negative pictures	**Functional connectivity analysis**	Significant group by time interaction were found in the connectivity scores of ACC-lMTHAL and ACC-rMTHAL LFBF correlation at rest. These interactions revealed increased LFBF correlation between these regions in depressed patients after treatment compared to healthy subjects.
Schaefer *et al*. 2006 [43]	GE Horizon 1.5 Tesla scanner, GE Medical Systems, Waukesha, Wisconsin	Passive viewing of positive social emotional pictures	**Whole brain analysis**	The stimulus × group × time interaction analysis showed for each of the three social stimulus types (social interaction, faces, sexual images), a distinguishable circuitry that was activated equally in non-depressed control subjects and post-treatment depressed subjects but showed a hypo-response in the depressed group pre-treatment. These structures include regions of prefrontal, temporal, and parietal cortices, insula, basal ganglia, and the hippocampus (increased activation).
Anand *et al*. 2007 [22]	General Electric (Waukesha, Wisc.) 1.5 T MRI scanner	Passive viewing or permit of negative pictures	**Functional connectivity analysis** and **ROI analysis:** between: pregenual ACC, Pallidostriatum, medial thalamus, and amygdala	A group by time interaction in left amygdala and left pallidostriatum. Depressed patients after treatment had decreased activation of the limbic regions. Healthy subjects exhibited only a small decrease in activation in the post-treatment session.
Walsh *et al*. 2007 [49]	neuro-optimized 1.5 Tesla GE LX System (General Electric, Milwaukee, Wisconsin	N-Back Verbal Working Memory Paradigm	**Whole brain analysis**	There was an interaction effect in the left caudate and right thalamus in which healthy control subjects showed a significant decrease in the quadratic load-response activity over time but the patient group showed no change from week 0 to week 2 followed by an increase in the load-response activity at week 8.
Robertson *et al*. 2007 [39]	General Electric 1.5-T LX Nvi scanner	Emotional Oddbal Task	**Whole brain analysis**	Treatment reduced fMRI activation during emotional distracters in several regions including right OFC, left dmPFC, right vmPFC, right ACC, right inferior PFC, right amygdala/parahippocampal area, right caudate, right fusiform gyrus, and left PCC. In left inferior PFC and left fusiform gyrus bupropion increased activation evoked by emotional distracters. Treatment increased activation to attentional targets in the following regions: right middle and inferior PFC, right caudate, and bilateral precuneus.

Table 2. contd….

Reference	MRI Assessment	fMRI Task Design	Analysis	Findings
Fu *et al.* 2007 [29]	neuro-optimized 1.5-T IGE LX System (General Electric, Milwaukee, Wis.)	Implicit processing of happy faces	**Whole brain analysis**	A significant group by time interaction in response to happy faces was observed in the cerebellum and extrastriate cortical regions. Post hoc analysis indicated that the overall capacity for processing happy faces was significantly lower in the acutely depressed patients than in the healthy subjects at baseline and that it increased significantly in the patients after antidepressant treatment.
Chen *et al.* 2008 [26]	General Electric IGE LX System operating at 1.5 T	Implicit processing of sad faces	**Functional connectivity analysis**	Patients with depression had a treatment-related increase in amygdala coupling with right prefrontal cortex, anterior cingulate cortex, insula, thalamus, caudate nucleus, and putamen. No such increase in functional coupling was observed in the control group.
Benedetti *et al.* 2009 [25]	3.0- Tesla scanner (Gyroscan Intera, Philips, Netherlands	Cognitive activation paradigm or go/no go task with morally tuned adjectives	**Whole brain analysis**	Significant valence x time interactions were detected in multiple brain areas, including medial and dorsolateral PFC, ACC, hippocampus and parahippocampal cortex. Activationin these areas was attenuated in response to negative stimuli after treatment, while it was increased in response to positive stimuli.
Keedwell *et al.* 2009 [33]	GE Signa 1.5T Neuro-optimised MR system (General Electric, Milwaukee, Wisconsin, USA) for gradient echo echoplanar imaging (EPI)	Passive viewing of emotional pictures	**Whole brain and ROI analysis:** amygdala, caudate, putamen, and subgenual ACC	No interaction between emotions and time for happy faces. Sad stimuli were associated with attenuated responses in the primary visual cortex following treatment. In contrast, there were greater responses in the left vlPFC following treatment.
Fales *et al.* 2009 [28]	Siemens 3T Allegra MRI scanner	Emotion-interference task	**ROI analysis:** rostral, pregenual and subgenual ACC and amygdala, dorsal ACC and dorsolateral PFC	Increased dlPFC activity to unattended fear-related stimuli following treatment. Activity in dlPFC in patients no longer differed from controls in after treatment. The left amygdala showed a significant four-way interaction. By T2, left amygdala activation for the fear-minus-neutral contrast in the depressed was decreased and no longer different from that of controls at T2 nor did they differ from control values at T1.
Lemogne *et al.* 2010 [34]	1.5-T whole-body scanner (SIGNA, GE, Milwaukee, WS, USA	Self-judgement task	**ROI analysis:** PFC	There was a session × group × condition interaction. This interaction was explained by a greater activation of the left dlPFC in 'self' versus 'general' condition, which was observed in patients during the first session but no longer during the second session (attenuated response).
Lopez-Sola *et al.* 2010 [36]	1.5 Tesla Signa system (General Electric, Milwaukee, WI	Pain experiment	**Whole brain analysis**	Group by time interactions were observed from baseline to week 1 fMRI assessments revealing a general effect of brain activation reductions in depressed patients and the opposite tendency in control subjects in the following regions: bilateral insulae, frontal and temporal opercula, basal ganglia, hypothalamic region, vmPFC, left hippocampus, middle temporal gyrus, subgenual–pregenual ACC regions and dlPFC. Significant group-by-time interactions were again observed from baseline to week 8, with group changes showing the direction observed in week 1 interaction analysis and involving a similar region network.
Wagner *et al.* 2010 [48]	1.5-T Siemens Magnetom Vision	The Stroop Color–Word task	**Whole brain analysis**	In the main effect of time, there was a significant decrease after treatment in the left middle temporal lobe, right inferior parietal lobule, right ventrolateral prefrontal cortex and bilaterally in the superior parietal lobe in the patient group. No group x time interaction test was reported.

Table 2. contd….

Reference	MRI Assessment	fMRI Task Design	Analysis	Findings
Lisiecka *et al.* 2011 [35]	3 T MRT Scanner (Signa HDx, GE Healthcare, USA	Matching of emotional faces	**Functional connectivity analysis**	After treatment, increased functional OFC connectivity was observed with the right cerebellum, right precuneus, the left middle cingulate cortex (MCC) and the left superior parietal gyrus extending to the left precuneus. A decrease in functional OFC connectivity was observed with the right MCC, the middle and left temporal gyrus (MTG) and the superior occipital gyrus, the right fusiform gyrus and the inferior temporal gyrus the left superior parietal gyrus, precuneus and postcentral gyrus, cuneus, calcarine fissure and angular gyrus following treatment.
Samson *et al.* 2011 [42]	3T MRT-Scanner (Signa HDx, GE Healthcare, Milwaukee, USA	Passive viewing of sad faces	**Whole brain and ROI analysis:** insula, caudate nucleus, amygdala and ACC	Following treatment, all patients exhibited greater activation in the right SMA (Group effect).
Arnone *et al.* 2012 [24]	Philips Intera 1.5-T MRI scanner	Implicit processing of emotional faces	**ROI analysis:** amygdala and **whole brain** exploratory analysis	Amygdala responses to fearful and happy faces did not significantly change with treatment in currently depressed patient but treatment attenuated bilateral amygdala responses to sad faces in patients who achieved full remission. No group x time interaction test was reported
Jiang *et al.* 2012 [53]	GE 1.5T MR scanner (General Elecric, Milwaukee, WI, USA	Emotional faces recognition task	**Whole brain analysis**	Following treatment, patients exhibited decreased activation in bilateral precentral gyrus, bilateral middle frontal gyrus, left middle temporal gyrus, bilateral postcentral gyrus, left cingulate and right parahippocampal gyrus, and increased activation in right superior frontal gyrus, bilateral superior parietal lobule and left occipital gyrus during sad facial expression recognition. After antidepressant treatment, patients also exhibited decreased activation in the bilateral middle frontal gyrus, bilateral cingulate and right parahippocampal gyrus, and increased activation in the right inferior frontal gyrus, left fusiform gyrus and right precuneus during happy facial expression recognition.
Stoy *et al.* 2012 [45]	1.5 Tesla scanner (Magnetom VISION Siemens	Monetary incentive delay task	**ROI analysis:** Ventral striatum	Group by time interaction in the left ventral striatum (increased after treatment) for anticipation of loss. Group comparisons between MDD patients and controls at baseline revealed blunted bilateral ventral striatal activation in MDD patients during loss anticipation and blunted right ventral striatal activation during gain anticipation. After treatment, patients and controls did not differ significantly in their ventral striatal activation, and both groups displayed strong activation during anticipation of both gain and loss.
Godlewska *et al.* 2012 [31]	3T Siemens TIM TRIO (Siemens AG, Erlangen, Germany	Implicit processing of emotional faces	Whole-brain and ROI analysis: amygdala	Group × condition interaction in right amygdala: Amygdala responses to fearful facial expressions were significantly greater in depressed patients compared to healthy controls. However, this response was normalised in patients receiving escitalopram (attenuation).
Rosenblau *et al.* 2012 [40]	1.5 Tesla scanner (Magnetom Vision®, Siemens, Erlangen	Passive viewing of expected or unexpected emotional pictures	**ROI analysis:** amygdala, MPFC, OFC, DLPFC and dorsal ACC	In the anticipation phase, a significant change of activation was observed in the right amygdala from the first to the second measurement point, in the depressed patients relative to the controls. Post hoc t-tests revealed a significant attenuation of amygdala activation in patients following treatment. In the control group, the change in amygdala activation did not reach significance. For the presentation phase, significant attenuation was revealed in activation of bilateral dlPFC, right lateral OFC and right medial OFC following treatment. These areas had shown a greater activation in the MDD group, at baseline, within the contrast negative versus neutral pictures.

Table 2. contd….

Reference	MRI Assessment	fMRI Task Design	Analysis	Findings
Wang *et al.* 2012 [51]	Siemens Trio 3-Tesla scanner (Siemens, Erlangen, Germany	Emotion judgment task	**Whole brain analysis**	In response to negative stimuli, greater activation in the right middle frontal gyrus (BA9) was seen in patients after antidepressant treatment than in unmedicated depressed patients. No group x time interaction effect was reported.
Tao *et al.* 2012 [46]	3-T MR imaging system (Philips Medical Systems, Best, the Netherlands	Implicit processing of fearful faces	**ROI analysis:** amygdala, OFC, and subgenual ACC	Group-by-time interaction effect for left and right amygdala (attenuation). The post hoc simple group effects indicated that patients had greater activation than the healthy comparison subjects in both the left and right amygdala at baseline, but not at week 8. Similar group-by-time interaction effect with the same direction were reported for the right orbitofrontal cortex and for bilateral subgenual ACC.
Ruhe *et al.* 2012 [41]	3 T Intera MRI scanner (Philips, Eindhoven, NL	Implicit processing of emotional faces	**ROI analysis:** amygdala	Attenuation of left amygdala activation during treatment was associated with amygdala SERT occupancy and response. No main time effect or group x time interaction effect on BOLD signal is reported
Rizvi *et al.* 2013 [38]	1.5 T GE Echospeed magnetic resonance imaging system (GE Medical Systems, Milwaukee, WI	Implicit processing of emotional pictures and passive viewing	**Whole brain analysis**	No treatment effects
Heller *et al.* 2013 [32]	General Electric 3 Tesla scanner (GE Medical Systems, Waukesha, WI	Emotion regulation task	**ROI analysis:** nucleus accumbens	Patients exhibited increased sustained nucleus accumbens activity and fronto-striatal connectivity after 2 months of treatment. None of these associations were observed in healthy comparison subjects. No time or group effect or group x time interaction was reported
Miller *et al.* 2013 [37]	3T Signa HDx scanner	Self-relevance of emotional words	**Whole brain analysis** and **ROI analysis:** subgenual ACC	No treatment effects
Victor *et al.* 2013 [47]	General Electric 3.0 T scanner (GE Signa, USA	Backward masking task with emotional faces	**Whole brain and ROI analysis:** pregenual ACC	Depressed patients showed attenuation of BOLD signal relative to the controls in responses to SN-HN following treatment in the right pgACC in the ROI analysis as well as in the whole brain analysis. The latter analysis also showed differences in the same direction in the right posterior cingulate cortex and left temporopolar cortex. In contrast, depressed patients showed an increased response compared to the controls in the post- vs. the pre-treatment conditions in the right lateral frontal polar cortex.
Wang *et al.* 2014 [49]	3.0-T Siemens MRI system (Siemens Medical Solutions, Germany	Resting-state fMRI	**Regional homogeneity analysis**	Compared to the unmedicated state, ReHo in the patients after treatment was decreased in the left dorsal medial prefrontal gyrus, the right insula and the bilateral thalamus, and increased in the right superior frontal gyrus. No group x time interaction test was reported

dlPFC: dorsolateral prefrontal cortex
vlPFC: ventrolateral prefrontal cortex
dmPFC: dorsomedial prefrontal cortex
vmPFC: ventromedial prefrontal cortex
OFC: Orbitofrontal cortex
ACC: Anterior cingulate cortex
SMA: Supplementary motor area
lMTHAL: left medial thalamus
rMTHAL: right medial thalamus
LFBF: Low Frequency Bold Fluctuations
ReHo: Regional homogeneity

used to examine medication-induced changes in brain activity varies across studies. The majority of the studies used visual stimuli with emotional valence and instructed subjects to either passively view or actively process the

emotional stimuli or engage in an irrelevant cognitive task during the presentation of emotional stimuli. Fewer studies examined cognitive processes (i.e. go/no go task, Stroop task), resting-state functional connectivity, or reward processes (monetary incentive task). The focus on emotion-related paradigms is mainly driven by the fact that affective processes are a core domain of the pathopsychophysiology of MDD and antidepressants mainly target networks implicated in emotion processing.

Converging evidence from studies using emotional stimuli suggests that antidepressants exert a normalizing effect on the depressed brain by attenuating abnormally elevated responses mainly to negative stimuli in limbic areas and more pronouncedly in amygdala [22, 24, 30, 31, 40, 41, 44, 46]. Although attenuation of amygdala responses following treatment is the most robust finding, a thorough investigation of the literature leads to the observation that less than half of the studies showed attenuation of amygdala responses to negative stimuli and most of these studies employed a paradigm where subjects implicitly process negative stimuli while being engaged on a cognitive task (usually gender identification task). Interestingly, only 2 out of 7 studies using implicit processing of negative stimuli did not report any amygdala attenuation following treatment and one of them showed treatment-induced changes in amygdala functional connectivity [26]. On the other hand, only 1 out of 7 passive viewing studies and none of the studies using explicit processing of emotional stimuli reported decreased amygdala responses following treatment. More importantly, the same studies that reported attenuated amygdala response following treatment also showed increased amygdala activation at baseline in depressed patients, compared to healthy controls, suggesting normalization of the abnormally elevated baseline amygdala response due to treatment. Therefore, the aforementioned distinction between implicit emotional processing tasks and more explicit or passive viewing tasks may be mainly driven by increased amygdala engagement during implicit processing in unmedicated depressed patients. One explanation of this dissociation is that group-related differences in amygdala reactivity to negative stimuli between unmedicated MDD patients and healthy controls are more pronounced in an implicit emotion processing task where inhibition of stimulus-driven limbic responses are essential for the successful performance of the cognitive task. On the other hand, during passive viewing or explicit processing of emotional stimuli no such inhibition of limbic responses is required and thus no group differences in amygdala reactivity are reported. This assumption is in line with a recent review [53] where the authors concluded that additional neuronal resources from the parietal and lateral prefrontal cortices are recruited by medicated MDD subjects during automatic attentional control of emotional information, and during automatic cognitive control. They argued that these additional resources act to override strong bottom-up emotional influences as part of an automatic emotion regulation strategy that may also occur during an implicit emotion processing paradigm. Despite the plausibility of this explanation, other factors may have contributed to the existing pattern of findings. For instance, 7 out of 8 studies reporting attenuation of amygdala responses after treatment performed region-of-interest (ROI) analysis using amygdala masks, raising the question of whether the effect attributed to the type of paradigm is confounded by the analysis method (i.e. ROI or whole brain).

Another robust treatment-related effect in the depression literature is the hyperactive PFC especially in response to negative stimuli [51]. It has been argued that antidepressants act to normalize the hypoactive baseline PFC response especially in response to negative stimuli [2]. Neural activity in the lateral PFC modulates limbic responses to emotional stimuli and inhibits enhanced emotional reactivity. Thus, normalized PFC activation following treatment may increase the ability for top-down control of emotional processes. Medication-related changes in PFC activity were reported in both emotional and cognitive paradigms. However, following treatment, enhancement of PFC activation is found in studies using affective paradigms such as passive viewing of emotional faces, emotion recognition task, and backward masking of emotional faces [28, 33, 42, 43, 47, 51] whereas attenuation of PFC activity is reported during cognitively demanding conditions such as the Stroop task, emotional oddball task, go/no go task, and self-judgment task [25, 34, 39, 48] in depressed patients. This dissociation may be related to the different cognitive demands of the two different types of paradigms or the presence or not of an emotional context. Alternatively, employment of automatic or voluntary emotion regulation strategies could also have contributed to differential PFC activation. It has been argued that additional neuronal resources from PFC are recruited by medicated MDD subjects mainly during automatic emotion regulation strategies while during voluntary emotion regulation MDD subjects displayed decreased PFC activation relative to HC [31].

The anterior cingulate cortex (ACC) extending from the subgenual part to dorsal ACC has also been implicated in MDD. Imaging studies have reliably shown increased baseline ACC activation especially in response to negative stimuli in MDD patients (see [2] for a meta-analysis). However, heterogeneous findings have been reported for the dorsal, pregenual and subgenual portion of ACC with the hyperactive baseline dorsal ACC being the most robust finding in the depression literature. Despite the relative heterogeneity in the baseline activity levels in MDD, medication-related changes converge on an attenuated ACC activity relative to baseline in a variety of tasks ranging from backward masking of emotional faces and implicit processing of emotional stimuli to Stroop Color–Word task [24, 25, 30, 33, 36, 39, 47, 48, 51]. Only one study reported increased activation of left ACC after antidepressant treatment [27]. Taken together, evidence from these longitudinal studies lends support for a normalizing effect of antidepressants on abnormally elevated baseline ACC activity that may reflect increased emotional appraisal and an over reactive salience network in response to negative stimuli.

Another major component of the salience network, the insular cortex, has also been implicated in MDD. Numerous imaging studies have shown increased baseline insular activity in MDD (see [2] for a meta-analysis). However, the pattern of medication-related changes in insula activity are more sparse (only five studies) and more heterogeneous in the depression literature. Following treatment with

antidepressants, two studies [27, 43] reported increased insular activation in MDD patients whereas three studies [30, 36, 51] reported attenuated insular responses. Despite the different direction of the treatment effect, antidepressants seem to have a normalizing effect in all these studies. The heterogeneity of findings related to baseline insular activation and the antidepressants effects probably reflect the heterogeneous function of this region and allow no firm conclusions to be drawn from these data.

Only few studies reported antidepressant medication effects on visual cortex. Treatment-related effects on visual cortex areas seem to be contingent to the valence of the stimuli as treatment increased activation in response to positive stimuli [30] and decreased activation in response to negative stimuli [33]. This pattern is partly similar to the one observed for limbic regions and it can be argued that antidepressants normalize response of the visual cortex in response to the baseline pattern. Importantly, the baseline pattern of activation in visual areas and especially in fusiform gyrus supports the hypothesis of a negativity bias in MDD and further suggests that this bias towards negative and away from positive stimuli may be introduced early at the perceptual level [1, 28, 54, 55]. Given the strong interaction between amygdala and visual cortex during emotional facial processing [56, 57], this pattern of activation in the visual cortex may be driven by visual-limbic feedback loop and may be biased in depression due to the hyperactive limbic system.

Another issue that to date has not been addressed sufficiently in the relevant literature is the effect of antidepressants on functional connectivity and especially on the functional interactions between cortical and subcortical areas. To our knowledge, only three studies have investigated patterns of functional connectivity following antidepressant treatment in depressed patients [23, 26, 35]. Evidence from these studies, converge on a view that antidepressant treatment enhances coupling between subcortical and cortical areas. Following treatment, Chen and colleagues [26] demonstrated increased functional connectivity between bilateral amygdala and prefrontal cortex, ACC, and subcortical regions during processing of sad faces. Similarly, Anand and colleagues [23] showed increased ACC functional connectivity with thalamus and striatal regions during passive viewing of negative pictures.

Taken together, the treatment-induced attenuation of amygdala and ACC activity, the enhancement of PFC activity, and the increased functional corticolimbic coupling especially in response to emotional stimuli lend support for a normalizing effect of antidepressants on limbic and PFC activity and at the same time enhancement of the functional interaction between these two networks in an effort to compensate for the emotion regulation deficits and to inhibit the increased emotional reactivity that characterize MDD patients.

PREDICTIVE NEURAL BIOMARKERS OF CLINICAL RESPONSE IN DEPRESSION

Response rates to first-line antidepressant treatment range from 50-75%. To date, no clinically useful marker has emerged that can reliably predict clinical response or guide treatment. The last 15 years, numerous neuroimaging studies have sought to identify neural biomarkers (functional and structural) that can predict symptom improvement in depressed patients. A recent meta-analysis [58] of fMRI and PET studies concluded that increased ACC activity extending into the orbitofrontal cortex and decreased baseline activation of right striatum and anterior insula in acutely depressed patients can predict clinical response to pharmacological or cognitive behavioral therapy (CBT).

However, there is substantial heterogeneity of findings implicating other brain regions such as visual cortex [59] or suggesting the inverse relationship between symptom improvement and brain activity. These discrepant findings may be explained by the heterogeneous patient groups, the variety of tasks used ranging from resting-state, to implicit emotional processing and from explicit emotional evaluation to non-emotional cognitive tasks, or the different types of treatment (i.e. pharmacological vs CBT). For instance, the well-replicated correlation between increased ACC and clinical response seems to be mainly driven by studies that employed tasks with emotional pictures or sad faces. On the other hand, resting-state studies showed hypermetabolism of ACC at baseline in subjects with poorer clinical response. Furthermore, ACC [58] and anterior insula [60] hyperactivity is more likely to predict response to medication, while hypoactivity in the same areas is associated with response to CBT suggesting that baseline activity in these two areas may in future serve as a criterionfor the type of first-line treatment that will most likely lead to remission [60].

Future studies addressing these questions would also benefit from the investigation of treatment-related changes in BOLD activity in the "predictive" regions. These changes can provide insights into the functional interpretation of the baseline effect. For instance, Siegle and colleagues [61] showed that low sgACC activity in patients compared to healthy controls predicts clinical response butremains low after treatment in responders indicating that a marker of clinical response is not necessarily a good neural target for therapy.

CONCLUSION

Taken together, results of pharmacological fMRI studies in healthy and depressed individuals present a pattern of decreased limbic (mainly amygdala) activation in response to aversive stimuli and either unchanged or increased neural activity to positive stimuli following antidepressant treatment. Interestingly depressed patients differentiate from healthy subjects in the antidepressant response in ACC. It seems that attenuation of ACC responses is specific to depressed patients and this may be relevant to the high predictive value of this area as neural marker of clinical response. It should be noted though that this comparison is severely compromised by the vast differences in the study designs and the duration of the treatment (longitudinal design for patients and double-blind, placebo-controlled for healthy subjects) between studies in healthy individuals and patients. Nonetheless, a normalizing effect of antidepressants

on limbic, ACC and PFC activity and at the same time enhancement of the functional interactions between these two networks is obvious in depressed patients.

It should be noted that the aforementioned model is only a simplified version of the complex nature of the antidepressant effects on the depressed brain. There is a lack of consistency of positive findings and a relatively great amount of null findings in the literature which could be attributed to differences in the patient population, type of medication and medication dose, the success rate of the pharmacological therapy and the type of analysis used (*e.g.* whole-brain exploratory or a priori ROI analysis). Another general limitation in this literature is the absence of placebo-controlled patient studies controlling for a medication-independent depression recovery. Most importantly, the context-specific and paradigm-dependent nature of activation findings has been neglected by previous reviews and meta-analyses on the topic. This review constitutes a first attempt to organize the existing literature based on the paradigm employed in each study. Using this classification, we offered some speculative explanations for the discrepant findings in the reviewed literature especially regarding the treatment effects on amygdala. Nonetheless, it is essential to address these questions by means of meta-analytic studies (provided enough single studies are available for such a meta-analysis) or single studies that can statistically investigate the effects of all these potential factors.

Another open question is whether and to what extent functional neuroimaging data at baseline can predict clinical response after treatment. Recent studies suggest that imaging data have enough predictive capacity to serve as prognostic markers [58]. However, high predictive accuracy at the individual level is required to translate these findings into clinical application. This can be achieved by pattern recognition methods such as support vector machines that have recently shown moderate sensitivity and specificity in discriminating between responders and non-responders at the individual level [62].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

This work has been supported by grants from the Deutsche Forschungsgemeinschaft (We 3638/3-1; SFB 636-subproject C6).

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Received: November 04, 2014 Revised: December 16, 2014 Accepted: December 19, 2014