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Abnormal amygdala-prefrontal effective connectivity to happy faces differentiates bipolar from major depression

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Abstract

Background—Bipolar disorder is frequently misdiagnosed as major depressive disorder delaying appropriate treatment and worsening outcome for many bipolar individuals. Emotion dysregulation is a core feature of bipolar disorder. Measures of dysfunction in neural systems supporting emotion regulation may therefore help discriminate bipolar from major depressive disorder.

Methods—Thirty-one depressed individuals, 15 bipolar depressed (BD) and 16 major depressed (MDD), *DSM-IV* diagnostic criteria, aged 18–55 years, matched for age, age of illness onset, illness duration, depression severity, and 16 age- and gender-matched healthy controls (HC) performed two event-related paradigms: labeling the emotional intensity of happy and sad faces, respectively. We employed dynamic causal modeling to examine significant among-group alterations in effective connectivity (EC) between right-and left-sided neural regions supporting emotion regulation: amygdala and orbitomedial prefrontal cortex (OMPFC).

Results—During classification of happy faces, we found profound and asymmetrical differences in effective connectivity between the OMPFC and amygdala. Left-sided differences involved top-down connections and discriminated between depressed and control subjects. Furthermore, greater medication load was associated with an amelioration of this abnormal top-down EC. Conversely, on the right side the abnormality was in bottom-up EC that was specific to bipolar disorder. These effects replicated when we considered only female subjects.

Conclusions—Abnormal left-sided top-down OMPFC-amygdala and right-sided bottom-up amygdala-OMPFC EC during happy labeling distinguish BD and MDD, suggesting different pathophysiological mechanisms associated with the two types of depression.

Keywords

Fmri; bipolar; disorder; major depression disorder; amygdala; orbitomedial prefrontal cortex; dynamic causal modeling

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Introduction

Bipolar disorder is one of the ten most debilitating illnesses worldwide(1), with a prevalence of at least 1%, poor clinical and functional outcome, a high suicide rate(2) and a huge societal cost(3). Among the reasons contributing to the illness's poor prognosis are the frequent misdiagnosis and late diagnosis of the disorder(4), leading to delays in appropriate treatment. Bipolar depression, the most frequent presentation, continues to be frequently misdiagnosed and inappropriately treated as major depressive disorder in individuals without a clear previous history of mania(3,5–7), while 35% of bipolar individuals take more than 10 years to receive a correct diagnosis(5). Increased accuracy in diagnosing bipolar disorder during depression as early as possible in illness course therefore remains a key goal to help improve the treatment and functional outcome of individuals with bipolar disorder.

Emotion dysregulation is a key clinical feature of bipolar disorder(8). Examination of functional abnormalities in key neural regions and systems supporting emotion processing and emotion regulation is therefore a promising way forward in the search for candidate biomarkers of bipolar disorder(9–11) that, in turn, may help improve diagnosis of bipolar disorder(12, 13). These key neural regions include the amygdala (important for emotion processing) and orbitomedial prefrontal cortex(OMPFC, including Brodmann Areas 11, 47 and 25), involved in different emotion regulatory subprocesses(14). An increasing number of functional neuroimaging studies have provided evidence for abnormal OMPFC and amygdala activity in bipolar disorder during emotion processing, especially during facial emotion processing(15). These studies reported greater subcortical limbic activity(amygdala, ventral striatum and hippocampus) to positive(happy) and negative (sad and fearful) emotional facial expressions in depressed, manic(16–18) and euthymic bipolar disorder(19–21) versus healthy adults, although some did not report increased amygdala and striatal activity to fearful faces in euthymic or stable bipolar disorder adults.

We recently examined OMPFC-amygdala anatomical connectivity in bipolar disorder and healthy adults using diffusion tensor imaging(DTI) and fractional anisotropy(FA)(22). Our major finding was a right-left asymmetry in fiber alignment in the uncinate fasciculus(UF) connecting OMPFC and amygdala. Specifically, we showed in bipolar disorder relative to healthy adults abnormally elevated left-sided UF FA(that may reflect greater longitudinal directional alignment of myelinated fibers in the uncinatefasciculus) and abnormally reduced right-sided UF FA(that may reflect more obliquely-oriented fibers in the uncinate fasciculus) (22). Our findings in this study parallel others showing an increased number of reconstructed longitudinally-aligned fibers in the left UF in bipolar disorder adults(23,24) or abnormal UF FA(25–27), and those reporting abnormal UF FA in psychosis and schizotypic(28–30).

These findings allowed us to postulate that abnormal right-left asymmetry in OMPFC-amygdala anatomic connectivity may relate to abnormal left versus right hemispheric processing of emotion that has previously been demonstrated in major depressive disorder depression(31,32), and may also represent a pathophysiologic mechanism for emotion dysregulation in bipolar disorder.

Few studies, however, have examined the extent to which abnormal functional integration between amygdala and OMPFC characterizes bipolar disorder. Functional connectivity(FC) refers to a correlation over time between activities in different neural regions. In contrast, effective connectivity(EC) refers to the impact that activity in one region exerts over that in another, and can be used to estimate forward(bottom-up) versus backward(top-down) connectivity between regions. EC can be examined using dynamic causal modeling(DCM), a technique for estimating, and making inferences about, the negative or positive influence that one region exerts over another, and how this is affected by experimental context(33). Only one

study has examined FC in bipolar disorder. In this study reduced FC between ventrolateral prefrontal cortex and amygdala was reported in manic bipolar disorder relative to healthy individuals during an emotion-labeling task(34). No previous studies have yet examined OMPFC-amygdala EC in bipolar disorder. Thus, the extent to which different patterns of abnormal functional integration between OMPFC and amygdala may distinguish bipolar disorder from major depressive disorder depression is also unknown.

We employed DCM and well-validated positive and negative emotion processing experiments (labeling happy and sad facial emotion experiments) to examine the extent to which:

1. Bipolar disorder and major depressive disorder depressed adults would show abnormal right and left top-down OMPFC-amygdala and/or bottom-up amygdala-OMPFC EC during happy and sad emotion processing;
2. Bipolar disorder and major depressive disorder depression would be associated with different patterns of abnormal right and left top-down and/or bottom-up EC between these regions.

METHODS and MATERIALS

Participants

The University of Pittsburgh Institutional Review Board approved the study protocol. Sixteen healthy control participants(HC) with no previous personal or family history of psychiatric illness in first and second degree relatives participated in the study. Thirty-one adults: fifteen with bipolar disorder, type I in depressed episode(BD) and sixteen with major depressive disorder in depressed episode(MDD), diagnosed according to DSM-IV criteria and the Structured Clinical Interview for DSM-IV, Research Version(SCID-P), participated in the study. MDD and BD did not differ in age(U=91,p=0.3), gender(χ^2(1)=1,p=0.6), Hamilton Depression Rating Scale(HDRS-25: U=82,p=0.13), age of illness onset(U=105.5,p=0.6) and illness duration(U=115,p=0.084). BD subjects had significantly greater medication load, reflecting greater number and dose of different psychotropic medications(U=51,p=0.006, see supplemental material for further information about computation of medication load and detailed participant medication information; Table S1), because they were being treated for BD rather than MDD depression. All had experienced at least two episodes of illness in the last 4 years. Some BD and some MDD had lifetime history of substance abuse or dependence disorders, and most were medicated(four were medication-free: two BD and two MDD; Table1). HC, MDD and BD depressed groups were age- and gender-ratio-matched (χ^2(2) =1.6,p=0.4 and χ^2(2)=1.9,p=0.5, respectively; Table1). All participants were right-handed and native English speaking. All participants were aware of the purpose of the study and gave written informed consent after explanation of the purpose of the research before participation in the study.

Exclusion criteria included history of head injury(from medical records and participant report), systemic medical illness, cognitive impairment(score<24 in the Mini-Mental State Examination, premorbid IQ estimate<85 using the National Adult Reading Test), Axis-II borderline personality disorder, and general exclusion criteria for MRI(presence/questionable history of metallic objects in the body, positive pregnancy test/self-reporting of pregnancy, and proneness to panicking in enclosed spaces). For HC, current alcohol and illicit substance abuse (determined by SCID-I, saliva and urine screen) were further exclusion criteria.

Paradigm

All individuals participated in two(happy and sad) 6-minute event-related experiments. Each experiment involved viewing 60 facial expressions from a standardized series(35). Individuals

viewed 20 prototypically happy(or sad) expressions; 20 mild happy (or sad) expressions, and 20 neutral expressions to represent the range of intensities of happy or sad emotion in each experiment. Each facial expression was presented for 2 seconds, with an inter-stimulus interval (ISI) of variable duration, according to a Poisson distribution (mean ISI=4.9s). We chose happy and sad facial expressions as examples of emotional stimuli as previous functional neuroimaging studies demonstrated abnormally increased activity in subcortical limbic regions (e.g. amygdala) and OMPFC to these specific emotional stimuli in BD and MDD(19,21,36–38). Participants were asked to label the emotion of each face by moving either the index (emotional faces) or middle finger(neutral faces) of the right hand to ensure that attention was directed to the emotional content of the face(see supplemental material for a schematic representation of the experiment). The labeling of emotional faces paradigm required subjects to consciously attend to(think about) the emotional content of the face stimuli; thus, neuronal activation in our regions of interest were very likely to encode the emotional valence and intensity of the stimuli.

In the present study, we focus on main findings from DCM analyses. See Supplemental Material for analysis and findings of standard functional specialization analyses regarding amygdala and OMPFC regions using SPM5 software(http://www.fil.ion.ucl.ac.uk/spm/; and Table S2), that shows that there were main effects of condition in OMPFC and amygdala BOLD signal for both experiments, a main effect of group for amygdala BOLD signal in the sad experiment, and group x interaction upon amygdala BOLD response in the happy experiment.

Functional integration: Dynamic Causal Modelling analyses

We chose bilateral amygdala and bilateral orbitomedial prefrontal cortex(OMPFC; specifically the BA11) as regions of interest for DCM analyses based on their known importance to emotion processing and emotion regulation, respectively, and their interconnections in both bottom-up and top-down directions via the UF, that we previously reported as abnormal in BD(22). We used DCM(33,39) in SPM5 software, to examine between group differences in right and left bottom-up amygdala-OMPFC and top-down OMPFC-amygdala EC. The aim of DCM is to estimate, and make inferences about, the influence that one neural system exerts over another and how the experimental context affects the neural system. In DCM, a reasonably realistic but simple neural model of interacting neural regions is constructed. DCM uses a previously-validated biophysical model of functional MRI measurements to estimate underling neuronal responses from observed hemodynamic responses(40); estimated underlying neuronal responses are then used to derive connectivity parameters, as described elsewhere(33). The neuronal(connectivity) and hemodynamic parameters are optimised using a variational expectation maximisation scheme(33). In this study we were primarily interested in the endogenous or baseline connectivity between the amygdala and OMPFC during emotional processing and the group-specific or between subject-differences in this coupling. To assess these differences we used a conventional summary statistic approach, where the within-subject estimates of coupling were passed to a second(between-subject) level for classical inference. Note that we did not use bilinear or modulatory terms in our DCM(to model changes in connectivity associated with emotional intensity). However, because we optimized the coupling parameters for DCMs in the happy and sad paradigms, we implicitly allow for the effects of emotional valence on coupling. In the following analyses, one can regard the estimates of top-down and bottom-up coupling as effective connectivity, subtending face processing, in the context of either happy or sad face judgments. Moreover, in the emotion labeling experiment the subjects had to consciously “think” about the emotion; therefore the valence and intensity are implicitly embedded in the neural activation in the DCM model.

For each session(i.e., subject and experiment) we modelled fMRI responses with one single DCM. This comprised bilateral amygdala and orbitofrontal cortical regions that were

connected, reciprocally with forward(bottom-up) and backwards(top-down) ipsilateral connections(Figure1). This provided eight effective connectivity estimates for each subject that were estimated under happy or sad experiments, in the right or left hemisphere, and were either forward or backwards. To account for individual differences, we extracted principal eigenvariates to summarize regional responses in anatomical templates centered on the regions above created with the Wake Forest University(WFU) Pick Atlas. The stimulus function, that encoded face presentation per se, entered each dynamic causal model through the amygdala and propagated to OMPFC via bottom-up, and back to the amygdala via top-down interconnections between the two regions(Figure1).

In DCM, the units of connections are per unit time and therefore correspond to rates: a strong connection means an influence that is expressed quickly or with a large rate-constant. A positive (i.e., greater than zero) endogenous connection indicates that “high” activity in the “source” region is associated with an increase in activity in the “target” region. Similarly for negative connections. The underlying model links rates of change in the target to the level of activity in the source(33).

Between-group differences in EC

Individual-specific estimates of EC were next entered into SPSS edition 15(SPSS Inc.) for examination with Kruskal-Wallis tests of the between group differences upon right and left bottom-up and top-down OMPFC-amygdala EC for happy and sad experiments. Each test was thresholded at p=0.006 to correct for the eight separate Kruskal-Wallis tests: one test for each laterality, emotion and direction. We deliberately decided to be very conservative in this multiple test correction because of the novelty of our study. Post hoc Mann-Whitney U tests were employed for subsequent between-group pairwise comparisons for each EC parameter showing a significant group difference($p<0.02$, to control for three pairwise between-group tests). Non-parametric tests were employed because EC measures were not normally distributed. Significant between-group differences in EC were then explored for possible relationships using Spearman rank correlation tests and Man-Whitney U tests, as appropriate, with the following variables: age, age of illness onset, illness duration, depression severity measured using the HRSD25, medication load, individual psychotropic medication classes and lifetime history of comorbid substance disorder, using a statistical threshold of p=0.05, as these were exploratory analyses.

RESULTS

Behavioral Analyses

There were no differences among groups in labeling of emotional face in both experiments ($p>0.05$-Table1). Moreover, no emotion labeling differences were found between the two depressed groups($p>0.1$–Table1).

Neuroimaging Data Analyses

Functional integration – Dynamic Causal Modeling: between group differences in EC—There was a significant group difference upon left-sided top-down OMPFC-amygdala EC during the happy experiment($\chi^2(2)=11.5$,$p=0.003$; Table 2). Relative to HC, both MDD and BD had significantly reduced EC(MDD: $U=52$,$p=0.004$, Cohen’s d effect size=0.95 and BD: $U=52$,$p=0.007$, $d=0.65$; Figure 2 and Table 3), although BD and MDD did not differ significantly on this measure. Observation of group-specific values revealed that this EC was *positive* in HC, close to zero in BD and *negative* in MDD(Table 2).

There was a between-group difference in right-sided bottom-up amygdala-OMPFC EC in the happy experiment($\chi^2(2)=9.9$,$p=0.007$) that just failed to meet our stringent threshold for

significance(0.006, controlling for multiple tests). This EC differed significantly between HC and BD (U=42, p=0.002; d=1.2) but not between MDD and HC(Table 3 and Figure2). MDD and BD differed on this measure, but at a threshold that failed to meet correction for multiple tests (U=64,p=0.027; d=0.42). Observation of group-specific values indicated that right-sided bottom-up amygdala-OMPFC EC was positive in HC and MDD but negative in BD(Table 2 and Table 3).

In the sad experiment, there was a trend between-group difference in left-sided top-down OMPFC-amygdala EC($\chi^2(2)=8.8$,p=0.01). MDD and BD both had significantly *reduced* left-sided top-down OMPFC-amygdala EC relative to HC(U=61.5,p=0.012, d=0.31 and U=55.5,p=0.011, d=0.42, respectively). BD and MDD did not differ significantly on this EC measure(Table 3).

Relationships between abnormal EC and illness history, medication load and demographic variables—Correlation analyses using Spearman Rank correlation tests were performed to examine relationships between clinical variables, left-sided top-down OMPFC-amygdala EC during the happy and sad experiments and right-sided bottom-up amygdala-OMPFC EC during the happy experiment in BD and MDD(Table 4).

Left-sided top-down OMPFC-amygdala EC in the happy experiment was positively correlated with medication load in MDD($r_s=0.64$, p=0.007), i.e., the greater the medication load, more positive the EC. There was also a negative relationship between this EC measure and age of illness onset in MDD($r_s=-0.5$, p=0.05). MDD taking, versus those not taking, benzodiazepines had greater left-sided top-down OMPFC-amygdala EC during the happy experiment(U=6, p=0.01). There was a trend association only between taking antipsychotics and this EC measure in BD.

For the right-sided bottom-up amygdala-OMPFC EC during the happy experiment, there was a negative relationship in MDD only with medication load($r_s=-0.6$, p=0.01): the greater the medication load, the closer to zero the EC.

In the sad experiment, performance showed a negative trend correlation with left-sided top-down OMPFC-amygdala EC when labeling the neutral faces in MDD.

There were no significant correlations between EC and age in both depressed groups.

In HC there were no significant relationships between EC and age at scan(happy left-side top-down EC: $r_s=0.2$, p=0.6; happy right-sided bottom-up EC: $r_s=0.4$, p=0.2; and sad left-sided top-down EC: $r_s=-0.3$, p=0.4) and experiment accuracy(happy left-side top-down EC emotional faces: $r_s=0.3$, p=0.2; neutral faces: $r_s=0.4$, p=0.1; happy right-sided bottom-up EC emotional faces: $r_s=-0.1$, p=0.8; neutral faces: $r_s=-0.1$, p=0.8; and sad left-sided top-down EC emotional faces: $r_s=0.2$, p=0.4; neutral faces: $r_s=-0.003$, p=0.99).

As the majority of study participants were female, and to exclude potential effects of gender upon EC in each group, we further examined EC in females only. In this subgroup we found exactly the same pattern of group differences: left-sided top-down OMPFC-amygdala EC ($\chi^2(2)=10.64$, p=0.005) and right-sided bottom-up amygdala-OMPFC EC ($\chi^2(2)=9.55$, p=0.008) in the happy experiment, and a trend difference in left top-down OMPFC-amygdala EC in the sad experiment($\chi^2(2)=6.45$, p=0.04). In the left-sided top-down OMPFC-amygdala EC during the happy experiment there were differences between MDD and HC(U=25, p=0.004; d=0.97), BD and HC(U=46,p=0.05; d=0.36), and between depressed groups(U=49.5,p=0.044; d=0.97), although the latter two differences did not survive after control for multiple tests. In the right-sided bottom-up amygdala-OMPFC EC during the happy experiment there was a significant difference between BD and HC(U=26,p=0.003; d=1.32), and between depressed

groups(U=45, p=0.026; d=0.41), although this latter difference did not survive after control for multiple tests. During the sad experiment, there were differences between BD and HC (U=40.5, p=0.025; d=0.53), MDD and HC(U=38.5,p=0.032; d=0.4), that did not survive after controlling for multiple tests.

DISCUSSION

This is the first study to examine EC between key neural regions in emotion regulatory neural systems in bipolar and major depression. We found that different patterns of abnormal left-sided top-down OMPFC-amygdala during happy emotion labeling distinguished bipolar and major depressed individuals(BD, MDD, respectively) from HC, while only BD differed from HC on right-sided bottom-up amygdala-OMPFC EC. MDD showed significantly greater negative left-sided top-down OMPFC-amygdala EC than HC, while BD showed significantly reduced positive left-sided top-down OMPFC-amygdala EC and greater negative right-sided bottom-up amygdala-OMPFC EC than HC.

The reduced left-sided top-down EC in the happy experiment in BD versus HC may reflect reduced regulation of left amygdala by OMPFC –i.e. a “disconnection” –during positive emotion processing. This parallels previous functional neuroimaging studies in BD reporting abnormally increased left-sided amygdala and striatal activity to happy faces(19,21,38), and abnormally decreased left-sided OMPFC activity during emotion regulation(41), that we previously highlighted(42). This left-sided reduction in top-down OMPFC-amygdala EC, possibly reflecting reduced regulation of amygdala by OMPFC during positive emotion processing, may represent a predisposition to elevated mood and mania in BD. Conversely, MDD showed left-sided top-down *negative* OMPFC-amygdala EC in the happy experiment. This may reflect increased inhibition of the left amygdala by left OMPFC to positive emotional stimuli that parallels previous functional neuroimaging findings in MDD of abnormally reduced left striatal activity to positive emotional stimuli(36,43). The increased negative left-sided top-down OMPFC-amygdala EC to happy faces may therefore represent an “over-regulation” by OMPFC of the amygdala to these stimuli and a potential neural basis for the increased negative and reduced positive emotional attentional bias that is frequently observed in major depression(44). Together, these findings suggest that different patterns of abnormal left-sided top-down OMPFC-amygdala EC during positive emotion processing may reflect different neural mechanisms in bipolar and major depression, and also support a role of the left hemisphere in positive emotion processing(32).

Only BD differed from HC on right-sided bottom-up amygdala-OMPFC EC during the happy experiment: this was positive in HC and MDD but negative in BD, suggesting an inverse functional relationship between right amygdala and OMPFC during happy emotion processing in BD –i.e. less amygdala activity associated with greater OMPFC activity. This pattern of abnormal right amygdala-OMPFC EC during the happy experiment is difficult to explain in the context of the hemispheric specialization of emotion theory above, but does suggest aberrant forward connectivity between right amygdala and right OMPFC during emotion processing in bipolar more than major depression. This finding also suggests that bipolar depression may be associated with functional abnormalities in neural systems supporting emotion regulation in *both* hemispheres, while major depression may be associated with a functional abnormalities predominantly within the left hemisphere, as has previously been observed in human lesion studies(45–47), and is suggested by the loss of normal left-right asymmetry in resting frontal activity in EEG studies of depression(48–51). The involvement of functional abnormalities in both hemispheres in bipolar depression parallels our previous observation of abnormalities in left and right amygdala-OMPFC white matter structure in bipolar disorder(22).

BD and MDD showed reduced left-sided top-down OMPFC-amygdala EC in the sad experiment, but the overall between group differences did not survive correction for multiple tests. This pattern of reduced left-sided EC in the sad experiment in both BD and MDD relative to HC is also difficult to explain in the context of existing theories regarding hemispheric specialization for emotion processing. Previous studies in MDD have, however, shown increased FC after treatment with antidepressants between left-sided subcortical limbic and OMPFC regions specifically during processing of negative emotional stimuli(52,53). This suggests that abnormally reduced left-sided OMPFC and subcortical limbic functional integration during negative emotion processing may be a state marker of depression in both BD and MDD, and that this may ameliorate with treatment in MDD.

Another interpretation of these EC asymmetry findings is that this might reflect sampling error and noise in making what is possibly a bilateral abnormality appears unilateral. While sampling error may differ between slices(i.e. along the transversal axis), there is, however, no evidence to suggest that it will also differ between homologous regions in the left and right hemispheres. Moreover, our asymmetry findings are consistent with previous reports of asymmetry in MDD, as we highlight above, as well as with our previous observation of asymmetric anatomical connectivity asymmetry in BD.

An alternative interpretation of our overall findings is that abnormal OMPFC-amygdala EC in BD and MDD might not be a specific correlate of labeling of emotional faces but a more general correlate of face processing. The regions included in the DCM model, however, are well known for their involvement in emotion processing and the task required participants to attend to the emotional valence of the stimuli; therefore it is most likely that our findings reflect the emotional component of the experiment.

There are limitations to this study. Almost all depressed individuals were medicated. This was necessary, given the need to recruit individuals in severe depressed episode with either well-established bipolar or recurrent major depression. We found no significant relationship between medication load and left-sided top-down OMPFC-amygdala EC in the happy experiment in BD, although there was a trend association between antipsychotics and this EC measure in BD, suggesting that these medications may have increased EC rather than contributing to our finding of abnormally decreased EC in BD. There was a significant positive correlation between left-sided top-down OMPFC-amygdala EC in the happy experiment and medication load in MDD, such that the greater the medication load, the less negative(i.e. less abnormal) the EC. The latter finding also indicates an ameliorative rather than confounding effect of medication upon this EC measure in MDD. When we further explored potential effects of different subclasses of medication, we found a significant increase in this EC measures EC only in MDD taking versus those not taking benzodiazepines. MDD also showed a negative association between medication load and right-sided bottom-up amygdala-OMPFC EC, but did not differ significantly form HC on this EC measure. Future studies could examine further the potential effects of psychotropic medication upon EC in BD and MDD populations.

Another limitation of this study was age range of 18 and 55 years, it is possible that some MDD may have not yet been beyond the age for possible development of bipolar disorder. Interestingly, however, MDD showed a significant *negative* relationship between age of illness onset and left-sided top-down OMPFC-amygdala EC during the happy experiment. MDD who developed depression at an older age and later in adolescence or adulthood, and who were therefore closer to being at the age beyond which it was *less* likely to develop bipolar disorder, were, in fact, *more* likely to show negative top-down OMPFC-amygdala EC in the happy experiment. This provides additional support for the pattern of negative left-sided top-down OMPFC-amygdala EC in the happy experiment being MDD-specific. When we restricted our analyses to females only, we observed a similar pattern of findings regarding abnormal EC in

BD and MDD as demonstrated by the entire groups, indicating that differences in gender ratio between groups did not contribute to our main findings.

Distinguishing bipolar disorder from major depression disorder depression is currently a major challenge in clinical practice, with a correct diagnosis of BD in only 20% of BD within the first year of seeking treatment(5), indicating a strong bias away from diagnosing bipolar disorder in patients presenting in depressed episode. We show that bipolar depression and major depression are associated with different patterns of abnormal functional integration between different regions in neural systems supporting emotion regulation, in both hemispheres during happy emotion processing. This finding in turn suggests that different pathophysiological mechanisms may underlie these two types of depression, and is a promising step forward toward identifying biological markers to distinguish between these different illnesses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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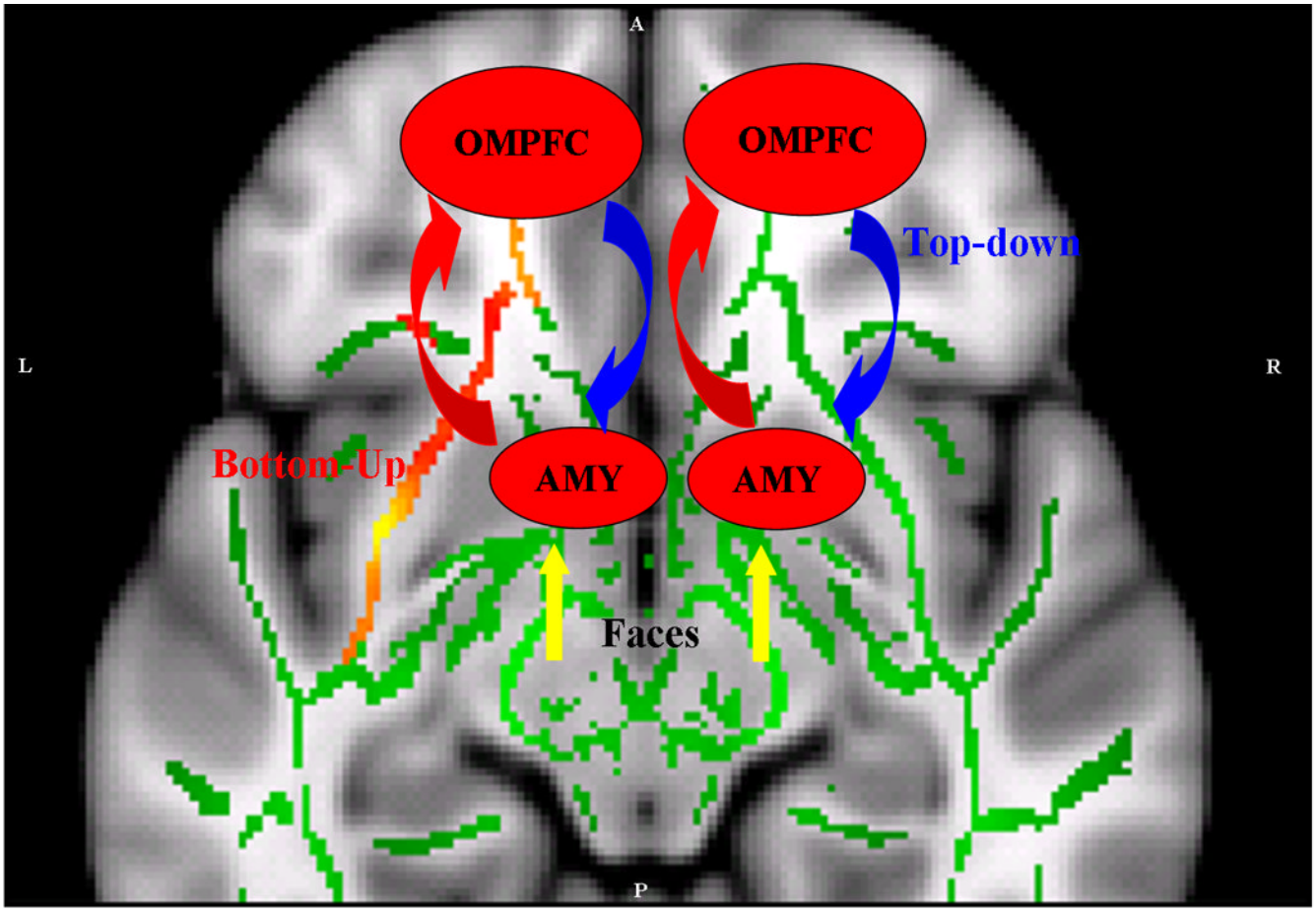

Figure 1. Schematic representation of the dynamic causal modeling

The face presentation entered (yellow arrow) the dynamic causal model through the amygdala and propagated to OMPFC via bottom-up (red arrow), and back to the amygdala via top-down (blue arrow) interconnections between the two regions through the unicinate fasciculus. AMY: amygdala; OMPFC: orbitomedial pre-frontal cortex; A: anterior; P: posterior; L: left and R: right side of the brain

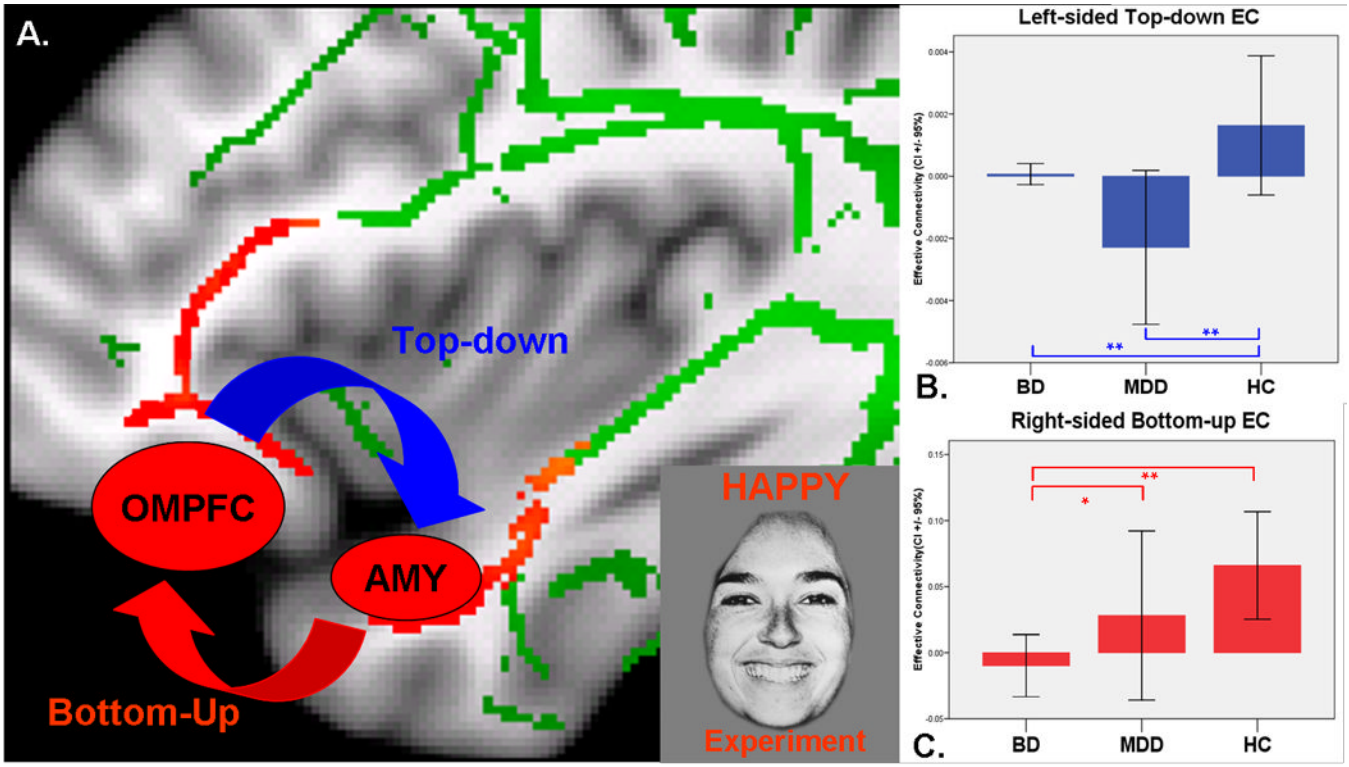

Figure 2. Effective Connectivity (EC) between OMPFC and amygdala

A. Representation of the bottom-up (red arrow) and top-down (blue arrow) endogenous connection between left amygdala and left OMPFC

B. Left-sided top-down OMPFC-amygdala EC in the happy experiment Happy experiment: negative EC in MDD relative to HC (**U=52, p=0.004; d=0.95) A close to zero effective connectivity in BD when relative to HC (**U=52, p=0.007; d=0.65). There were no difference between the two depressed groups on this EC measure (*U=83; p=0.14; d=0.67).

C. Right-sided bottom-up amygdala-OMPFC EC in the happy experiment Happy experiment: reduced EC in MDD relative to HC (**U=110, p=0.5; d=0.37). A close to zero effective connectivity in BD relative to HC (**U=42, p=0.002; d=1.2). There was a trend difference between the two depressed groups on this EC measure (*U=64; p=0.027; d=0.42).

Table-1

Demographic and Clinical Variables

	Group (N)	Mean [SD]	Statistics	P Value (2-tailed)
Age at Scan	HC (16) MDD (16) BD (15)	28.3 [8.4] 32.3 [9.7] 36.6 [11.9]	$\chi^2(2)=1.6$ U=91	0.4 0.25
Gender (M/F)	HC (4 / 12) MDD (3 / 13) BD (1 / 14)	25 / 75% 18.8 / 81.2% 6.7 / 93.3%	$\chi^2(2)=1.9$ $\chi^2(1)=1$	0.5 0.6
Age of Illness Onset	MDD (16) BD (15)	18.9 [7.3] 22.3 [10.4]	U=105.5	0.6
Illness Duration	MDD (16) BD (15)	13.4 [9.6] 14.2 [9.8]	U=115	0.084
Medication Load	MDD (16) BD (15)	1.8 [1.2] 3.9 [2.3]	**U=51**	**0.006**
HRSD-25	MDD (16) BD (15)	24.6 [6] 21.5 [6.4]	U=82	0.132
Lifetime Presence of Alcohol/Drugs Abuse or Dependence YES/NO)	MDD (16) BD (15)	3/13 4/9 [a]	$\chi^2(1)=0.6$	0.7
Behavioural Responses to SAD Emotional Labeling Experiment Emotional faces)	HC (16) MDD (16) BD (15)	67.7% [18.4] 64.4% [22.3] 54.3% [23.1]	$\chi^2(2)=2.6$ U=90	0.27 0.24
Behavioural Responses to SAD Emotional Labeling Experiment Neutral faces)	HC (16) MDD (16) BD (15)	83.1% [22.5] 72.8% [23.4] 73.3% [33.6]	$\chi^2(2)=3.6$ U=94	0.16 0.3

	Group (N)	Mean [SD]	Statistics		P Value (2-tailed)	
Behavioural Responses to HAPPY Emotional Labeling Experiment (Emotional faces)	HC (16) MDD (16) BD (15)	90.94% [6.6] 85% [15.4] 69.3% [30.1]	$\chi^2(2)=5.3$	U=81	**0.07**	0.12
Behavioural Responses to HAPPY Emotional Labeling Experiment (Neutral faces)	HC (16) MDD (16) BD (15)	89.4% [8.9] 83.4% [18.9] 73.7% [33.3]	$\chi^2(2)=0.8$	U=108	0.68	0.63

HC: healthy control participants; MDD major depression disorder patients in depressed episode; BD: bipolar disorder patients in depressed episode; SD: standard deviation; HRSD-25: 25-item Hamilton Rating Scale for Depression

[a] information for one subject was not available

Table-2

s in Effective Connectivity in BD, MDD and Healthy Controls

	HC			MDD				BD					
		95% CI			95% CI				95% CI				
ean	SD	lower bound	Upper Bound	Mean	SD	lower bound	Upper Bound	Mean	SD	lower bound	Upper Bound	F	P
44	0.07	0.004	0.083	0.0304	0.18	−0.064	0.125	−0.0004	0.02	−0.01	0.01	$\chi^2(2)=2.2$	0.3
02	0.004	−0.001	0.004	−0.0023	0.005	−0.005	0.0002	0.0001	0.001	−0.0003	0.0004	$\chi^2(2)=11.5$	**0.003****
66	0.08	0.025	0.107	0.0282	0.12	−0.036	0.092	−0.0098	0.04	−0.033	0.014	$\chi^2(2)=9.9$	**0.007***
02	0.01	−0.001	0.005	0.00001	0.01	−0.004	0.004	−0.0010	0.004	−0.003	0.001	$\chi^2(2)=1.6$	0.4
04	0.16	−0.081	0.089	0.0329	0.05	0.005	0.06	0.0419	0.11	−0.02	0.104	$\chi^2(2)=0.5$	0.8
05	0.02	−0.004	0.014	0.0005	0.004	−0.002	0.003	−0.0010	0.003	−0.003	0.001	$\chi^2(2)=8.8$	**0.01***
18	0.07	−0.018	0.053	0.0363	0.06	0.006	0.067	0.0407	0.12	−0.025	0.106	$\chi^2(2)=0.4$	0.8
01	0.003	−0.001	0.003	0.00002	0.003	−0.002	0.002	−0.0002	0.004	−0.002	0.002	$\chi^2(2)=1.3$	0.5

MDD major depression disorder patients in depressed episode; BD: bipolar disorder patients in depressed episode; OMPFC orbitomedial prefrontal cortex

on for multiple tests

multiple tests; SD: standard deviation; CI confidence interval for mean

Table-3

Post Hoc Effective Connectivity in Happy and Sad Experiments

	BD vs MDD			BD vs HC			MDD vs HC		
	Mann-Whitney U	**P value**	**Cohen's d effect size**	**Mann-Whitney U**	**p value**	**Cohen's d effect size**	**Mann-Whitney U**	**p value**	**Cohen's d effect size**
HAPPY Experiment									
Left-sided Top-down OMPFC-amygdala EC	83.0	0.14	0.67	52.0	**0.007****	**0.65**	52.0	**0.004****	**0.95**
Right-sided Bottom-up amygdala-OMPFC EC	64.0	**0.027***	**0.42**	42.0	**0.002****	**1.20**	110.0	0.5	0.37
SAD Experiment									
Left-sided Top-down OMPFC-amygdala EC	108.5	0.65	0.42	55.5	**0.011****	**0.42**	61.5	**0.012****	**0.31**

OMPFC: orbitomedial prefrontal cortex; HC: healthy control participants; MDD major depression disorder patients in depressed episode; BD: bipolar disorder patients in depressed episode;p value does not survive correction for multiple tests

* p value does not survive correction for multiple tests

** p value survives correction for multiple tests

Table-4

Relation Between Effective Connectivity, Clinical, Demographic and Experiment Performance Variables in the Two Depressed Groups

	HAPPY Experiment								SAD Experiment			
	Left-sided Top-down OMPFC-amygdala EC				Right-sided Bottom-up amygdala-OMPFC EC				Left-sided Top-down OMPFC-amygdala EC			
	MDD (n=16)		BD (n=15)		MDD (n=16)		BD (n=15)		MDD (n=16)		BD (n=15)	
	rho	p value	rho	p value	rho	p value	rho	p value	rho	p value	rho	p value
Age at Scan	0.12	0.66	−0.20	0.47	−0.16	0.56	−0.16	0.56	−0.09	0.73	−0.10	0.71
Age of Illness Onset	**−0.50**	**0.05****	−0.39	0.15	0.27	0.31	−0.14	0.61	0.02	0.95	−0.07	0.81
Illness Duration	0.35	0.18	0.09	0.76	0.03	0.91	0.15	0.59	−0.04	0.89	−0.12	0.67
Medication Load	**0.64**	**0.007****	0.09	0.75	**−0.60**	**0.01****	0.42	0.12	−0.02	0.95	−0.36	0.19
HRSD-25	0.26	0.34	−0.22	0.43	−0.21	0.43	−0.08	0.77	−0.14	0.61	0.18	0.53
Accuracy Emotional face	0.24	0.36	0.14	0.62	0.26	0.33	0.32	0.25	−0.21	0.44	0.24	0.40
Accuracy Neutral face	<0.01	0.99	−0.20	0.46	−0.06	0.82	−0.20	0.48	**−0.46**	**0.07***	−0.03	0.91
	MW	p value	MW	p value	MW	p value	MW	p value	MW	p value	MW	p value
Mood Stabilizators (ON/OFF)	N/A		21.00	0.48	N/A		17.00	0.24	N/A		23.00	0.64
Anti Psychotic Medications (ON/OFF)	10.00	0.20	**12.50**	**0.07***	15.00	0.54	24.00	0.64	14.00	0.46	16.00	0.16
Anti Depressants (ON/OFF)	1.00	0.16	23.50	0.85	1.00	0.16	20.00	0.54	0.00	0.10	16.00	0.27
Benzodiazepines (ON/OFF)	**6.00**	**0.01****	26.50	0.95	14.00	0.13	25.00	0.81	25.00	0.78	15.00	0.16
Lifetime Presence of Alcohol/ Drugs Abuse or Dependence (YES/NO)	19.00	0.95	8.00	0.12	17.00	0.74	12.00	0.35	14.00	0.46	13.00	0.44

OMPFC: orbitomedial prefrontal cortex; MDD major depression disorder patients in depressed episode; BD: bipolar disorder patients in depressed episode; MW: Mann-Whitney U; rho: Spearman Rank correlation; HRSD-25: 25-item Hamilton Rating Scale for Depression

* trend towards significance

** p value survives exploratory analysis

N/A: does not apply because no MDD individual was taking any mood stabilizers; In healthy controls there were no significant relationships between EC and age and experiment accuracy