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Anticipation-related brain connectivity in bipolar and unipolar depression: a graph theory approach

Anna Manelis,[1] Jorge R. C. Almeida,[2] Richelle Stiffler,[1] Jeanette C. Lockovich,[1] Haris A. Aslam[1] and Mary L. Phillips[1]

Bipolar disorder is often misdiagnosed as major depressive disorder, which leads to inadequate treatment. Depressed individuals versus healthy control subjects, show increased expectation of negative outcomes. Due to increased impulsivity and risk for mania, however, depressed individuals with bipolar disorder may differ from those with major depressive disorder in neural mechanisms underlying anticipation processes. Graph theory methods for neuroimaging data analysis allow the identification of connectivity between multiple brain regions without prior model specification, and may help to identify neurobiological markers differentiating these disorders, thereby facilitating development of better therapeutic interventions. This study aimed to compare brain connectivity among regions involved in win/loss anticipation in depressed individuals with bipolar disorder (BDD) versus depressed individuals with major depressive disorder (MDD) versus healthy control subjects using graph theory methods. The study was conducted at the University of Pittsburgh Medical Center and included 31 BDD, 39 MDD, and 36 healthy control subjects. Participants were scanned while performing a number guessing reward task that included the periods of win and loss anticipation. We first identified the anticipatory network across all 106 participants by contrasting brain activation during all anticipation periods (win anticipation + loss anticipation) versus baseline, and win anticipation versus loss anticipation. Brain connectivity within the identified network was determined using the Independent Multiple sample Greedy Equivalence Search (IMaGES) and Linear non-Gaussian Orientation, Fixed Structure (LOFS) algorithms. Density of connections (the number of connections in the network), path length, and the global connectivity direction ('top-down' versus 'bottom-up') were compared across groups (BDD/MDD/healthy control subjects) and conditions (win/loss anticipation). These analyses showed that loss anticipation was characterized by denser top-down fronto-striatal and fronto-parietal connectivity in healthy control subjects, by bottom-up striatal-frontal connectivity in MDD, and by sparse connectivity lacking fronto-striatal connections in BDD. Win anticipation was characterized by dense connectivity of medial frontal with striatal and lateral frontal cortical regions in BDD, by sparser bottom-up striatum-medial frontal cortex connectivity in MDD, and by sparse connectivity in healthy control subjects. In summary, this is the first study to demonstrate that BDD and MDD with comparable levels of current depression differed from each other and healthy control subjects in density of connections, connectivity path length, and connectivity direction as a function of win or loss anticipation. These findings suggest that different neurobiological mechanisms may underlie aberrant anticipation processes in BDD and MDD, and that distinct therapeutic strategies may be required for these individuals to improve coping strategies during expectation of positive and negative outcomes.

1 Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, University of Pittsburgh, Pittsburgh, PA, USA
2 Department of Psychiatry and Human Behaviour, Alpert Medical School of Brown University, Providence, RI 02912, USA

Correspondence to: Anna Manelis,
Department of Psychiatry, Western Psychiatric Institute and Clinic,

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121 Meyran Avenue, Loeffler Building, Room 306,
Pittsburgh, PA 15213, USA
E-mail: anna.manelis@gmail.com

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Abbreviations: BDD = depressed individuals with bipolar disorder; BIC = Bayesian Information Criterion; HRSD = Hamilton Rating Scale for Depression; IMaGES = Independent Multiple sample Greedy Equivalence Search; LOFS = Linear non-Gaussian Orientation, Fixed Structure; MDD = depressed individuals with major depressive disorder; SEM = structural equation modelling; YMRS = Young Mania Rating Scale

Introduction

Bipolar disorder and major depressive disorder are debilitating mood disorders that result in psychosocial, emotional and cognitive dysfunction of affected individuals. The prevalence of depressive symptoms makes it clinically challenging to distinguish bipolar disorder from major depressive disorder, especially during depressive episode (Hirschfeld *et al.*, 2003). Neuroimaging studies that focus on understanding the differences in abnormal brain functioning underlying emotional and cognitive impairments in depressed individuals with bipolar disorder (BDD) and depressed individuals with major depressive disorder (MDD) may help to identify neurobiological markers differentiating these disorders, thus helping to develop better therapeutic strategies and improve treatment outcomes (Phillips and Kupfer, 2013; Phillips and Swartz, 2014).

Previous studies showed that depressed individuals are impaired in processing of reward and loss (Martin-Soelch, 2009; Eshel and Roiser, 2010). One component of reward/loss processing is reward/loss anticipation (Berridge and Robinson, 2003; Gard *et al.*, 2006) during which a neutral stimulus predicts receipt of either reward or punishment, thus evoking a relevant motivational state (Robinson *et al.*, 2014). In healthy individuals, reward anticipation relies on functioning of ventral striatum signalling about the level of anticipated reward (Knutson *et al.*, 2001; Schultz, 2002), anterior cingulate cortex activating as a function of anticipatory arousal (Critchley *et al.*, 2001) and effort (Croxson *et al.*, 2009), and parietal regions processing outcome predictability (Platt and Glimcher, 1999; Verney *et al.*, 2003; Ernst *et al.*, 2004).

Depressed individuals, relative to healthy control subjects, show reduced expectation of positive outcomes (Meehl, 1975; Davidson *et al.*, 2002; Treadway *et al.*, 2009; Sherdell *et al.*, 2012), and increased expectation of negative outcomes (Andersen *et al.*, 1992; Strunk *et al.*, 2006; Strunk and Adler; 2009). These altered anticipation patterns may be associated with altered functioning of striatal and prefrontal cortices and may depend on current diagnosis (i.e. major depressive disorder versus bipolar disorder) and mood state (Mason *et al.*, 2012; Nusslock *et al.*, 2012; Caseras *et al.*, 2013; Chase *et al.*, 2013; Ubl *et al.*, 2015; Yip *et al.*, 2015). The only study that directly compared anticipation-related brain activation patterns in bipolar disorder versus MDD versus healthy control subjects showed increased left ventrolateral prefrontal cortex activation in BDD versus MDD and healthy control subjects, but reduced anterior cingulate cortex activation in bipolar disorder and MDD versus healthy control subjects during reward anticipation (Chase *et al.*, 2013). Other studies showed reduced ventral striatum (VS), orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) activation during reward anticipation and reduced ACC activation during loss anticipation in MDD versus healthy control subjects (Ubl *et al.*, 2015); increased VS activation during reward anticipation (Mason *et al.*, 2012; Nusslock *et al.*, 2012), but decreased VS activation during loss anticipation (Yip *et al.*, 2015) in euthymic individuals with bipolar disorder versus healthy control subjects; and a negative correlation between depressive symptoms and VS activation during reward anticipation in individuals with major depressive disorder, bipolar disorder, attention deficit hyperactivity disorder, alcohol dependency and schizophrenia independently of current psychiatric diagnosis (Hägele *et al.*, 2015).

Altered activation in a selected region cannot fully explain complex patterns of cognitive and emotional impairments in psychiatric disorders. It is, therefore, important to examine functioning of a whole network including effective connectivity among the regions (Van Horn and Poldrack, 2009; Worbe, 2015). Specifically, in addition to aberrant anticipation-related activation patterns in prefrontal cortical-VS circuitry, BDD and MDD may also have distinct aberrant patterns of brain connectivity among these regions (Phillips and Swartz, 2014). To date, there has been no systematic attempt to characterize and compare functional and effective connectivity in BDD, MDD and healthy control subjects during reward and loss anticipation.

The present study aimed to fill this gap using Bayesian network approaches: the Independent Multiple sample Greedy Equivalence Search (IMaGES; Ramsey *et al.*, 2010), and Linear non-Gaussian Orientation, Fixed Structure (LOFS) algorithms (Ramsey *et al.*, 2011). Due to IMaGES search-based nature, this method allows examination of larger networks without *a priori* model specification (Mumford and Ramsey, 2014) and to overcome the limitations of previous clinical neuroimaging studies (e.g. using dynamic causal modelling) that limited models to three to four regions of interest (Phillips and Swartz, 2014). IMaGES and LOFS were specifically designed for a multi-subject functional MRI data processing, have been able to identify

over 95% of connections in simulation studies (Ramsey *et al.*, 2010), and have already been successfully used in studies of healthy individuals (Boukrina *et al.*, 2014; Manelis and Reder, 2014; Mills-Finnerty *et al.*, 2014) and individuals with autism (Hanson *et al.*, 2013). The models are described in terms of the number of connections, path length (Bullmore and Sporns, 2009), and the global connectivity direction ('top-down' versus 'bottom-up').

Based on previous studies of brain connectivity in BDD, MDD and healthy control subjects (Almeida *et al.*, 2009; Versace *et al.*, 2010), we hypothesized that anticipation-related connectivity patterns would depend not only on participants' diagnoses (BDD versus MDD versus healthy control subjects), but also on the specific anticipation condition (win anticipation versus loss anticipation). Anticipation involves emotional and motivational components, and previous studies showed increased resting state connectivity in the affective and cognitive control networks for depressed individuals versus healthy control subjects (Sheline *et al.*, 2010). Based on this, we hypothesized that depressed individuals would have more connections within the anticipation network than healthy control subjects.

Materials and methods

Participants

Participants were recruited from general community through advertisements, from universities (University of Pittsburgh, Carnegie Mellon University), counselling and medical centres, Western Psychiatric Institute and Clinic (WPIC) outpatient clinics and community mental health clinics through advertisements and referrals. Some patients were referred from other WPIC research studies. We also presented information about the study monthly at the WPIC's Intensive Outpatient Program groups. All diagnoses were made by a trained clinician and confirmed by a psychiatrist(s). The study was approved by the University of Pittsburgh Institutional Review Board. All participants gave written informed consent before participation in the study. They were right-handed, native English speakers. The three groups of participants [BDD (with bipolar disorder type I) = 36, MDD = 46, healthy control subjects = 42] were matched on age, gender and IQ. Healthy control subjects had no family history of psychiatric disorders.

Patients were diagnosed according to DSM-IV criteria and the Structure Clinical Interview for DSM-IV, Research Version (SCID-P; First *et al.*, 1995), had a Hamilton Rating Scale for Depression (HRSD-25; Hamilton, 1960) score $\geqslant 10$, and a Young Mania Rating Scale (YMRS; Young *et al.*, 1978) score $\leqslant 10$ on the day of the scan. The relatively low threshold of HRSD-25 = 10 was used to allow recruitment of depressed individuals with bipolar disorder who had subthreshold depression severity at the time of assessment, but who had recently had higher severity depression. Of all patients, only one patient with bipolar disorder had a HRSD-25 score of 11. All other patients had HRSD-25 scores $\geqslant 15$. Table 1 reports participants' clinical characteristics. Exclusion criteria included history of head injury, systemic medical illness, cognitive impairment (score < 24 on the Mini-Mental State Examination; Folstein *et al.*, 1975), premorbid IQ < 85 measured by the National Adult Reading Test (Blair and Spreen, 1989), current alcohol/drug abuse, metal in the body, pregnancy, and claustrophobia. Data from five BDD, seven MDD and six healthy control subjects were excluded from the analyses due to excessive motion in the scanner (> 2 mm) or errors rate > 2, leaving 31 BDD, 39 MDD and 36 healthy control subjects in the dataset.

To account for different medications we calculated total medication load using the following steps (Hassel *et al.*, 2008): (i) all psychotropic medications were classified as follows: antidepressant, anxiolytic/benzodiazepine, mood stabilizer, antipsychotic, or unknown/other psychotropic; (ii) each medication was assigned a medication load based on the 'usual therapeutic dose' where 1 = lower than usual therapeutic dose and 2 = higher than or equal to usual therapeutic dose. e.g. < 1000 mg of lithium per day = 1, $\geqslant 1000$ mg of lithium per day = 2; and (iii) medication loads were summed by class or across all five classes listed above to obtain the total medication load for a given study participant.

Measuring medication load has several advantages: (i) patients who remain medication-free are unlikely to be matched for illness severity with patients who require medication; (ii) medicated MDD and BDD are more representative of the patient population versus those who are not medicated; (iii) total medication load calculation allows avoidance of multiple comparisons among various medication subgroups; and (iv) total medication load reflects both the dose and variety of various medications taken by BDD and MDD (Hassel *et al.*, 2008).

Task

During the guessing task (Forbes *et al.*, 2009; Supplementary Fig. 1), participants were presented with a 4-s question mark to guess whether the number is greater than '5' by pressing a corresponding button. After that, they were shown either a 6-s win anticipation (upward arrow) screen suggesting a possibility to win money (12 trials), or a 6-s loss anticipation (downward arrow) screen suggesting a possibility to lose money (12 trials). A 1-s feedback (win, loss, or no-change outcomes) was followed by a 9-s intertrial interval. Participants received $1 for each win and lost 50 cents for each loss.

Neuroimaging data acquisition and analyses

Acquisition

Functional MRI data were acquired at the University of Pittsburgh using a Siemens MAGNETOM TrioTim 3 T MR system. A high-resolution structural image ($1 \times 1 \times 1$ mm) was acquired using MPRAGE (repetition time = 2200 ms, echo time = 3.29 ms, field of view = 256, flip angle = 9°, 192 slices). Functional data (240 volumes) were collected using a gradient-echo, echo-planar sequence (voxel size: $3.2 \times 3.2 \times 3.1$ mm, repetition time = 2000 ms, echo time = 28 ms, field of view = 205, flip angle = 90°, 39 slices).

Preprocessing

The images were preprocessed and analysed using FSL5.0.8 (www.fmrib.ox.ac.uk/fsl). Preprocessing included non-linear

Table 1 Demographic and clinical characteristics of healthy and depressed participants

	BDD ($n = 31$)	MDD ($n = 39$)	HC ($n = 36$)	Group differences	Tukey HSD for three groups, or t-test/chi-square test for BD versus MDD
Gender, male/female	7/24	8/31	10/26	$\chi^2 = 0.6$, $P = 0.75$	
Age, years, mean (SD)	33.38 (8.44)	31.51 (7.99)	32.78 (6.10)	F (2,103) = 0.6, $P = 0.6$	
NART IQ, mean (SD)	112.00 (8.54)	113.20 (8.45)	112.92 (6.97)	F (2,103) = 0.2, $P = 0.8$	
Level of education	5.45 (1.12)	6.33 (1.24)	6.56 (1.21)	F (2,103) = 7.8, $P = 0.001$	BD < MDD,HC; HC = MDD
HRSD-25 score, mean (SD)	25.52 (7.24)	26.97 (5.77)	1.72 (2.20)	F (2,103) = 246.9, $P < 0.001$	BD,MDD > HC; BD = MDD
YMRS score, mean (SD)	3.84 (2.90)	3.97 (2.77)	0.50 (1.11)	F (2,103) = 24.4, $P < 0.001$	BD,MDD > HC; BD = MDD
State anxiety score, mean (SD)	55.97 (10.83)	57.23 (8.28)	26.81 (7.02)	F (2,103) = 139.3, $P < 0.001$	BD,MDD > HC; BD = MDD
Trait anxiety score, mean (SD)	60.53 (9.13)	59.18 (9.61)	26.00 (5.62)	F (2,103) = 186.5, $P < 0.001$	BD,MDD > HC; BD = MDD
Mania age at onset, years, mean (SD)	23.03 (8.57)	na	na		
Mania duration, years, mean (SD)	10.35 (7.68)	na	na		
Depression age at onset, years, mean (SD)	18.10 (7.21)	18.36 (7.24)	na		$t(68) = -0.15$, P = ns
Depression duration, years, mean (SD)	15.28 (8.71)	13.15 (7.53)	na		$t(68) = 1.1$, P = ns
Illness age at onset, years, mean (SD)	17.03 (4.92)	18.36 (7.24)	na		$t(68) = 1.7$, P = ns
Illness duration, years, mean (SD)	16.35 (8.17)	13.15 (7.53)	na		$t(68) = -0.87$, P = ns
Number of mania episodes	1.94 (1.03)	na	na		
Number of depression episodes	3.13 (1.38)	2.92 (1.01)	na		$t(68) = 0.7$, P = ns
Psychotropic medication load, mean (SD)	3.77 (2.47)	2.20 (2.00)	na		$t(68) = 2.9$, $P = 0.005$
Antipsychotic, taking/not taking	19/12	3/36	0/36		$\chi^2 = 23.0$, $P < 0.001$
Antidepressant, taking/not taking	12/19	26/13	0/36		$\chi^2 = 5.4$, $P = 0.02$
Mood stabilizer, taking/not taking	20/11	6/33	0/36		$\chi^2 = 17.9$, $P < 0.001$
Benzo, taking/not taking	8/23	10/29	0/36		$\chi^2 = 0$, P = ns

Depressed individuals with bipolar disorder (BDD) and depressed individuals with major depressive disorder (MDD) are contrasted on clinical variables that are present in patient groups, but absent in healthy control (HC) subjects. Given that the *F*-test yields significant results, Tukey's HSD *post hoc* tests were performed in order to compare BDD, MDD and healthy control subjects. na = not applicable; NART IQ = National Adult Reading Test intelligence quotient; SD = standard deviation; YMRS scores in both groups of depressed individuals were driven mainly by higher scores on the Irritability item (Item 5, scored out of 8 points). For this item, the mean score of 1.4 (SE = 0.22, maximum score = 4 reported in two participants) was observed in BDD, and the mean score of 1.7 (SE = 0.17, maximum score = 4 reported in three participants) was observed in MDD. The mean scores for all other items were < 0.65 and were significantly lower than the mean scores for Irritability (all *P*-values < 0.001 in both depressed groups).

noise reduction using SUSAN (http://fsl.fmrib.ox. ac.uk/fsl/fslwiki/SUSAN); motion correction with MCFLIRT (Jenkinson *et al.*, 2002), non-brain removal using BET (Smith, 2002), spatial smoothing with a Gaussian kernel of full-width at half-maximum = 6 mm; multiplicative mean intensity normalization of the volume at each time point; high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 30.0 s). A haemodynamic response function was modelled using a Gamma function.

Unexpected artefacts were detected using the independent component analysis (ICA)-based data exploration using MELODIC (Beckmann and Smith, 2004) and FIX (Grianti *et al.*, 2014; Salimi-Khorshidi *et al.*, 2014) (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIX). The number of dimensions (ICA components) was estimated using the Laplace approximation to the Bayesian evidence of the model order (Minka, 2000; Beckmann and Smith, 2004). Trained-weights files supplied with FIX were used as training data. The quality of FIX classification was checked in 25 participants randomly chosen from a set of 106. For each noise component selected by FIX, we carefully examined a thresholded IC map and a corresponding time course, to make a decision about whether that specific component might be considered as noise (Tohka *et al.*, 2008; Kelly *et al.*, 2010). This quality assurance analysis suggested that FIX successfully detected noise components.

The high-resolution structural images were segmented using the fsl_anat script to separate white matter, grey matter and CSF, and to also segment subcortical structures. The white matter and CSF masks were then coregistered with functional images, and their timecourses were extracted from the preprocessed functional data for further analyses. Motion outliers (time points where the functional MRI signal was corrupted due to subject motion) were identified using the fsl_motion_outliers script (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLMotionOutliers). A confound matrix from this analysis was then combined with the white matter and CSF time courses and used as a confound variable of no interest in the first-level analyses.

Blood oxygenation level-dependent images were registered to the high-resolution structural (MPRAGE) images using FLIRT (Jenkinson and Smith, 2001; Jenkinson *et al.*, 2002), the high-resolution images were registered to the MNI152_T1_2 mm template using FNIRT (Andersson *et al.*, 2007), and the two resulting transformations were concatenated and applied to the original blood oxygenation level-dependent image to transform it to MNI space. Preprocessed data were submitted to a first-level analysis with Guessing, Win anticipation, Loss anticipation, Feedback and Error trials as regressors.

Group-level analyses were conducted using FLAME1. Significant activation clusters were determined by thresholding

Z-statistic images in the whole brain mask at $z > 3.72$ (uncorrected voxel wise $P < 0.0001$) and a corrected cluster significance threshold (Worsley, 2001) of $P < 0.05$. The anticipation network was derived across all participants (BDD, MDD and healthy control subjects; total number = 106). All analyses were whole-brain. We hypothesized that some brain regions would support general anticipation processes independently of emotional valence of anticipated outcomes. Such non-specific anticipation processes may include motivation to perform the task, remembering task-specific rules during anticipation periods, planning of future motor responses, etc. Brain activation characterizing these non-specific (or general) anticipation processes was examined by contrasting all anticipation trials (Win anticipation + Loss anticipation) versus baseline. Based on previous research, we also hypothesized that other brain regions (e.g. VS) would be more sensitive to anticipation of positive versus negative (and vice versa) outcomes. These regions were determined by contrasting win anticipation versus loss anticipation, and vice versa. The brain regions identified during these analyses comprised the anticipation network that is defined as a set of regions activating during anticipation periods and underlying emotion non-specific and emotion-specific anticipation processes.

Graph analysis

The IMaGES algorithm is a Bayesian search algorithm that starts with an empty graph for a set of regions of interest (21 regions of interest in our study). The algorithm then tests all possible models with one connection and computes the Bayesian Information Criterion (BIC) score for each subject. A model with the highest mean BIC score across all datasets (i.e. across all participants) is selected and the algorithm starts searching for the second connection, taking into account the fact that one connection is already present in the model. The algorithm continues to add connections to the model, one at a time, every time selecting a model with the highest mean BIC score, until the BIC score is no longer improved. After that, the algorithm removes connections from the model, one at a time, until the BIC score can no longer be improved (Ramsey *et al.*, 2010, 2011). The IMaGES algorithm determines the presence of connections (or edges) between the regions of interest (or nodes) in the network and produces a Markov equivalence class of models consisting of directed acyclic graphs that have the same structure. The IMaGES algorithm ensures that directed acyclic graphs do not include any connectivity cycles (or triangulation) by increasing a penalty in the BIC score.

After IMaGES identified connections within each model, a directed acyclic graph for each group/condition was submitted to the LOFS algorithm that oriented those connections using the R3 rule (Ramsey *et al.*, 2014). LOFS determined the connections orientation (i.e. a causal relationship between two regions of interest) by exploiting the fact that the residuals of any incorrect linear model will be more Gaussian than the residuals of the correct model with independent non-Gaussian sources of error (Ramsey *et al.*, 2011, 2014; Mumford and Ramsey, 2014). The degree of non-Gaussianity was estimated using the Anderson-Darling score (Anderson and Darling, 1952).

A total of six graph models were created (Win/Loss anticipation × BDD/MDD/healthy control subjects). All graphs had the same nodes—the regions of interest comprising the anticipation network. Time series (30–36 repetition times each) were extracted from each region of interest using Featquery. For a large region of interest that covered three brain regions, we extracted time series from a 6-mm radius sphere drawn around the local maxima coordinates. Graph analyses were conducted using TETRAD-V (v.5.1.2-3; http://www.phil.cmu.edu/projects/tetrad). First, condition-specific time series from all regions of interest for all participants in a group were submitted to IMaGES with increasing penalty discount in the Bayesian Information Criterion (BIC) score to avoid 'triangulation' (when three regions of interest are connected to each other) and the possibility of spurious causal connections (Ramsey *et al.*, 2010, 2011, 2014; Mumford and Ramsey, 2014). Then, we submitted the outcome from the IMaGES algorithm to the LOFS algorithm. We then estimated model goodness-of-fit to each set of data by submitting the outcomes of the LOFS algorithm to a structural equation modelling (SEM) estimator that estimated the values of parameters for a SEM parametric model with a regression optimizer.

Given that the dependence between the two variables in a directed acyclic graph is 'conditioned on all other variables in the directed acyclic graph' (Guo *et al.*, 2014), each connection in the directed acyclic graph should be considered in the context of the whole graph, not as an independent variable. The IMaGES search algorithm includes several steps to identify a winning model, but the algorithm steps are not a source of the variation. An outcome of the algorithm is deterministic. Once a winning model has been identified, it is independent of any search process. If the edge (or the connection) is detected, its presence is statistically significant as justified by the improvement in the BIC score. If the edge is absent, that means that adding that edge to the model did not improve the model fit. Given that during model search the algorithm always selects a model with the best BIC score, the final model is the best model for the set of variables for a sample of subjects. Two directed acyclic graphs can be compared in terms of presence versus absence of a specific connection (or edge) in the two models. If the connection is present in both models, the strength of connections (i.e. the SEM coefficients) can be compared using inferential statistics.

Further in the text, the presence of a specific connection without considering its orientation is indicated with a dash (e.g. RVS–RFCm), and the connectivity direction is indicated with an arrow (e.g. RVS→RFCm). The graphs will be described in terms of density of connections (the number of connections in the network), path length (the number of connections to travel from one region to another) (Bullmore and Sporns, 2009), and the global connectivity direction ('top-down' versus 'bottom-up').

Exploratory analyses

Exploratory analyses examined linear relationships between the connectivity strength (indicated by the SEM coefficients) for all connections in the model discovered by IMaGES and oriented by LOFS for each patient group (BDD, MDD) and each anticipation condition (Win/Loss anticipation) to predict the HRSD-25 and YMRS scores as well as the total illness duration, total number of manic/depressive episodes and medication load.

In addition, we conducted a series of *t*-tests to compare the SEM coefficients for patients who were ON/OFF antidepressants, antipsychotics, benzodiazepines and mood stabilizers. Given multiple comparisons, all *P*-values were Bonferroni

corrected for the number of comparisons (0.05/number of connections in each network).

Results

Abbreviations for brain regions referred to hereafter are presented in Box 1.

Box 1 Brain area designations

ACC = anterior cingulate cortex
DLPFC = dorsolateral prefrontal cortex
LAng = left angular gyrus
LFP = left frontal pole
LFPm = left medial frontal pole
LIFG = left inferior frontal gyrus
LLOCinf = left lateral occipital cortex inferior division
LMFG = left middle frontal gyrus
LMTG = left middle temporal gyrus
LOFg = left fusiform gyrus
LOP/ROP/OP = left/right/occipital pole
LVS = left ventral striatum
OFC = orbitofrontal cortex
OFg = right and left occipital fusiform gyrus
PFC = prefrontal cortex
RAng = right angular gyrus
RDLPFC = right dorsolateral prefrontal cortex
RFCm = right medial prefrontal cortex
RFP = right frontal pole
RFPm = right medial frontal pole
RLOCinf = right lateral occipital cortex
RMFG = right middle frontal gyrus
ROFg = right fusiform gyrus
RVS = right ventral striatum
VS = ventral striatum

Functional MRI

Consistent with previous studies (Ernst *et al.*, 2004; Fan *et al.*, 2007), anticipatory processes activated bilateral prefrontal cortical (PFC) regions, left middle temporal gyrus (LMTG), parietal and occipital regions in the All anticipation > baseline contrast. A left frontopolar cluster covered three regions: left frontal pole (LFP), left middle frontal gyrus (LMFG) and left inferior frontal gyrus (LIFG). Win anticipation elicited greater activation in the right medial prefrontal cortex (RFCm), bilateral VS and occipital pole (OP) than loss anticipation. Loss anticipation elicited greater activation in bilateral fusiform gyrus (OFg) than win anticipation (Fig. 1 and Table 2; see Supplementry Table 1 for All anticipation < baseline activations).

Given that education and medication load differed across the groups (in particular, BDD versus MDD, see Table 1), we tested whether the anticipation network derived from the whole sample would change if education and medication load were used as covariates in the analyses. The results of these analyses revealed no association between education level and anticipation-related brain activation, as well as between medication load and anticipation-related brain activation in either brain region, at least at the threshold that was chosen for this study. The anticipation network revealed in this analysis was very similar (almost identical) to the network identified in the main analysis that did not use education and medication load as covariates (Supplementary Table 2).

Graphical modelling in reward and loss anticipation regions

Independently of group and condition, LIFG was disconnected from other region, and the posterior and medial regions of the postcentral/precentral gyrus were connected only to each other. Another 18 regions comprised 'occipital' and 'fronto-parietal-temporo-striatal' subnetworks.

Occipital subnetwork

The 'occipital' subnetwork included bilateral occipital regions (LOFg, ROFg, LLOCinf, RLOCinf, LOP, and ROP) connected to each other with five connections (Fig. 2). LLOCinf–RLOCinf, RLOCinf–ROFg and RLOCinf–ROP were common connections for all groups and conditions. Healthy control subjects and MDD had similar connectivity patterns. In addition to common connections, they had LOFg–ROFg, LLOCinf–LOP connection for win anticipation, and LOP–ROP, LOFg–LLOCinf connections for loss anticipation. BDD had similar connectivity patterns for win and loss anticipation (common connections, ROFg→LOFg, LOP–ROP) that differed from those in healthy control subjects and MDD. The LOP–ROP connection during win anticipation was stronger for BDD ON versus BDD OFF antipsychotics: $t(29) = -4.87$, P-value < 0.001, with significantly stronger connectivity in BDD who were OFF antipsychotic medications.

Fronto-parietal-temporo-striatal subnetwork

The fronto-parietal-temporo-striatal subnetwork included frontal (RFP, LFP, RDLPFC, RMFG, LMFG, RFPm, RFCm), striatal (RVS, LVS), parietal (RAng,LAng) and temporal (LMTG) regions (Fig. 3). Four connections, three of which were between the homologous brain regions, were common for all three groups and both anticipation conditions (LAng–RAng, LFP–RFP, LVS–RVS, and RDLPFC–RFP).

For win anticipation, connectivity density was the highest in individuals with bipolar disorder (11 connections), followed by MDD (10 connections), and healthy control subjects (nine connections). The longest connectivity path was observed in BDD and included four right frontal regions: RFCm→RFPm→RFP→RDLPFC. The longest connectivity paths in healthy control subjects and MDD included three regions (healthy control subjects: RAng→LAng→LMTG; MDD: RAng→RDLPFC→RFP, and LVS→RFCm→RFPm).

For loss anticipation, connectivity density was the highest in healthy control subjects (11 connections), followed by MDD (10 connections) and BDD (eight connections). Among three groups, the longest connectivity path was observed in MDD and included seven regions connected

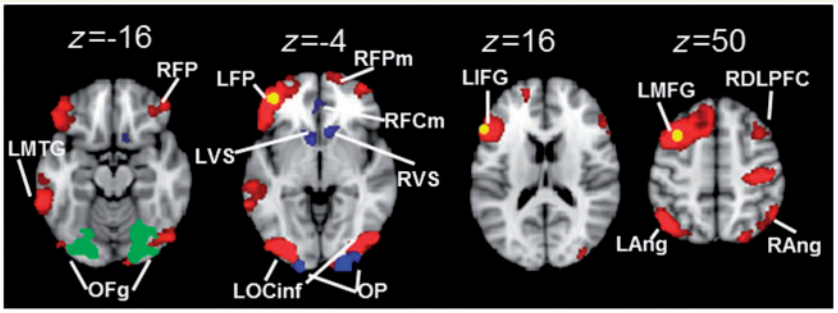

Figure 1 Anticipation-related network. Activation maps thresholded at $z > 3.72$ ($P < 0.0001$) and a corrected cluster significance threshold of $P < 0.05$. Activation for the All Anticipation periods > baseline contrast is in red, the local maxima for a large left frontopolar cluster is in yellow, win anticipation > loss anticipation contrast in in blue, and loss anticipation > win anticipation contrast is in green. The three local maxima for a large left PFC cluster are in yellow.

Table 2 Anticipation-related brain activation

	Region	*n* voxels	*Z*-max	*x*	*y*	*z*
Win and loss anticipation: increases ($z > 3.72$, $P < 0.05$)						
L	Frontal pole (LFP)	8514	7.75	−42	48	−8
L	Inferior frontal gyrus (LIFG)	–	7.54	−56	24	12
L	Middle frontal gyrus (LMFG)	–	7.75	−34	14	54
L	Angular gyrus (LAng)	2115	8.05	−46	−62	40
R	Lateral occipital cortex, inferior division (RLOCinf)	1828	8.31	34	−86	8
R	Angular gyrus (RAng)	1295	6.29	50	−60	34
L	Lateral occipital cortex, inferior division (LLOCinf)	1216	7.87	−28	−90	−2
L	Middle temporal gyrus (LMTG)	1088	6.55	−64	−44	−12
R	Postcentral/precentral lateral (RPostPre,l)	741	6.31	34	−24	52
R	Dorsolateral prefrontal cortex (RDLPFC)	643	5.64	50	30	24
R	Frontal pole, lateral (RFP)	582	5.8	38	58	−4
R	Middle frontal gyrus (RMFG)	246	5.08	38	16	54
R	Frontal pole, medial (RFPm)	193	5.05	16	66	−2
R	Postcentral/precentral gyrus, medial (RPostPrem)	155	5.04	8	−32	56
Win anticipation > loss anticipation ($z > 3.72$, $P < 0.05$)						
R	Occipital pole (ROP)	556	7.85	22	−98	0
R	VS (accumbens) (RVS)	189	5.19	8	18	−8
L	VS (accumbens) (LVS)	170	4.75	−8	10	−4
L	Occipital pole (LOP)	135	5.71	−16	−106	−6
R	Medial frontal cortex/ paracingulate gyrus (RFCm)	118	4.28	10	46	−10
Loss anticipation > win anticipation ($z > 3.72$, $P < 0.05$)						
R	Occipital fusiform gyrus (ROFg)	834	6.79	22	−88	−18
L	Occipital fusiform gyrus (LOFg)	569	5.94	−30	−82	−22

L = left; R = right; B = bilateral.

in the bottom-up direction: RFCm→RFPm→RFP→RDLPFC→RAng→RMFG. The longest path in healthy control subjects included four regions connected in the top-down direction: RFP→RFPm→RFCm→RVS. The longest path in BDD also included four regions, but they were connected in the bottom-up direction: RAng→RDLPFC→RFP→LFP. Interestingly, no fronto-striatal connectivity was observed in BDD during loss anticipation.

Exploratory analyses

There was no association between connectivity strength and HRSD-25 scores, illness duration and a total number of manic/depressive episodes in either BDD or MDD groups in either win or loss anticipation conditions. There was an association between the strength of connections in the loss anticipation network [$F(16,22) = 2.36$, P-value = 0.03, $R^2 = 0.63$, adjusted $R^2 = 0.36$] and YMRS scores in MDD. MDD with higher YMRS scores had weaker LAng–LMTG, but stronger LVS–RVS connectivity. Below is the equation to compute YMRS scores for MDD.

$$\text{YMRS} = 1.6 - 6.8(\text{SEM coefficient for LMTG} \rightarrow \text{LAng}) + 6(\text{SEM coefficient for LVS} \rightarrow \text{RVS}) \quad (1)$$

There was also an association between the strength of connections in the loss anticipation network [$F(14,16) = 3.25$,

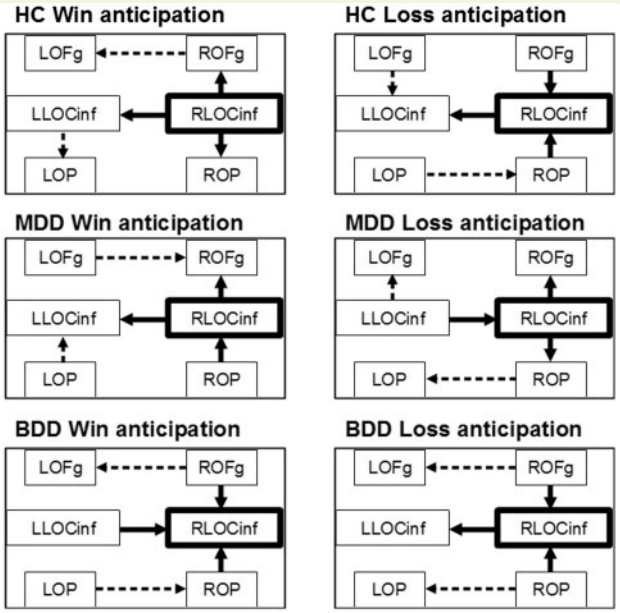

Figure 2 Connectivity within the occipital subnetwork. The arrows show a connection (edge) orientation. Thick frames denote regions with three connections going to or from these regions. Connections common for all groups and conditions are shown in solid arrows, while all other connections are shown in dashed arrows.

P-value = 0.013, $R^2 = 0.74$, adjusted $R^2 = 0.51$] and a total medication load in BDD. BDD with greater medication load had weaker RDLPFC–RFP and LLOCinf–RLOCinf connectivity, but stronger RLOCinf–ROP, RLOCinf–ROFg, LAng–RAng, LLOCinf–RLOCinf, and RAng–RDLPFC connectivity. Below is the equation to compute medication load for BDD.

$$\begin{aligned}\text{Medication load} = & -5.8 \\ & +8.5(\text{SEM coefficient for RAng} \rightarrow \text{RDLPFC}) \\ & -5.8(\text{SEMcoefficient for RDLPFC} \rightarrow \text{RFP}) \\ & +6.7(\text{SEM coefficient for RAng} \rightarrow \text{LAng}) \\ & +14.8(\text{SEMcoefficient for ROP} \rightarrow \text{RLOCinf}) \\ & +11.4(\text{SEM coefficient for ROFg} \rightarrow \text{RLOCinf}) \\ & -7.5(\text{SEMcoefficient for RLOCinf} \rightarrow \text{LLOCinf}) \\ & +4.6(\text{SEM coefficient for ROP} \rightarrow \text{LOP}) \end{aligned} \quad (2)$$

Discussion

Understanding the functioning of large-scale brain networks and their relationship to psychiatric disorders has potential to provide novel insights into underlying neural mechanisms of these disorders (Menon, 2011). This is the first study to assess functional and effective connectivity in a large-scale anticipation network in BDD versus MDD versus healthy control subjects using graph theory methods. The major finding was that BDD and MDD with comparable levels of current depression differed from each other and healthy control subjects in density of connections, connectivity path length, and the connectivity direction as a function of win/loss anticipation. Healthy control subjects had sparse connectivity for win anticipation, but denser connectivity for loss anticipation that was characterized by 'top-down' fronto-striatal and fronto-parietal connectivity. BDD versus healthy control subjects and MDD had denser connectivity for win anticipation, but sparser connectivity for loss anticipation lacking fronto-striatal connections. In MDD, win and loss anticipation were characterized by the same connectivity density, and the 'bottom-up' connectivity direction in the fronto-parietal-temporo-striatal subnetwork with longer path length for loss than win anticipation.

Although it might be difficult to interpret the results when both hypo- and hyper-connectivity may be considered aberrant, this concept becomes much easier to understand if we make parallels between brain connectivity and a peripheral biological measure routinely examined in clinical practice, for example, the amount of thyroid hormone. Having too much or too little thyroid hormone are both considered abnormal, and lead to different problems with physical health. In the same way, having over-connected, or under-connected patterns of neural network connectivity may be abnormal, and may be associated with different psychiatric disorders, as our present data suggest. Whether a person has 'too much', or 'not enough' of thyroid hormone is determined by comparing an individual's values with the normative laboratory range of measurements of this hormone. As there are no 'normative laboratory range of measurements' for brain connectivity (yet), we compared brain connectivity values of patients with those of healthy

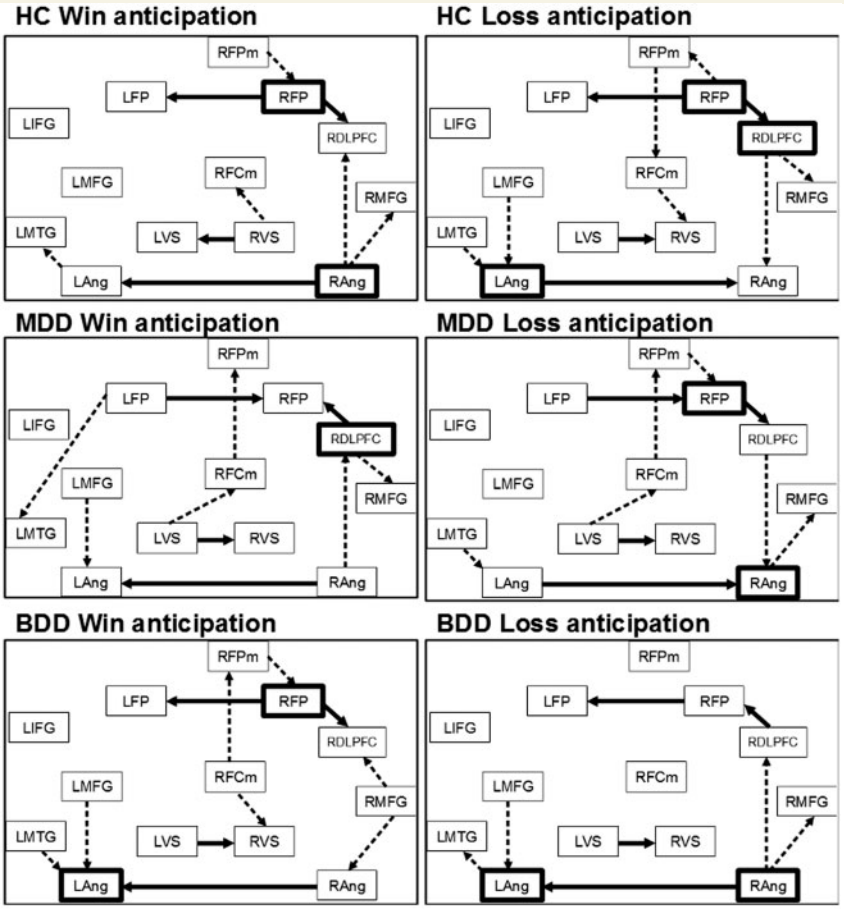

Figure 3 Connectivity within the fronto-parietal-temporo-striatal sub-network. The arrows show a connection (edge) orientation. Thick frames denote regions with three connections going to or from these regions. Connections common for all groups and conditions are shown in solid arrows, while all other connections are shown in dashed arrows. Abbreviations are presented in Box 1.

controls. In this way, we were able to determine the extent to which each of the two patient groups differed from, and were abnormal relative to, the healthy control range of connectivity values.

Previous studies suggest that hyper-connectivity may be a neural signature of depression by showing that depressed individuals versus healthy control subjects had increased intrinsic resting state connectivity in the affective, cognitive control, and default mode networks (Sheline *et al.*, 2010), and that electroconvulsive therapy (ECT) treatment-related reductions in functional connectivity between medial PFC, DLPFC and parietal cortices correlated with reduction in depressive symptoms (Perrin *et al.*, 2012). Our study, however, demonstrated that hyper-connectivity was not a neural signature of depression *per se*, but, rather, depended on whether depressed individuals suffered from major depressive disorder or bipolar disorder, and the anticipatory context (i.e. anticipating winning or losing money). For example, hyper-connectivity during anticipation of potentially rewarding outcomes, shown by BDD, but not by MDD, may be a biomarker of impulsive, risky, pleasure-seeking behaviours that characterize predisposition to mania.

Anticipation involves attentional, emotional and motivational components (Berridge *et al.*, 2003; Gard *et al.*, 2006; Robinson *et al.*, 2014) that may rely on different connectivity patterns depending on the emotional valence of an anticipatory condition. During loss anticipation, participants expect to lose money, which, in turn, may induce such negative feelings as sadness, fear, anger, decrease in motivation to continue the task, etc. During this condition, healthy control subjects had the highest (of all groups) connectivity density and distinct 'top-down' connectivity direction from RFP down to RVS and parietal cortex. While having more connections in the network may be energetically costly (Bullmore and Sporns, 2009), it may also help healthy control subjects to 'pre-regulate' negative emotions related to potential monetary loss by downregulating VS response. During win anticipation, participants expect to gain money, which, in turn, may induce such positive feelings as happiness, joy, increase in interest and motivation to continue task performance, etc. During this condition, connectivity density in the fronto-parietal-temporo-striatal subnetwork in healthy control subjects was the lowest compared with other groups, and lateral frontal regions involved in prospective (Burgess *et al.*, 2007) and working

(Owen *et al.*, 2005) memory were disconnected from VS and medial PFC, potentially because no emotion regulation was required during win anticipation.

MDD had the same connectivity density and a 'bottom-up' connectivity pattern originating in LVS for win and loss anticipation. During loss anticipation, changes in LVS resulted in activation changes in parietal and multiple frontal regions involved in emotion regulation and attentional control (Phillips *et al.*, 2008*a*; Kanske *et al.*, 2011), which may have impaired the ability of MDD to downregulate negative emotions during anticipation of monetary loss. The fact that YMRS score was associated with stronger subcortical but weaker cortical connectivity during loss anticipation in MDD may perhaps reflect a relationship between YMRS score and irritability during depressive episode in MDD, where thinking about potential loss is associated with increased irritability, and associated with reduced 'top-down' cognitive control processes. Indeed, YMRS scores in both groups of depressed individuals were driven mainly by higher scores on the Irritability item (Table 1). During win anticipation, LVS was disconnected from lateral frontal and parietal regions, thus allowing those regions to function independently of anticipated or perceived reward value. Similarities in connectivity density for win and loss anticipation in MDD may suggest that negative biasing and low anticipatory pleasure (Sherdell *et al.*, 2012) characterize both types of anticipation, not only anticipation of negative events (Abler *et al.*, 2007; Hamilton *et al.*, 2012; Strigo *et al.*, 2013).

During loss anticipation, BDD, compared with MDD and healthy control subjects, had much sparser connectivity that lacked fronto-striatal connections. Interestingly, of eight connections associated with loss anticipation in BDD, four connections were common across all groups and all condition (LAng–RAng, LFP–RFP, LVS–RVS, and RDLPFC–RFP), and two connections were common across all groups during loss anticipation (LAng–LMTG and RAng–RDLPFC). Most connections were either going to, or from, the angular gyrus. One function of the angular gyrus is to guide visual attention to relevant information related to reward and punishment (Studer *et al.*, 2014). The path originating from LAng or RAng did not extend to medial PFC and VS, regions involved in evaluation of potential reward values or tracking rewarding outcomes (Knutson *et al.*, 2003), suggesting a neural mechanism for blocking disturbing visual information from further processing. This distinguished BDD from MDD, whose negative bias during processing of negative cues resulted in the spread of activation across multiple frontal and parietal regions.

Win anticipation in BDD, compared to MDD and healthy control subjects, was characterized by denser connectivity in the fronto-parietal-temporo-striatal subnetwork. Changes in RFCm activation influenced activation in RVS and multiple frontal regions involved in emotion regulation and attentional control (Phillips *et al.*, 2008*a*; Kanske *et al.*, 2011). Given that one function of the RFCm is to track rewarding outcomes (Knutson *et al.*, 2003), this connectivity pattern suggests increased attention to the perceived value of potential reward, and may, in turn, be associated with the well-documented finding of increased reward sensitivity in bipolar disorder (Lawrence *et al.*, 2004; Nusslock *et al.*, 2012; Caseras *et al.*, 2013; Whitton *et al.*, 2015).

In contrast to recent findings of hyper-connectedness and hyper-efficiency in occipital regions during resting state for individuals with seasonal depression versus healthy control subjects (Borchardt *et al.*, 2015), in our study, patients with MDD and healthy control subjects did not differ in their occipital connectivity patterns. Occipital connectivity in BDD, however, differed from that in patients with MDD and healthy control subjects, and was characterized by greater number of inter-hemispheric versus intra-hemispheric connections, which may reflect a compensatory mechanism for underlying intra- and inter-hemispheric white matter pathology (Brambilla *et al.*, 2009; Frank *et al.*, 2015).

One limitation of this study was the recruitment of medicated BDD and MDD. While recruiting drug-free individuals may be preferable for functional MRI studies (Yip *et al.*, 2015), some studies suggest that psychotropic medications improve brain functioning in individuals with bipolar disorder (Haldane *et al.*, 2008; Phillips *et al.*, 2008*b*). In addition, it is ethically difficult to ask participants to stop taking medications. Focusing on unmedicated participants is also likely to bias the study by limiting recruitment to participants with lower illness severity. We would also like to note that while comparing non-medicated participants might remove the potential confound of medication, such a comparison would not reflect the reality, in which MDD and BDD require different medications. Removing the medication confound from the study may thus result in a comparison of BDD and MDD that is not generalizable to typical MDD and BDD populations. Furthermore, we worked hard to include MDD and BDD in the same mood state with comparable levels of current depression and mania, which necessarily resulted in BDD and MDD taking different medications. Our exploratory analyses showed that taking versus not taking psychotropic medications did not affect connectivity strength in the fronto-parietal-temporo-striatal subnetwork, where most significant between-group differences were found. Total medication load (Hassel *et al.*, 2008) was associated with connectivity strength, but only during loss anticipation and only in bipolar disorder. This result cannot, however, explain the sparse connectivity pattern in bipolar disorder given that greater medication load was mostly associated with greater connectivity strength among the regions.

While the different types of medications in depressed individuals may potentially affect the connectivity patterns observed in this study, simulation studies suggest that IMaGES are relatively robust to moderate between-subject variation (Ramsey *et al.*, 2010). It is most likely that IMaGES are able to detect the connections that are common across all (or most) participants in the sample

(independently of medication type and combination). The connections that are specific to some participants only (e.g. those taking mood stabilizers) will probably not receive a high mean BIC score, and, as a result, will not be included to the model. It is thus probable that the connectivity patterns identified in this study are generalizable for each sample. While it is reasonable to suggest the subjects who are, for example, taking mood stabilizers would have less dense connectivity during, for example, win anticipation, because mood stabilizers aim to balance excitation and inhibition processes, our sample was not sufficiently large to test this hypothesis directly.

In summary, this is the first study to demonstrate that BDD and MDD with comparable levels of current depression and mania differed from each other and healthy control subjects in density of connections, connectivity path length, and connectivity direction during win or loss anticipation. We showed that both decreased and increased connectivity density may be aberrant, by disrupting the balance between excitation and inhibition processes in the network, and by triggering maladaptive emotional and behavioural responses. While a smaller number of connections may limit cross-talk among regions, a greater number of connections may lead to faster spread of activation in the network, simultaneous activation of multiple regions, and network over-excitation. In BDD, aberrant connectivity patterns included hyper-connectivity during win anticipation, but hypo-connectivity during loss anticipation. In MDD, aberrant patterns were characterized by a 'bottom-up' connectivity direction during win and loss anticipation that may have impeded ability to regulate emotions related to anticipated win and loss.

The ultimate goal of clinical neuroimaging is to contribute to clinical practice by helping practicing physicians determine appropriate treatment options on an individual basis. Indicators of neural functioning, such as neural activation and neural connectivity patterns, may also be measures that can help in diagnostic decision-making. Our findings suggest different neural mechanisms underlying aberrant anticipation processes in BDD and MDD, and suggest that distinct therapeutic interventions may be required for these two groups of individuals to improve coping strategies during anticipation of positive and negative outcomes. For example, knowing that ECT decreases fronto-parietal connectivity (Perrin *et al.*, 2012), we can hypothesize that such treatment may benefit MDD during anticipation of negative outcomes, because it can reduce bottom-up influences on the frontal cortex, thus allowing MDD to use higher order cognitive strategies for emotion regulation. Such treatment will not necessarily benefit bipolar disorder, however, because ECT may diminish the sparse neural connectivity in these individuals during anticipation of negative outcomes, and may thus further impair the already aberrant ability of these individuals to prepare to cope with potentially negative outcomes. Future studies are needed to replicate these findings, to identify trajectories in connectivity patterns corresponding to a decrease or increase in depressive/manic symptoms over time, in order to predict the onset of the next mood episode, and to determine the extent to which these connectivity patterns predate development of bipolar disorder or major depressive disorder in at-risk individuals.

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Supplementary material

Supplementary material is available at *Brain* online.

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