Author/s:
Rive, MM;Redlich, R;Schmaal, L;Marquand, AF;Dannlowski, U;Grotegerd, D;Veltman, DJ;Schene, AH;Ruhé, HG

Title:
Distinguishing medication-free subjects with unipolar disorder from subjects with bipolar disorder: state matters

Date:
2016-11-01

Citation:
Rive, M. M., Redlich, R., Schmaal, L., Marquand, A. F., Dannlowski, U., Grotegerd, D., Veltman, D. J., Schene, A. H. & Ruhé, H. G. (2016). Distinguishing medication-free subjects with unipolar disorder from subjects with bipolar disorder: state matters. Bipolar Disorders, 18 (7), pp.612-623. https://doi.org/10.1111/bdi.12446.

Received Date : 18-May-2016

Revised Date : 30-Sep-2016

Accepted Date : 01-Oct-2016

Article type : Original Article

Distinguishing medication-free subjects with unipolar disorder from subjects with bipolar disorder: state matters

Maria M Rive[a,*], Ronny Redlich[b,*], Lianne Schmaal[c], André F Marquand[d], Udo Dannlowski[b], Dominik Grotegerd[b], Dick J Veltman[e], Aart H Schene[a,d,f,**], Henricus G Ruhé[a,g,**]

[a]Program for Mood Disorders, Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [b]Department of Psychiatry, University of Munster, Muenster, Germany, [c]Department of Psychiatry and Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands, [d]Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands, [e]Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands, [f]Department of Psychiatry, Radboud University Medical Center, Nijmegen, The Netherlands, [g]Department of Psychiatry, Mood and Anxiety Disorders, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

*These authors share first authorship.

**These authors share senior authorship.

Corresponding author:

Maria M. Rive

Program for Mood Disorders, PA3-221
Department of Psychiatry
Academic Medical Center
University of Amsterdam
P.O. Box 22660
1100 DD Amsterdam, The Netherlands
Fax.: +31-20-891-3701
E-mail: m.m.rive@amc.uva.nl

Running head: Distinguishing medication-free MDD and BD

Abstract

Objectives: Recent studies have indicated that pattern recognition techniques of functional magnetic resonance imaging (fMRI) data for individual classification may be valuable to discriminate major depressive (MDD) and bipolar disorder (BD). Importantly, medication may have affected previous classification results since patients with MDD and BD use different classes of medication. Furthermore, almost all studies investigated only depressed subjects. Therefore, we focused on medication-free subjects. We additionally investigated whether classification would be mood state independent by including both depressed and remitted subjects.

Methods: We applied Gaussian Process Classifiers to investigate discriminative power of structural MRI (gray matter volumes of emotion regulation areas) and resting state fMRI [resting-state networks implicated in mood disorders: default mode network (DMN), salience network (SN), and lateralized frontoparietal networks (FPN)] in depressed (n = 42) and remitted (n = 49) medication-free subjects with MDD and BD.

Results*:* Depressed subjects with MDD and BD could be classified based on gray matter volumes of emotion regulation areas as well as DMN functional connectivity with 69.1% prediction accuracy. Prediction accuracy using the FPNs and SN did not exceed chance level. Remitted subjects with MDD and BD could not be discriminated.

***Conclusions**:* For the first time we show that medication-free subjects with MDD and BD can be differentiated based on structural MRI as well as resting-state functional connectivity. Importantly, results indicate that research concerning diagnostic neuroimaging tools distinguishing MDD and BD should consider mood state, since only depressed subjects with MDD and BD could be correctly classified. Future studies in greater samples are needed to investigate whether results can be generalized to medication-naïve or first-episode subjects.

Key words: bipolar disorder – diagnosis – fMRI – machine learning – major depressive disorder – mood state

Differentiation between major depressive disorder (MDD) and bipolar disorder (BD) in an early phase is important, since treatment strategies and prognosis differ for these disorders. Misdiagnosis may result in inadequate pharmacological therapy, which is associated with prolonged illness duration and risk for recurrence. Unfortunately, current diagnostic tools (i.e., questionnaires and clinical interviews) poorly distinguish between the depressed episode of MDD and BD due to comparable symptom profiles (1). If previous (hypo) manic episodes have not been recognized, or are yet to appear, BD is prone to be misdiagnosed as MDD.

Identifying specific neural dysfunctions as biomarkers for MDD or BD could therefore enhance diagnostic accuracy. There is considerable evidence that these mood disorders are associated with altered structure and function of different neuronal regions and networks, particularly those involved in attention, emotion processing and cognitive control, both during task performance (2–6) and rest (7, 8) [for reviews/meta-analyses, see (9–16)]. However, previous mass univariate functional magnetic resonance imaging (fMRI) studies are not yet clinically applicable since results were observed at group level and are consequently not useful for individual prediction (17, 18).

One way to classify *individual* subjects based on fMRI data is the use of multivariate pattern recognition analysis (MVPA) or supervised machine learning (17–20). Briefly, this technique

involves the 'training' of a computer algorithm in order to predict to which predefined category an observation belongs (17).

Previous MVPA studies distinguishing MDD from BD, using various imaging modalities, yielded prediction accuracies ranging from 59% to 90% (20–25) (*Supplementary Table S1*). However, in these studies medication use was allowed, which may have affected results: the discriminative ability of neural activity or structural patterns could have (partly) been driven by differential acute effects of ongoing antidepressants in MDD versus mood stabilizers use in subjects with BD on brain function or structure. In addition, only depressed subjects with MDD and BD were included in previous studies [except (26)]. Therefore, it is not clear whether MDD and BD are still distinguishable while in remission. Since MDD and BD are both highly recurrent, this would be relevant to know, e.g., when deciding on type of maintenance treatment against future relapses.

Importantly, one of the previous MVPA studies showed that classifiers to differentiate depressed, medicated MDD from BD based on structural MRI (sMRI) data (gray matter volumes of emotion regulation areas) are generalizable to independent replication samples (25). Within-subject structural MRI data are relatively stable (27), which is likely to result in good test/retest reliability, a prerequisite for diagnostic tools (28). Another advantage of sMRI is that assessment is comparatively easy, facilitating clinical implementation. Furthermore, a recent meta-analysis showed robust differences in gray matter volume between subjects with MDD and BD in regions important for emotion regulation (e.g., smaller volumes in the right dorsolateral prefrontal cortex and left hippocampus in MDD compared to BD) (16). Thus, sMRI may be particularly suitable for classification of MDD and BD. Nevertheless, fMRI has also proven to be useful for psychiatric classification (17, 20). Compared to task-related fMRI, resting state fMRI (RS-fMRI) may be of special interest for this purpose, because resting-state networks (RSNs) are less susceptible to task compliance and independent of specific task paradigms. Furthermore, RSNs show consistency across different subject groups, analysis methods and types of scanning protocols (28). Moreover, several RSNs have been implicated in mood disorders: the default mode network (DMN) (7, 29–40); the left and right lateralized frontoparietal networks (FPN) (40–47); and the salience network (SN) (2, 35, 40, 48, 49).

In the current study, we used sMRI and RS-fMRI data (connectivity of the DMN, left and right FPN, and SN) to examine the discriminative potential of Gaussian Process Classifier (GPC)-based pattern recognition analysis in subjects with MDD and BD. The aim of our study was to investigate whether MDD–BD discrimination is also possible in medication-free subjects and whether mood state would influence performance of the classifier. Since we are the first to classify currently medication-free MDD and BD and also the first to classify remitted subjects [except one study in medicated samples (26)], this study was explorative.

Methods and materials

Subjects

We used sMRI and RS-fMRI data of 36 subjects with bipolar I disorder (BD-I) and bipolar II disorder (BD-II) (10 depressed: BDd; 26 remitted: BDr) and 44 subjects with MDD (22 depressed: MDDd and 23remitted: MDDr; 22 MDDr for RS-fMRI due to missing data of one subject). All subjects were free of antidepressants, antipsychotics, and mood stabilizers for ≥ 1 month and were matched for age, gender, education, and depression severity. Part of this sample has been described elsewhere (50). The study was approved by the Medical Ethical Committee of the Academic Medical Center, Amsterdam, The Netherlands. All subjects provided written informed consent, obtained according to the Declaration of Helsinki of 1975 (see *Supplementary Data* for additional details).

Additional inclusion criteria for subjects with MDD and BD [diagnosis assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)] were: (i) age 18–60 years, (ii) a history of at least two major depressive episodes (MDEs), (iii) age at first mood episode ≤ 40 years, (iv) current MDE or remission [i.e., not fulfilling the criteria of MDE or (hypo)manic episode], and (v) illness duration of ≥ 5 years since the first episode (in order to reduce the chance of including late MDD-to-BD converters in the MDD group). Exclusion criteria for subjects with MDD and BD were: (i) electroconvulsive therapy ≤ 2 months before scanning, (ii) current (hypo)mania, (iii) current psychotic symptoms, (iv) a comorbid Axis-I disorder (assessed by SCID-I) except for anxiety disorders occurring in the context of the

mood disorder, (v) a diagnosis of cluster B personality disorder [assessed by SCID-II, if suspected based on (hetero)anamnestic information], and (vi) current use of any psychotropic medication (stopped ≤ 1 month before scanning). Incidental benzodiazepine use was allowed, but was stopped ≥ 1 day before scanning. In addition, subjects with MDD were excluded when they had a history of (hypo)manic derailment after antidepressant use or a first-degree family history of BD (to prevent inclusion of subjects with MDD with possible BD traits). Subjects with BD were excluded if (hypo)manic episodes solely appeared during the use of antidepressants, again to insure inclusion of 'true' subjects with BD; and in case of a Young Mania Rating Scale (YMRS) score > 8, to prevent inclusion of subjects with BD with (subclinical) (hypo)manic symptoms. Furthermore, for all subjects contra-indications for MRI-scanning led to exclusion: a history of head trauma or neurological disease, severe general physical illness, claustrophobia, or implanted metal objects.

MRI data acquisition

Resting-state fMRI and structural data were acquired on a 3.0 Tesla MRI scanner (Philips Intera, Philips Medical Systems, Best, the Netherlands) with body coil excitation and an 8-channel SENSE head coil. For the functional resting-state scan the following parameters were used: echo time (TE) = 30 msec, repetition time (TR) = 2300 msec, flip angle = 80°, matrix = 96 × 96, number of slices = 40, ascending slice order, field of view (FOV) = 220 × 120 × 220 mm^3, voxel size = 2.29 × 2.29 × 3.00 mm^3. In total, 200 dynamics were acquired with a total duration of 7 min and 51 sec. For the T1-weighted structural image, parameters were: TE = 4.6 msec, TR = 9.6 ms,ed flip angle = 8°, matrix = 256 × 256, number of slices = 182, FOV = 218 × 256 × 256 mm^3, voxel size = 1.0 × 1.0 × 1.2 mm^3, total duration = 7 min.

Data analysis

Resting state networks. For the resting-state data, Statistical Parametric Mapping (SPM8, Wellcome Trust Center for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/SPM8) was used for the following preprocessing steps: slice timing; realignment and unwarping to correct for subject motion; co-registration of functional and structural data; segmentation; spatial normalization into standard

stereotactic space using the Montreal Neurological Institute (MNI) template and resampling to 3-mm isotropic voxels; smoothing of data with an 8-mm full-width at half-maximum (FWHM) Gaussian kernel.

For group independent components analysis we used the GIFT toolbox (51) (http://icatb.sourceforge.net). Intensity normalization was used to improve the accuracy and test-retest reliability of the independent components analysis (ICA) output (52). Twenty independent components were extracted from the data [based on the minimum description length criteria (51)], using the Infomax ICA algorithm. The stability of extracted independent components was determined by repeating the Infomax algorithm 10 times in ICASSO.

Of the 20 extracted components, 11 RSNs were identified by visual comparison of aggregate spatial maps with the literature (28, 53, 54). We used the spatial maps [created by back-reconstruction and reflecting the connectivity and degree of coactivation within the RSN (52)] of the RSNs of interest (DMN, FPNs, and SN) as input patterns for classification (Fig.1 and *Supplementary Table S2*). The cluster quality index of all three RSNs was 0.98, indicating highly stable ICA decomposition (52).

ICA identifies motion-related sources, which are incorporated in 'noise' independent components (in the same way as vascular, ventricular, and susceptibility artifacts) (52, 55, 56), and thus selected RSNs are considered denoised from major motion effects. However, to ascertain that MDD versus BD classification results are not due to differences in possible residual motion-related variance present in the RSNs, we also compared motion between subjects with MDD and BD (see *Supplementary Data* for details). Motion did not significantly differ between remitted ($p = 0.90$) and depressed ($p = 0.20$) subjects with MDD and BD.

Gray matter volumes. For the structural data, we applied voxel based morphometry (VBM) according to Redlich et al. (25), involving bias-correction, tissue classification, normalization to MNI-space using linear (12-parameter affine) and nonlinear transformations within a unified model, including high-dimensional DARTEL normalization, using default parameters of the VBM8-toolbox (http://dbm.neuro.unijena.de/vbm). The resulting modulated gray matter images were smoothed with a Gaussian kernel of 8-mm FWHM. Subsequently,

quality of all scans was checked by visual inspection and the check quality function implemented in the VBM-toolbox.

MVPA. For MVPA, binary Gaussian Process Classifiers (GPCs), as implemented in the Pattern Recognition for Neuroimaging Toolbox (http://www.mlnl.cs.ucl.ac.uk/pronto) were applied (57). GPC is a supervised machine learning technique similar to Support Vector Machine (SVM) that provides an additional benefit of predictive probabilities of class membership (58). Probabilistic predictions can be easily recalibrated to accommodate variations in disease prevalence (20). This is important for future clinical translation purposes of MVPA studies, since prevalence of psychiatric disease in clinical practice is usually different from the prevalence in the samples under investigation. Moreover, GPC allows us to account for the imbalance of our depressed groups (the MDD group being twice the size of the BD group), calculating a balanced sensitivity and specificity not biased by differences in group sizes. The used classification model contains a single hyper-parameter, which controls the scale of the latent function used to model class differences and therefore assists in the calibration of the predictive probabilities. The value for this hyper-parameter was set by maximizing the marginal likelihood of the model (model evidence) under a Gaussian approximation. This is referred to as Type II maximum likelihood and is a standard approach in the literature (58, 59).

To assess the diagnostic potential of *each RSN* with respect to subjects with MDD versus BD and mood state, each subject's RSN spatial map of the DMN, SN and FNPs were entered separately into independent GPCs. Features were restricted to the gray matter voxels of the regions belonging to each specific RSN. Therefore, for each network a binary mask was constructed by combining the a priori binary gray matter mask from SPM8 with the masks derived from the spatial maps of the given network across subjects (resulting from a one sample *t*-tests, testing for activations, thresholded at $p < 0.05$ family-wise error whole-brain corrected). To assess the diagnostic potential of *gray matter volume* with respect to MDD versus BD subjects and mood state, each subject's gray matter image was entered into the GPC and restricted to emotion regulation areas by a previously described emotion regulation mask, comprising the entire prefrontal cortex, mid-cingulate cortex (MCC), anterior cingulate cortex (ACC), amygdala, thalamus, striatum and hippocampal formation (22, 25).

We used a leave-one-out cross-validation strategy to estimate the generalization ability of our classifier. The GPC provided probabilistic predictions for each diagnostic category for each subject. These were converted to categorical predictions by applying a threshold according to the frequency of classes in the training set. Since the classifiers were unbalanced (i.e. , different class sizes), balanced accuracy measures (the mean of sensitivity and specificity) were computed to assess the overall categorical performance of each classifier, accommodating this imbalance. Statistical significance was determined by permutation testing (58). For each RSN and for gray matter volume, the following classification problems were defined: MDDd versus BDd; and MDDr versus BDr. Feature weights were computed to visualize the relative importance of each voxel in the decision function of the GPC, displaying the pattern of functional connectivity used by the algorithm to discriminate each group. To validate results with an independent algorithm, we repeated the above analyses using the SVM (see *Supplementary Data*). Post-hoc, but only for illustrative purposes, we performed classical mass-univariate analysis on the data that would prove to be useful for classification of subjects with MDD and BD (see *Supplementary Data*).

Results

Demographics and clinical characteristics

Subjects with MDD and BD in the depressed and remitted subject groups were matched for age, gender, education, IQ, and Hamilton Depression Rating Scale (HDRS) score, age of illness onset, and illness duration (all $p > 0.05$) (Table 1); the number of previous MDEs differed between the remitted ($p = 0.05$) and depressed subgroups ($p = 0.02$). Furthermore, six subjects with MDD and four subjects with BD had comorbid anxiety disorders ($p > 0.05$). Three subjects (1 MDDd, 1 MDDd, 1 BDr) used benzodiazepines ante noctem (temazepam and oxazepam: stopped 40–48 hours before scanning; lorazepam: quit 17 hours before scanning). Bipolarity Index (BI) (60) scores differed significantly between the MDDd/r and BDd/r groups ($p < 0.001$), indicating a high level of bipolarity in the BD groups compared to the MDD groups.

Pattern classification

The GPC was able to predict diagnostic group based on patterns of DMN connectivity and of gray matter volume, but only for the depressed state (Table 2). DMN functional connectivity patterns discriminated subjects with MDDd from subjects with BDd with 69.1% accuracy ($p = 0.02$; sensitivity 70.0%; specificity 68.2%; positive predictive value 50.0%; negative predictive value 83.3%). Prediction accuracies on basis of gray matter volume patterns were also above chance level for subjects with MDDd versus subjects with BDd, with 69.1% accuracy ($p = 0.02$; sensitivity 70.0%; specificity 68.2%; positive predictive value 50.0%; negative predictive value 83.3%). Prediction accuracies of the GPC applied to patterns of FPN and SN connectivity were not above chance level (all $p > 0.05$).

Using the SVM, balanced prediction accuracies again were only significantly above chance level for the MDDd versus BDd classification (*Supplementary Table S3*), indicating that the effect of state was independent of the type of classifier that was applied.

Although the discriminating connectivity patterns are multivariate and therefore encompass all the features, we additionally report the weight vectors contributing to discriminate subjects with MDDd from subjects with BDd. Regarding the DMN, highest weight vectors favored subjects with MDDd relative to subjects with BDd and were found in the superior temporal pole/insula [Brodmann area (BA) 47], angular gyrus, inferior parietal gyrus, (pre)cuneus (BA 7/31), calcarine sulcus, mid-cingulate cortex (MCC) (BA 32/24), anterior cingulate cortex (ACC) (BA24), and medial orbitofrontal cortex (OFC); lowest weight vectors favored BDd relative to MDDd and were found in the posterior cingulate (PCC) (BA 23/29), (pre)cuneus (BA 7/5), and middle frontal gyrus (Fig. 2A). Regarding gray matter volume, highest weight vectors favored subjects with MDDd relative to subjects with BDd and were found in the parahippocampal gyrus, middle frontal gyrus, and superior frontal gyrus, orbital part/gyrus rectus; lowest weight vectors favored BDd relative to MDDd and were found in the middle frontal gyrus (a.o. BA 6), MCC (BA 24/31), ACC (BA 9), caudate/pallidum/putamen (Fig. 2B).

Post-hoc uncorrected mass univariate analysis for the relevant comparisons (MDDd versus BDd; DMN and gray matter volumes) demonstrated intensity differences in areas grossly corresponding to those with the highest weights in the MVPA analysis (*Supplementary Table S4* and *Supplementary Fig. S1*).

Discussion

In the current study, we investigated the discriminative power of patterns of gray matter volume and resting-state functional connectivity to distinguish MDD from BD by applying a Gaussian Process Classifier. Of note, we examined medication-free subjects in two different mood states (depressed and remitted). We found that DMN connectivity as well as gray matter volume can be used to discriminate between both mood disorders in the depressed state. In contrast, we were not able to discriminate remitted patient groups, either using resting state fMRI connectivity or gray matter data. Therefore, our results suggest that it is important to consider mood state for classification of MDD and BD in future studies.

Corroborative with our findings, previous evidence indicates depression specific volume abnormalities in emotion regulation areas in mood disorders. For example, previous mass univariate studies in unmedicated MDD found that volume reductions of the hippocampus, prefrontal cortex, thalamus, caudate and pallidum, as well as amygdala enlargement, were specific for the depressed state (61–64). In (medicated) BD, reduced orbitofrontal, prefrontal and amygdala volumes, as well as increased volume of the PCC/parahippocampal gyrus were depression specific too (65–67). Thus, there is substantial evidence that at least part of MDD/BD-specific volumetric abnormalities found during depression may reverse when subjects achieve remission; consequently, gray matter volume patterns in remitted MDD and BD may be too much alike to be used for classification. Although absence of evidence is not evidence of absence, a recent MVPA-study using SVM applied to subcortical volumes also failed to classify MDDr and BDr (26).

However, the relationship between mood state and the DMN is less clear. Treatment-response studies with medication or vagal nerve stimulation reported state-dependent DMN changes in MDD (68–70) which may be partly due to remission itself rather than the

treatment provided. In BD, a small pilot study reported state-dependent abnormal suppression of activity in specific DMN components (hippocampus during depression, rostral anterior cingulate cortex (rACC) during remission) (71). Thus, there are some indications that DMN functioning changes when remission is achieved; possibly, these changes abolish MDD/BD differences present during depressed states. Taken together, during remission, neurobiological differences may be too few or too small to allow for classification between MDD and BD.

Our study design adds to knowledge that without acute effects of medication depressed subjects with MDD and BD could still be classified, with accuracy rates comparable to those found in previous MVPA studies with medicated depressed subjects with MDD and BD. This could not be assumed a priori. It has been demonstrated that antidepressants (used in the treatment of MDD) and mood stabilizers (lithium, anti-epileptics, antipsychotics; used in the treatment of BD) may potentially alter gray matter volume, activity and connectivity of regions implicated in the differentiation between MDD and BD, e.g., amygdala, hippocampal, striatal, ACC, PCC, and DLPFC volume [see e.g., (61, 68, 72-78)]; lateral and medial prefrontal, (sg)ACC and amygdala activity [see e.g., (79–86)]; and default mode, reward, emotional and task-positive network connectivity (68, 87–92). Although it is generally thought that successful medication has normalizing effects, some studies have shown deviant results (93, 94). For example, as discussed in a review by Hafeman et al. (94), atypical antipsychotics have the potential to overcorrect abnormalities in neural activity, leading to prefrontal hyperactivity (95). Furthermore, medication can have additional effects on neural activity beyond the specific activity differences between patients and healthy individuals, as shown in a study comparing medication-free subjects with BD with medicated subjects with BD (96). Even in case of similar medication, such additional, non-normalizing effects could be different in subjects with MDD compared to BD, due to illness by treatment interactions. Moreover, specific classes of medication, let alone interactions between drugs in case of polypharmacy (more common in BD than in MDD) may all influence neural activity (94). Thus, because of an association between diagnosis and type of medication, and/or illness by treatment interactions, use of different medication in samples with distinct psychiatric disorders may have biased the performance of sensitive pattern classification tools to distinguish between various psychiatric disorders. With our study, we bypassed potential

acute effects of current medication and demonstrated the utility of MVPA for differential diagnosis of currently medication-free depressed MDD and BD. Although our sample was not medication-naïve, our results provide a first clue in the development of individual, clinically applicable diagnostic tools without the influence of confounding medication. This is relevant because MDD and BD ideally should be accurately diagnosed *before* starting medication, i.e., in a current unmedicated state, since providing wrong therapy can have serious adverse consequences.

Furthermore, our results extend findings of previous MVPA studies using emotional fMRI paradigms (21–23), arterial spin labelling (24) and sMRI (25,26) by demonstrating that resting-state DMN connectivity patterns are also valuable for classification of depressed subjects with MDD and BD. This finding suggests that the nature of DMN abnormalities differs between both mood disorders during the depressed state. Apparently, neurobiological differences exist despite phenomenological similarities. These differences may reflect either a pathway involved in the vulnerability for (hypo)manic derailment, or scarring effects due the experience of previous (hypo)manic episodes. Such pathway associated with vulnerability for or the effects of (hypo)mania may be juxtaposed to a specific depression-related pathway. In fact, these pathways may represent two independent dimensions (mania and depression) instead of one single mood dimension, as suggested by recent family studies, showing independent transmission of depression and mania (97–100). During depression, the pathway involved in the dimension of mania may not be phenomenologically expressed, but still present. Moreover, as proposed by Strakowski et al., depression may be a non-specific response to brain injury (e.g., due to the excitatory processes present during (hypo)mania in BD, versus other types of stressors in MDD) (101).

Limitations

There are some limitations to our study. First, by the use of supervised machine learning prediction accuracy cannot exceed clinical assessment, since groups are predefined based on this clinical information (17). However, our results add to existing knowledge by demonstrating that classification results are state-dependent. We did not investigate

(hypo)mania; yet, in case of (hypo)mania the diagnosis of bipolar disorder is clear without further fMRI investigation. Second, our sample sizes of subgroups were small, limiting discriminative power and generalizability. Recruitment of medication-free depressed subjects with BD proved to be challenging: given the serious and possible life-threatening nature of BD depression in particular, patients diagnosed with BD before were often treated immediately. Our failure to classify subjects with MDD and BD belonging to the remitted subgroup may be due to this small sample size; on the other hand, subjects belonging to the even smaller depressed groups could be classified correctly. Hypothetically, this correct classification may also be due to relatively higher homogeneity in the smaller depressed groups versus higher heterogeneity in larger remitted groups (20). Our study should thus be considered hypothesis generating, adding to current knowledge that it is possible to distinguish MDD and BD even without current effects of medication, and that mood state (and thus possibly also depression severity) may be an important issue to consider for development of diagnostic tools. These results need to be confirmed in larger samples. Third, we included both subjects with BD-I and BD-II. Due to our small sample size, it was not possible to stratify for bipolar subtype. However, BD-II may be considered an intermediate between BD-I and MDD (bipolar spectrum); hence, if the BD subtype would have affected our results, inclusion of subjects with BD-II would likely have reduced the observed differences. Fourth, by investigating medication-free subjects we may have introduced a selection bias, by inclusion of less vulnerable or less severe cases who could manage without maintenance treatment, at least for some period. However, most of the medication-free depressed patients were prescribed relevant psychotropics immediately after scanning, which is in contrast with this hypothesis of lower severity. Fifth, most of our participants were medication-free but not medication-naïve, which limits generalization to medication-naïve subjects. Despite evidence of reversibility of (volumetric) medication effects (102, 103), we cannot rule out long-term effects of previous medication. Sixth, we have no reliable information regarding handedness, which may differ between groups. Handedness may affect laterality of neuroimaging results, due to differences in organization between the dominant and non-dominant hemisphere (e.g., language areas are located in the dominant hemisphere, which is the left hemisphere in all right-handed, but only in a proportion of left-handed individuals). However, to the best of our knowledge, to date there is no evidence for effects of handedness to multivariate classification of mood disorders. Therefore, we would

expect only a minor influence of handedness on the results, if any. Finally, due to our cross-sectional design we cannot establish whether differences between MDD and BD represent specific preexisting *vulnerability* or result from differential 'scarring' due to previous episodes. Replication of our results considering mood state and testing of medication effects is needed in studies with greater sample sizes, combining medication-free and medicated subjects with MDD and BD in (mild to severely) depressed and remitted states.

Conclusions

Our results indicate that both volumetric data and resting-state functional connectivity data can aid in distinguishing between MDD and BD. Importantly, we demonstrate that also medication-free patients can be differentiated, but only during a moderate to severe major depressive episode. The latter stresses the importance of taking mood state in consideration when developing diagnostic tools. To further investigate the predictive power of classifiers, longitudinal studies in medication-naïve, first-episode depressed subjects are needed. Combining more diverse data modalities [e.g., neuroimaging and clinical data (symptom profiles, family history, and comorbidity), blood biomarkers and/or genetics] may enhance discriminative power. Future research should also focus on the development of stepwise diagnostic pipelines, using the most efficient but least difficult, burdensome and least expensive examinations first in the diagnostic process.

Acknowledgements

We gratefully acknowledge the patients and controls who participated in the MRI-scanning. This work is supported by a grant from the Netherlands Organization for Health Research and Development (ZonMw), program Mental Health, education of investigators in mental health (OOG; #100-002-034) to MMR. HGR is supported by a NWO/ZonMW VENI-Grant #016.126.059. UD is supported by grants of the Innovative Medizinische Forschung (IMF) of the Medical Faculty of Münster (DA120309, DA111107, and DA211012). LS is supported by The Netherlands Brain Foundation [Grant #F2014(1)-24] and the Neuroscience Campus Amsterdam Scientific Excellence Grant (IPB-SE-15-PSYCH-Schmaal). AFM gratefully acknowledges support from the NWO under the Gravitation Programme (Grant #024.001.006).

Disclosures

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

References

1. Goodwin GM, Anderson I, Arango C, Bowden CL, Henry C, Mitchell PB, et al. ECNP consensus meeting. Bipolar depression. Nice, March 2007. Eur Neuropsychopharmacol 2008;18:535–49.
2. Hamilton J, Etkin A, Furman DJ, Lemus MG, Johnson RF, Gotlib IH. Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of baseline activation and neural response data. Am J Psychiatry 2012;169:693–703.
3. Phillips ML, Ladouceur CD, Drevets WC. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol Psychiatry 2008;13:829, 833–57.
4. Townsend J, Altshuler LL. Emotion processing and regulation in bipolar disorder: a review. Bipolar Disord 2012; 14: 326–339.
5. Rive MM, van Rooijen G, Veltman DJ, Phillips ML, Schene AH, Ruhé HG. Neural correlates of dysfunctional emotion regulation in major depressive disorder. A systematic review of neuroimaging studies. Neurosci Biobehav Rev 2013;37:2529–53.
6. Redlich R, Dohm K, Grotegerd D, Opel N, Zwitserlood P, Heindel W, et al. Reward processing in unipolar and bipolar depression: A functional MRI study. Neuropsychopharmacology 2015;40:2623–31.
7. Wang L, Hermens DF, Hickie IB, Lagopoulos J. A systematic review of resting-state

functional-MRI studies in major depression. J Affect Disord 2012;142:6–12.

8. Vargas C, López-Jaramillo C, Vieta E. A systematic literature review of resting state network--functional MRI in bipolar disorder. J Affect Disord 2013;150:727–35.

9. Cardoso de Almeida JR, Phillips ML. Distinguishing between unipolar depression and bipolar depression: current and future clinical and neuroimaging perspectives. Biol Psychiatry 2013;73:111–8.

10. Delvecchio G, Fossati P, Boyer P, Brambilla P, Falkai P, Gruber O, et al. Common and distinct neural correlates of emotional processing in bipolar disorder and major depressive disorder: a voxel-based meta-analysis of functional magnetic resonance imaging studies. Eur Neuropsychopharmacol 2012;22:100–13.

11. Konarski JZ, McIntyre RS, Kennedy SH, Rafi-Tari S, Soczynska JK, Ketter TA. Volumetric neuroimaging investigations in mood disorders: bipolar disorder versus major depressive disorder. Bipolar Disord 2008; 10: 1–37.

12. Bora E, Fornito A, Yücel M, Pantelis C. Voxelwise meta-analysis of gray matter abnormalities in bipolar disorder. Biol Psychiatry 2010;67:1097–105.

13. Kempton MJ, Salvador Z, Munafo MR, Geddes JR, Simmons A, Frangou S, et al. Structural neuroimaging studies in major depressive disorder. Arch Gen Psychiatry. 2011;68:675–90.

14. Kempton MJ, Geddes JR, Ettinger U, Williams SCR, Grasby PM. Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. Arch Gen Psychiatry. 2008;65:1017–32.

15. Koolschijn MP, Van Haren NEM, Lensvelt-Mulders GJLM, Hulshoff Pol HE, Kahn RS. Brain volume abnormalities in major depressive disorder: A meta-analysis of magnetic resonance imaging studies. Hum Brain Mapp. 2009;30:3719–35.

16. Wise T, Radua J, Via E, Cardoner N, Abe O, Adams TM, et al. Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: evidence from voxel-based meta-analysis. Mol Psychiatry 2016;1–9.

17. Orrù G, Pettersson-Yeo W, Marquand AF, Sartori G, Mechelli A. Using Support Vector Machine to identify imaging biomarkers of neurological and psychiatric disease: a

critical review. Neurosci Biobehav Rev 2012;36:1140–52.

18. Fu CHY, Costafreda SG. Neuroimaging-based biomarkers in psychiatry: clinical opportunities of a paradigm shift. Can J Psychiatry 2013 Sep;58:499–508.

19. Klöppel S, Abdulkadir A, Jack CR, Koutsouleris N, Mourão-Miranda J, Vemuri P. Diagnostic neuroimaging across diseases. Neuroimage 2012;61:457–63.

20. Wolfers T, Buitelaar JK, Beckmann C, Franke B, Marquand AF. From estimating activation locality to predicting disorder: a review of pattern recognition for neuroimaging-based psychiatric diagnostics. Neurosci Biobehav Rev 2015;57:328–49.

21. Grotegerd D, Stuhrmann A, Kugel H, Schmidt S, Redlich R, Zwanzger P, et al. Amygdala excitability to subliminally presented emotional faces distinguishes unipolar and bipolar depression: An fMRI and pattern classification study. Hum Brain Mapp 2014;35:2995–3007.

22. Grotegerd D, Suslow T, Bauer J, Ohrmann P, Arolt V, Stuhrmann A, et al. Discriminating unipolar and bipolar depression by means of fMRI and pattern classification: a pilot study. Eur Arch Psychiatry Clin Neurosci 2013;263:119–31.

23. Mourão-Miranda J, Almeida JRC, Hassel S et al. Pattern recognition analyses of brain activation elicited by happy and neutral faces in unipolar and bipolar depression. Bipolar Disord 2012; 14: 451–460.

24. Almeida JRC, Mourao-Miranda J, Aizenstein HJ, Versace A, Kozel FA, Lu H, et al. Pattern recognition analysis of anterior cingulate cortex blood flow to classify depression polarity. Br J Psychiatry 2013;203:310–1.

25. Redlich R, Almeida JJR, Grotegerd D, Opel N, Kugel H, Heindel W, et al. Brain morphometric biomarkers distinguishing unipolar and bipolar depression: A voxel-based morphometry-pattern classification approach. JAMA Psychiatry 2014;71:1222–30.

26. Sacchet MD, Livermore EE, Iglesias JE, Glover GH, Gotlib IH. Subcortical Volumes Differentiate Major Depressive Disorder, Bipolar Disorder, and Remitted Major Depressive Disorder. J Psychiatr Res 2015;68:91–8.

27. Eggert LD, Sommer J, Jansen A, Kircher T, Konrad C. Accuracy and reliability of

automated gray matter segmentation pathways on real and simulated structural magnetic resonance images of the human brain. PlosOne. 2012;7:e45081.

28. van den Heuvel MP, Hulshoff Pol HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol 2010;20:519–34.

29. Marchetti I, Koster EHW, Sonuga-Barke EJ, De Raedt R. The default mode network and recurrent depression: a neurobiological model of cognitive risk factors. Neuropsychol 2012;22:229–51.

30. Ongür D, Lundy M, Greenhouse I, Shinn AK, Menon V, Cohen BM, et al. Default mode network abnormalities in bipolar disorder and schizophrenia. Psychiatry Res 2010;183:59–68.

31. Mamah D, Barch DM, Repovš G. Resting state functional connectivity of five neural networks in bipolar disorder and schizophrenia. J Affect Disord 2013;150:601–9.

32. Meda SA, Gill A, Stevens MC, Lorenzoni RP, Glahn DC, Calhoun VD, et al. Differences in resting-state functional magnetic resonance imaging functional network connectivity between schizophrenia and psychotic bipolar probands and their unaffected first-degree relatives. Biol Psychiatry 2012;71:881–9.

33. Calhoun V, Sui J, Kiehl K, Turner J, Allen E, Pearlson G. Exploring the psychosis functional connectome: aberrant intrinsic networks in schizophrenia and bipolar disorder. Front Psychiatry 2012;2:1–13.

34. Liu C-H, Ma X, Li F, Wang Y-J, Tie C-L, Li S-F, et al. Regional homogeneity within the default mode network in bipolar depression: a resting-state functional magnetic resonance imaging study. PLoS One 2012;7:e48181.

35. Teng S, Lu C-F, Wang P-S, Hung C-I, Li C-T, Tu P-C, et al. Classification of bipolar disorder using basal-ganglia-related functional connectivity in the resting state. Conf Proc IEEE Eng Med Biol Soc 2013; 1057–60.

36. Fernández-Corcuera P, Salvador R, Monté GC, Salvador Sarró S, Goikolea JM, Amann B, et al. Bipolar depressed patients show both failure to activate and failure to de-activate during performance of a working memory task. J Affect Disord 2013;148:170–8.

37. Chai XJ, Whitfield-Gabrieli S, Shinn AK, Gabrieli JDE, Nieto Castañón A, McCarthy JM, et al. Abnormal medial prefrontal cortex resting-state connectivity in bipolar disorder and schizophrenia. Neuropsychopharmacology 2011;36:2009–17.

38. Sheline YI, Price JL, Yan Z, Mintun MA. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proc Natl Acad Sci USA 2010;107:11020–5.

39. Hamilton JP, Furman DJ, Chang C, Thomason ME, Dennis E, Gotlib IH. Default-mode and task-positive network activity in major depressive disorder: implications for adaptive and maladaptive rumination. Biol Psychiatry 2011;70:327–33.

40. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. Large-scale network dysfunction in major depressive disorder. JAMA Psychiatry 2015;72:603–11.

41. Borkowska A, Rybakowski JK. Neuropsychological frontal lobe tests indicate that bipolar depressed patients are more impaired than unipolar. Bipolar Disord 2001; 3: 88–94.

42. Najt P, Bayer U, Hausmann M. Right fronto-parietal dysfunction underlying spatial attention in bipolar disorder. Psychiatry Res 2013;210:479–84.

43. Wei M, Qin J, Yan R, Li H, Yao Z, Lu Q. Identifying major depressive disorder using Hurst exponent of resting-state brain networks. Psychiatry Res 2013;214:306–12.

44. Veer IM, Beckmann CF, van Tol M-J, Ferrarini L, Milles J, Veltman DJ, et al. Whole brain resting-state analysis reveals decreased functional connectivity in major depression. Front Syst Neurosci 2010;4:1–10.

45. Sweeney JA, Kmiec JA, Kupfer DJ. Neuropsychologic impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. Biol Psychiatry 2000;48:674–84.

46. Lois G, Linke J, Wessa M. Altered functional connectivity between emotional and cognitive resting state networks in euthymic bipolar I disorder patients. PLoS One 2014;9:e107829.

47. Buchanan A, Wang X, Gollan JK. Resting-state functional connectivity in women with Major Depressive Disorder. J Psychiatr Res 2014;59:38–44.

48. Victor TA, Furey ML, Fromm SJ, Bellgowan PSF, Öhman A, Drevets WC. The extended functional neuroanatomy of emotional processing biases for masked faces in major depressive disorder. PLoS One 2012;7:e46439.

49. van Tol M-J, Veer IM, van der Wee NJA, Aleman A, van Buchem MA, Rombouts SARB, et al. Whole-brain functional connectivity during emotional word classification in medication-free Major Depressive Disorder: Abnormal salience circuitry and relations to positive emotionality. NeuroImage Clin 2013;2:790–6.

50. Rive MM, Mocking RJT, Koeter MWJ, van Wingen G, de Wit S, van den Heuvel OA, et al. State dependent differences in emotion regulation between unmedicated bipolar and major depressive disorder. JAMA Psychiatry. 2015;72:687–96.

51. Calhoun VD, Adali T, Pearlson GD, Pekar JJ. A method for making group inferences from functional MRI data using independent component analysis. Hum Brain Mapp. 2001;14:140–51.

52. Allen EA, Erhardt EB, Damaraju E, Gruner W, Segall JM, Silva RF, et al. A baseline for the multivariate comparison of resting-state networks. Front Syst Neurosci 2011;5:2.

53. Rosazza C, Minati L. Resting-state brain networks: literature review and clinical applications. Neurol Sci 2011;32:773–85.

54. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007;27:2349–56.

55. McKeown MJ, Hansen LK, Sejnowsk TJ. Independent component analysis of functional MRI: What is signal and what is noise? Curr Opin Neurobiol. 2003;13:620–9.

56. Kochiyama T, Morita T, Okada T, Yonekura Y, Matsumura M, Sadato N. Removing the effects of task-related motion using independent-component analysis. Neuroimage. 2005;25:802–14.

57. Schrouff J, Rosa MJ, Rondina JM, Marquand AF, Chu C, Ashburner J, et al. PRoNTo: Pattern Recognition for Neuroimaging Toolbox. Neuroinformatics 2013;11:319–37.

58. Marquand A, Howard M, Brammer M, Chu C, Coen S, Mourão-Miranda J. Quantitative prediction of subjective pain intensity from whole-brain fMRI data using Gaussian

processes. Neuroimage 2010;49:2178–89.

59. Rasmussen C, Willams CKI. Gaussian Processes for Machine Learning. Cambridge, Massachusetts: The MIT Press; 2006.

60. Sachs GS. Strategies for improving treatment of bipolar disorder: integration of measurement and management. Acta Psychiatr Scand. 2004;10:S7–17.

61. Arnone D, McKie S, Elliott R, Juhasz G, Thomas EJ, Downey D, et al. State-dependent changes in hippocampal grey matter in depression. Mol Psychiatry 2013;18:1265–72.

62. van Eijndhoven P, van Wingen G, van Oijen K, Rijpkema M, Goraj B, Verkes RJ, et al. Amygdala Volume Marks the Acute State in the Early Course of Depression. Biol Psychiatry 2009;65:812–8.

63. Salvadore G, Nugent AC, Lemaitre H, Luckenbaugh DA, Tinsley R, Cannon DM, et al. Prefrontal cortical abnormalities in currently depressed versus currently remitted patients with major depressive disorder. Neuroimage 2011;54:2643–51.

64. Nugent AC, Davis RM, Zarate Jr. CA, Drevets WC. Reduced thalamic volumes in major depressive disorder. Psychiatry Res Neuroimaging 2013;213:179–85.

65. Nery FG, Chen H-H, Hatch JP et al. Orbitofrontal cortex gray matter volumes in bipolar disorder patients: a region-of-interest MRI study. Bipolar Disord 2009; 11: 145–153.

66. Foland-Ross LC, Brooks JO, Mintz J, Bartzokis G, Townsend J, Thompson PM, et al. Mood-state effects on amygdala volume in bipolar disorder. J Affect Disord 2012;139:298–301.

67. Brooks III JO, Bonner JC, Rosen AC, Wang PW, Hoblyn JC, Hill SJ, et al. Dorsolateral and dorsomedial prefrontal gray matter density changes associated with bipolar depression. Psychiatry Res Neuroimaging 2009;172:200–4.

68. Fu CH, Costafreda SG, Sankar A, Adams TM, Rasenick MM, Liu P, et al. Multimodal functional and structural neuroimaging investigation of major depressive disorder following treatment with duloxetine. BMC Psychiatry 2015;15:1–11.

69. Qin J, Wei M, Liu H, Chen J, Yan R, Yao Z, et al. Altered anatomical patterns of depression in relation to antidepressant treatment: Evidence from a pattern recognition analysis on the topological organization of brain networks. J Affect Disord

2015;180:129–37.

70. Fang J, Rong P, Hong Y, Fan Y, Liu J, Wang H, et al. Transcutaneous vagus nerve stimulation modulates default mode network in major depressive disorder. Biol Psychiatry 2016;79:266-73.

71. Rey G, Desseilles M, Favre S, Dayer A, Piguet C, Aubry J-M, et al. Modulation of brain response to emotional conflict as a function of current mood in bipolar disorder: Preliminary findings from a follow-up state-based fMRI study. Psychiatry Res Neuroimaging 2014;223:84–93.

72. Lai C-H, Wu Y-T. Duloxetine's modest short-term influences in subcortical structures of first episode drug-naïve patients with major depressive disorder and panic disorder. Psychiatry Res Neuroimaging. 2011;194:157–62.

73. Atmaca M, Ozdemir H, Cetinkaya S, Parmaksiz S, Belli H, Kursad Poyraz A, et al. Cingulate gyrus volumetry in drug free bipolar patients and patients treated with valproate or valproate and quetiapine. J Psychiatr Res. 2007;41:821–7.

74. Germana C, Kempton MJ, Sarnicola A, Christodoulou T, Haldane M, Hadjulis M, et al. The effects of lithium and anticonvulsants on brain structure in bipolar disorder. Acta Psychiatr Scand. 2010;122:481–7.

75. Hajek T, Kopecek M, Höschl C, Alda M. Smaller hippocampal volumes in patients with bipolar disorder are masked by exposure to lithium: a meta-analysis. J Psychiatry Neurosci 2012;37:333–43.

76. Hajek T, Cullis J, Novak T et al. Hippocampal volumes in bipolar disorders: opposing effects of illness burden and lithium treatment. Bipolar Disord 2012; 14: 261–270.

77. Hajek T, Bauer M, Simhandl C, Rybakowski J, O'Donovan C, Pfennig A, et al. Neuroprotective effect of lithium on hippocampal volumes in bipolar disorder independent of long-term treatment response. Psychol Med 2014;44:507–17.

78. Smith R, Chen K, Baxter L, Fort C, Lane RD. Antidepressant effects of sertraline associated with volume increases in dorsolateral prefrontal cortex. J Affect Disord 2013;146:414–9.

79. Arce E, Simmons AN, Lovero KL, Stein MB, Paulus MP. Escitalopram effects on insula

and amygdala BOLD activation during emotional processing. Psychopharmacology (Berl);196:661–72.

80. Mayberg H. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. Br Med Bull 2003;65:193–207.

81. Rose EJ, Simonotto E, Spencer EP, Ebmeier KP. The effects of escitalopram on working memory and brain activity in healthy adults during performance of the n-back task. Psychopharmacology (Berl) 2006;185:339–47.

82. Haldane M, Jogia J, Cobb A, Kozuch E, Kumari V, Frangou S. Changes in brain activation during working memory and facial recognition tasks in patients with bipolar disorder with Lamotrigine monotherapy. Eur Neuropsychopharmacol 2008;18:48–54.

83. Pavuluri MN, Passarotti AM, Fitzgerald JM, Wegbreit E, Sweeney JA. Risperidone and divalproex differentially engage the fronto-striato-temporal circuitry in pediatric mania: a pharmacological functional magnetic resonance imaging study. J Am Acad Child Adolesc Psychiatry 2012;51:157–70.

84. Harmer CJ, Mackay CE, Reid CB, Cowen PJ, Goodwin GM. Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. Biol Psychiatry 2006;59:816–20.

85. Fales CL, Barch DM, Rundle MM, Mintun MA, Mathews J, Snyder AZ, et al. Antidepressant treatment normalizes hypoactivity in dorsolateral prefrontal cortex during emotional interference processing in major depression. J Affect Disord 2009;112:206–11.

86. Norbury R, Taylor MJ, Selvaraj S, Murphy SE, Harmer CJ, Cowen PJ. Short-term antidepressant treatment modulates amygdala response to happy faces. Psychopharmacology (Berl) 2009;206:197–204.

87. van Wingen GA, Tendolkar I, Urner M, van Marle HJ, Denys D, Verkes R-J, et al. Short-term antidepressant administration reduces default mode and task-positive network connectivity in healthy individuals during rest. Neuroimage 2013;88C:47–53.

88. Wang L, Xia M, Li K, Zeng Y, Su Y, Dai W, et al. The effects of antidepressant treatment on resting-state functional brain networks in patients with major depressive disorder.

Hum Brain Mapp 2015;36:786–78.

89. McCabe C, Mishor Z. Antidepressant medications reduce subcortical-cortical resting-state functional connectivity in healthy volunteers. Neuroimage 2011;57:1317–23.

90. McCabe C, Mishor Z, Filippini N, Cowen PJ, Taylor MJ, Harmer CJ. SSRI administration reduces resting state functional connectivity in dorso-medial prefrontal cortex. Mol Psychiatry 2011;16:592–4.

91. Versace A, Thompson WK, Zhou D, Almeida JRC, Hassel S, Klein CR, et al. Abnormal left and right amygdala-orbitofrontal cortical functional connectivity to emotional faces: state versus trait vulnerability markers of depression in bipolar disorder. Biol Psychiatry 2010;67:422–31.

92. Almeida JRC De, Versace A, Mechelli A, Hassel S, Quevedo K, Kupfer DJ, et al. Abnormal amygdala-prefrontal effective connectivity to happy faces differentiates bipolar from major depression. Biol Psychiatry 2009;66:451–9.

93. Delaveau P, Jabourian M, Lemogne C, Guionnet S, Bergouignan L, Fossati P. Brain effects of antidepressants in major depression: a meta-analysis of emotional processing studies. J Affect Disord 2011;130:66–74.

94. Hafeman DM, Chang KD, Garrett AS, Sanders EM, Phillips ML. Effects of medication on neuroimaging findings in bipolar disorder: an updated review. Bipolar Disord 2012; 14: 375–410.

95. Weiss EM, Siedentopf C, Golaszewski S, Mottaghy FM, Hofer A, Kremser C, et al. Brain activation patterns during a selective attention test--a functional MRI study in healthy volunteers and unmedicated patients during an acute episode of schizophrenia. Psychiatry Res 2007;154:31–40.

96. Adler CM, Holland SK, Schmithorst V, Tuchfarber MJ, Strakowski SM. Changes in neuronal activation in patients with bipolar disorder during performance of a working memory task. Bipolar Disord 2004; 6: 540–549.

97. Vandeleur CL, Merikangas KR, Strippoli M-PF, Castelao E, Preisig M. Specificity of psychosis, mania and major depression in a contemporary family study. Mol Psychiatry 2014;19:209–13.

98. Merikangas KR, Cui L, Heaton L, Nakamura E, Roca C, Ding J, et al. Independence of familial transmission of mania and depression: results of the NIMH family study of affective spectrum disorders. Mol Psychiatry 2014;19:214–9.

99. McGuffin P Andrew M, Sham P, Katz R, Cardno A. RF. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Arch Gen Psychiatry. 2003;60:497–502.

100. Merikangas KR. Mania with and without depression in a community sample of US adolescents. Arch Gen Psychiatry 2012;69:943.

101. Strakowski SM, Adler CM, DelBello MP. Is Depression simply a nonspecific response to brain injury? Curr Psychiatry Rep. 2013;15:386.

102. Boonstra G, van Haren NEM, Schnack HG, Cahn W, Burger H, Boersma M, et al. Brain volume changes after withdrawal of atypical antipsychotics in patients with first-episode schizophrenia. J Clin Psychopharmacol. 2011;31:146–53.

103. Tang Y, Yu X, Zhang X, Xia W, Wu X, Zou X, et al. Single-dose intravenous administration of antiepileptic drugs induces rapid and reversible remodeling in the brain: Evidence from a voxel-based morphometry evaluation of valproate and levetiracetam in rhesus monkeys. Neuroscience 2015;303:595–603.

Table 1. Demographic and clinical characteristics

	MDDr (n = 23)[a]	BDr (n = 26)[b]	MDDd (n = 22)	BDd (n = 10)[c]	MDDr versus BDr		MDDd versus BDd	
					t/χ^2	p-value	t/χ^2	p-value
Age, years, mean (SD)	42.7 (10.4)	42.7 (10.7)	43.8 (8.8)	38.8 (11.1)	0.001	1.0	1.3	0.2
Gender, M/F, n	8/15	10/16	7/15	4/6	0.07	0.8	0.2	0.7
Education: low/middle/high, n[d]	3/7/13	2/7/16	3/11/8	0/5/5	0.4	0.8	1.7	0.4
No. of previous MDE's, median [range][e]	4.0 [2–20]	6.5 [2–20]	3.0 [2–20]	10.0 [3–20]		**0.05**[f]		**0.02**[f]
IQ, mean (SD)	100.3 (10.6)	101.5 (9.5)	97.0 (16.1)	101.0 (11.8)	0.4	0.7	0.9	0.4
Age of illness onset, years, mean (SD)	23.2 (9.1)	23.6 (8.7)	25.9 (8.4)	20.3 (8.1)	0.1	0.9	1.7	0.1
Duration of illness, years, mean (SD)	20.8 (11.3)	19.2 (10.5)	17.3 (10.1)	18.7 (12.2)	0.5	0.6	0.3	0.7

HDRS score, mean (SD)	6.4 (5.0)	5.5 (5.5)	22.0 (5.5)	22.3 (6.8)	0.6	0.6	0.1	0.9
Comorbid anxiety disorder, n[g]	3	2	3	2	0.4	0.5	0.2	0.6
Medication-naïve, n	5	2	6	1	2.0	0.2	1.8	0.6
Duration of medication-free period, n[h]					5.5	0.09	0.4	1.0
1–3 months	4	6	4	3				
3–12 months	1	9	2	2				
>12 months	8	6	8	4				
Duration of remission, n[i]					2.5	0.4	–	–
1 week–3 months	7	7	–	–				
3–12 months	4	10	–	–				
>12 months	8	6	–	–				
History of substance use disorder, n	5	13	6	3	3.8	0.07	0.03	1.0
Duration of remission substance use disorder, n[j]					2.4	0.2	2.3	0.3
3–6 months	0	4[k]	0	1				
>6 months	5	7	6	2				
Current substance use, n								
Alcohol	16	20	13	8	0.3	0.7	1.3	0.4
Tobacco	5	9	8	4	1.2	0.3	0.04	1.0
Drugs (incidental)	1	4	1	0	1.5	0.4	0.4	1.0
Benzodiazepine use, n (%)	0 (0)	1 (3.8)[l]	1 (4.5)[m]	1 (10.0)[n]				

Within the depressed and remitted groups, there were no significant differences between MDD and BD regarding demographic or clinical characteristics, except for the number of previous episodes. BDd = bipolar disorder, depressed state; BDr = bipolar disorder, remitted state; MDDd = major depressive disorder, depressed state; MDDr: major depressive disorder, remitted state; MDE = major depressive episode; SD = standard deviation; M = male; F = female; HDRS = Hamilton Depression Rating Scale (17 items).

[a]For resting state: n = 22.

[b]10 subjects with bipolar II disorder.

[c]Six subjects with bipolar II disorder.

[d]Low: primary education or preparatory middle-level applied education; middle: higher general continued education or middle-level applied education; high: preparatory scientific education, higher applied education, or scientific education. Missing values: 1 BDr.

[e]>20 episodes are set on 20 episodes; reported are median and range. Missing values: 3 BDr.

[f]Kruskall–Wallis test comparing medians.

[g]Hypochondria, specific phobia, social phobia, panic disorder, and obsessive compulsive disorder.

[h]Missing values: 5 MDDr, 3 BDr, 2 MDDd; all subjects were at least one-month free of medication.

[i]Missing values: 4 MDDr, 3 BDr.

[j]Missing values: 2 BDr.

[k]Alcohol/cannabis abuse/dependence till 5–6 months before scanning.

[l]Lorazepam 2.5 mg: quit 17 hours before scanning.

[m]Oxazepam 25 mg: quit 48 hours before scanning.

[n]Temazepam 20 mg: quit 40 hours before scanning.

Table 2. Classification results using Gaussian Process Classifier

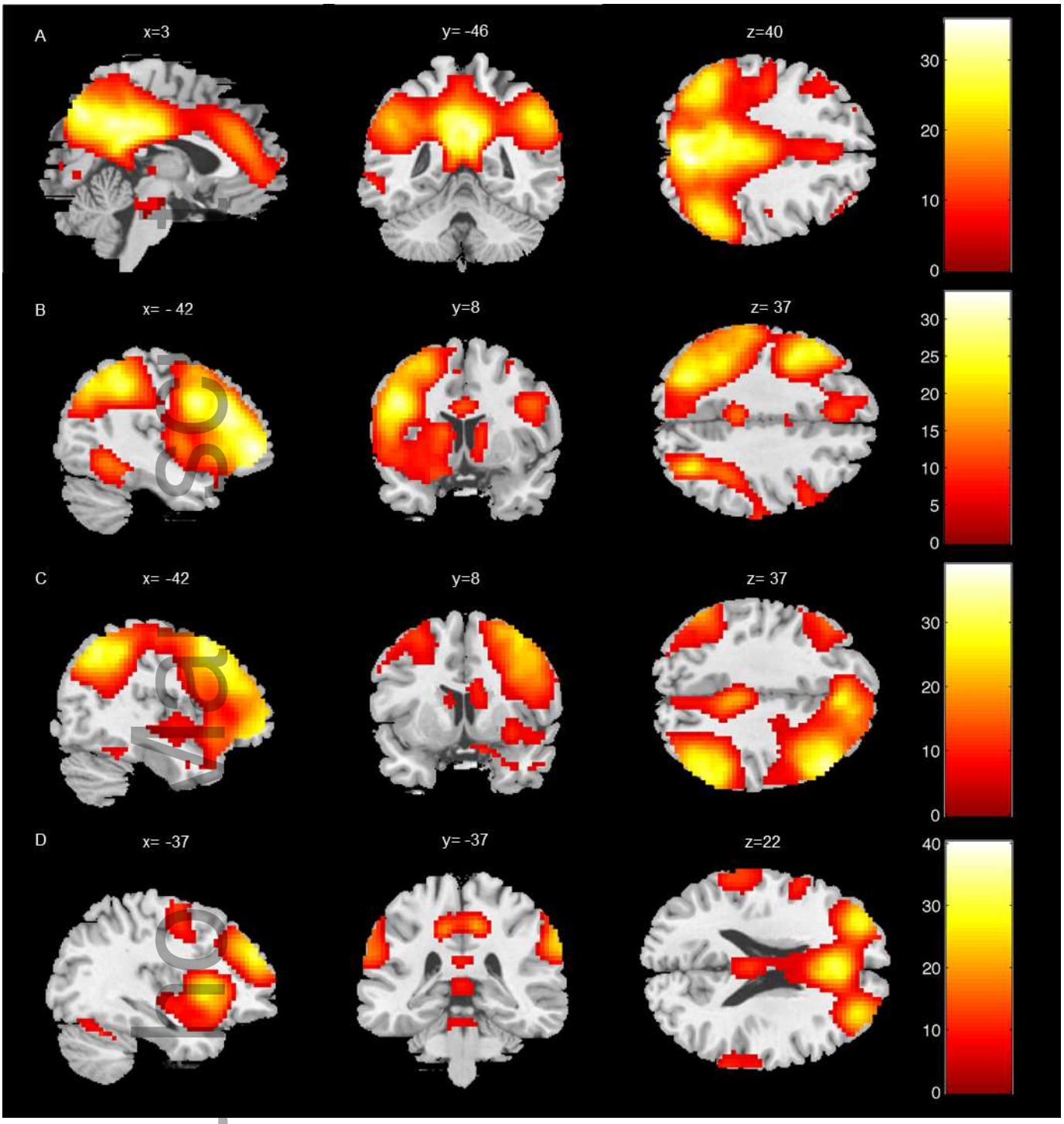
	Balanced accuracy (%)	Class accuracy (%)		Class predictive value		p-value
Data		Sensitivity	Specifity	PPV	NPV	
Default mode network						
MDDd versus BDd	69.1	70.0	68.2	50.0	83.3	0.02
MDDr versus BDr	50.3	46.2	54.6	54.6	46.2	0.46
Gray matter volume of emotion regulation areas						
MDDd versus BDd	69.1	70.0	68.2	50.0	83.3	0.02
MDDr versus BDr	60.0	61.5	59.0	64.0	56.5	0.01

Default mode network activity and gray matter volume patterns discriminated significantly between depressed subjects with major depressive disorder (MDD) and bipolar disorder (BD) (indicated with gray shading). For both modalities, sensitivity (i.e., the true positive rate in subjects with BD) is reasonably high, decreasing the risk of missing subjects with BD and thereby preventing ineffective antidepressant treatment, which leads to prolonged illness duration, recurrence, and overall worse prognosis. Specificity (i.e., the true negative rate in non-BD subjects) is also relatively high, reducing the risk of erroneous prescription of BD medication and false positive diagnosis as BD in subjects with MDD. Although dependent on the prevalence of MDD and BD in the clinical population to be tested, which is not necessarily the prevalence in our population (MDD: BD = 2:1 in the depressed group) we also mention the positive and negative predictive values (reflecting the probability of disease after the test result is known). Positive predictive value is number of true positives divided by number of positive predictions; negative predictive value is number of true negatives divided number of negative predictions. BDd = bipolar disorder, depressed state; BDr = bipolar disorder, remitted state; MDDd: major depressive disorder, depressed state; MDDr = major depressive disorder, remitted state; NPV = negative predictive value; PPV = positive predictive value.

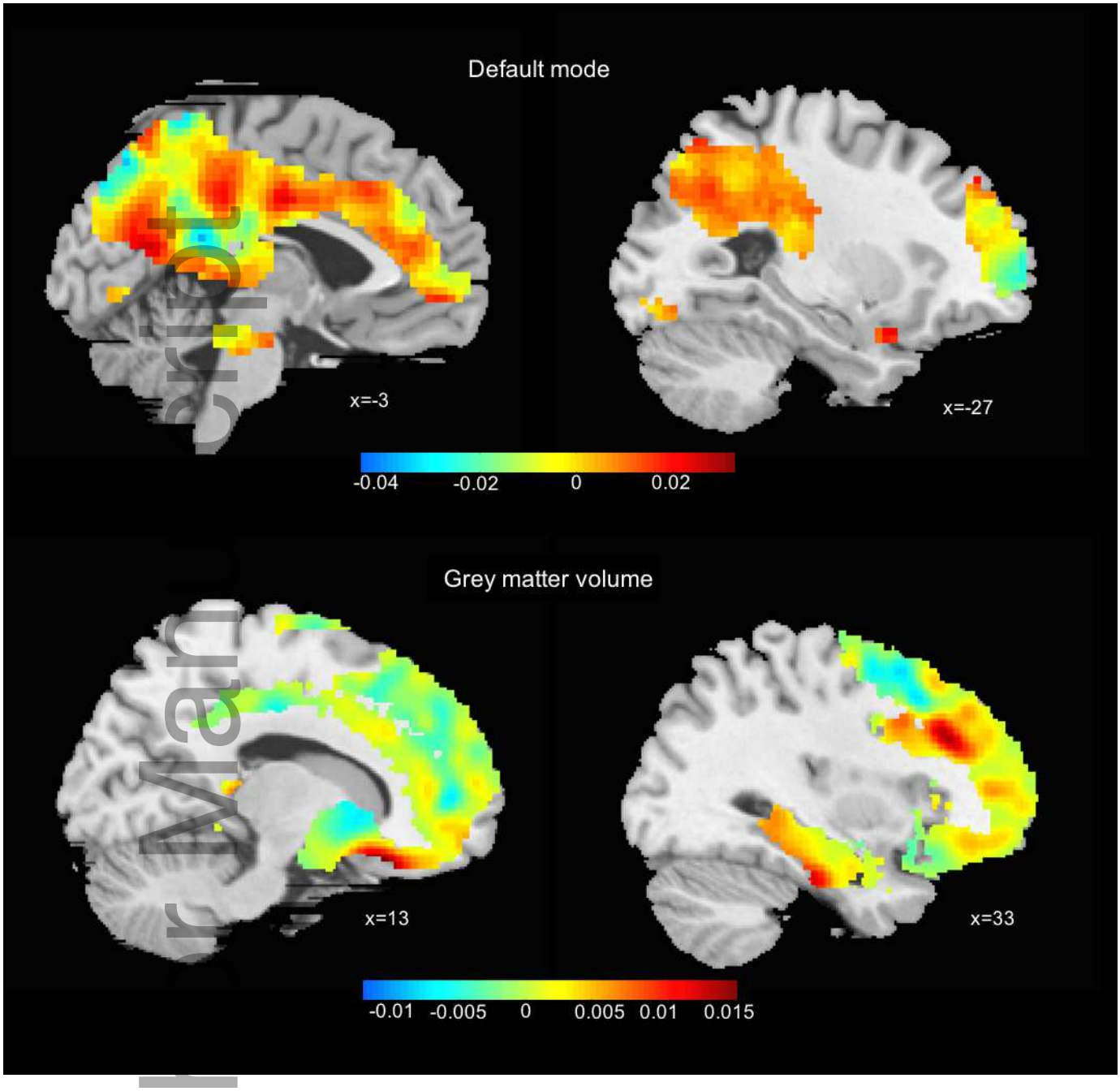
Figure legends

Fig 1. Resting state networks of interest. **(A)** default mode network; **(B)** left frontoparietal network; **(C)** right frontoparietal network; **(D)** salience network. Displayed are the one sample *t*-tests of the spatial maps across subjects, whole brain $p < 0.05$ family-wise error corrected. Voxel intensities represent the connectivity and degree of co-activation within the resting state network.

Fig 2. Weight maps of depressed major depressive disorder (MDDd) versus depressed bipolar disorder (BDd) classification. Weight maps are based on the default mode network and gray matter data. Weight maps of the default mode network (above) and gray matter data (below) displaying the positive and negative weights of the classification problem MDDd versus BDd. Negative weights (blue) represent the voxels contributing to classification as a BDd subject; positive weights (red) represent the voxels contributing to classification as an MDDd subject.



bdi_12446_f1.tif



bdi_12446_f2.tiff