



King's Research Portal

DOI:

[10.1016/j.biopsych.2016.10.028](https://doi.org/10.1016/j.biopsych.2016.10.028)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Kambeitz, J., Cabral, C., Sacchet, M. D., Gotlib, I. H., Zahn, R., Serpa, M. H., Walter, M., Falkai, P., & Koutsouleris, N. (2016). Detecting Neuroimaging Biomarkers for Depression: A Meta-Analysis of Multivariate Pattern Recognition Studies. *Biological psychiatry*. <https://doi.org/10.1016/j.biopsych.2016.10.028>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

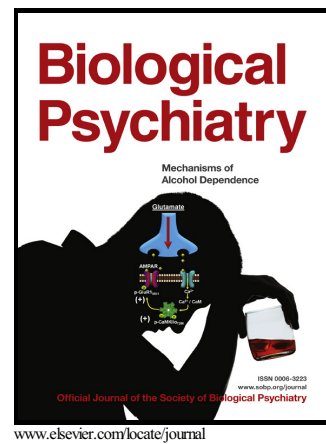
Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Author's Accepted Manuscript

Detecting Neuroimaging Biomarkers for Depression: A Meta-Analysis of Multivariate Pattern Recognition Studies
Neuroimaging Biomarkers of Depression

Joseph Kambeitz, Carlos Cabral, Matthew D. Sacchet, Ian H. Gotlib, Roland Zahn, Mauricio H. Serpa, Martin Walter, Peter Falkai, Nikolaos Koutsouleris



PII: S0006-3223(16)32980-8
DOI: <http://dx.doi.org/10.1016/j.biopsych.2016.10.028>
Reference: BPS13046

To appear in: *Biological Psychiatry*

Cite this article as: Joseph Kambeitz, Carlos Cabral, Matthew D. Sacchet, Ian H. Gotlib, Roland Zahn, Mauricio H. Serpa, Martin Walter, Peter Falkai and Nikolaos Koutsouleris, Detecting Neuroimaging Biomarkers for Depression: A Meta-Analysis of Multivariate Pattern Recognition Studies
Neuroimaging Biomarkers of Depression, *Biological Psychiatry*, <http://dx.doi.org/10.1016/j.biopsych.2016.10.028>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Detecting neuroimaging biomarkers for depression: A meta-analysis of multivariate pattern recognition studies

Short title: Neuroimaging biomarkers of depression

Joseph Kambeitz, MD^{1#}, Carlos Cabral, MA¹, Matthew D. Sacchet, ScB², Ian H. Gotlib, PhD², Roland Zahn, MD³, Mauricio H. Serpa, MD^{4,5}, Martin Walter, Prof^{6,7}, Peter Falkai, Prof¹, Nikolaos Koutsouleris, Prof¹

¹Department of Psychiatry, Ludwig-Maximilians University Munich, Munich, Germany

²Neurosciences Program and Department of Psychology, Stanford University, Stanford California, United States of America

³Institute of Psychiatry, King's College London, London, United Kingdom

⁴Laboratory of Psychiatric Neuroimaging, Institute and Department of Psychiatry, University of Sao Paulo, Sao Paulo, Brazil

⁵Center for Interdisciplinary Research on Applied Neurosciences (NAPNA), University of Sao Paulo, Sao Paulo, Brazil

⁶Clinical Affective Neuroimaging Laboratory, Department of Behavioural Neurology, Leibniz Institute for Neurobiology, Magdeburg, Germany

⁷Department of Psychiatry and Psychotherapy, Eberhard Karls University, Tuebingen, Germany

#Corresponding author: Joseph Kambeitz MD, Dipl.-Psych., Address: Nußbaumstraße 7, 80336 Munich, Germany, Email: joseph.kambeitz@med.uni-muenchen.de, Phone: +4989/440052731, Fax: +4989/440055776

Key words: affective disorder, classification, prediction, sensitivity, specificity, diagnosis

Abstract

Introduction

Multiple studies have examined functional and structural brain alteration in patients diagnosed with from Major Depressive Disorder (MDD). The introduction of multivariate statistical methods allows investigators to utilize data concerning these brain alterations to generate diagnostic models that accurately differentiate patients with MDD from healthy controls. However, there is substantial heterogeneity in the reported results, the methodological approaches, and the clinical characteristics of participants in these studies.

Method

We conducted a meta-analysis of all studies using neuroimaging (volumetric measures derived from T1 weighted images, task-based functional MRI, resting-state MRI, or diffusion-tensor imaging) in combination with multivariate statistical methods to differentiate patients diagnosed with MDD from healthy controls.

Results

Thirty-three ($k=33$) samples including $n=912$ patients with MDD and $n=894$ healthy control subjects were included in the meta-analysis. Across all studies, patients with MDD were separated from healthy control subjects with 77% sensitivity and 78% specificity. Classification based on resting-state MRI (sensitivity of 85%, specificity of 83%) and on DTI data (sensitivity of 88%, specificity of 92%) outperformed classification based on structural

MRI (sensitivity of 70%, specificity of 71%) and task-based functional MRI (sensitivity 74%, specificity 77%).

Discussion

Our results demonstrate the high representational capacity of multivariate statistical methods to identify neuroimaging-based biomarkers of depression. Future studies are needed to elucidate whether multivariate neuroimaging analysis has the potential to generate clinically useful tools for the differential diagnosis of affective disorders and the prediction of both treatment response and functional outcome.

Introduction

Major Depressive Disorder (MDD) has a lifetime prevalence of 14.6%, making it one of the most common psychiatric disorders worldwide (1). Reliable diagnosis of MDD is a primary prerequisite for effective pharmacological and psychological interventions (2). Currently, the diagnosis of depression is based on the phenomenological evaluation of symptoms and behaviour by trained clinicians. Scientists have posited that neuroimaging holds 'diagnostic potential' given findings in multiple studies of significant anomalies in brain structure (3–5), function (6–8), and neurochemistry (9; 10) in patients suffering from depression. Even though these meta-analyses indicate that brain changes are replicable across studies, the alterations are often small and do not allow a reliable differentiation between patients and controls(11). Thus, neuroimaging markers are not included in clinical practice to guide decisions concerning psychiatric diagnosis (12; 13). This might result from the higher costs associated with neuroimaging examinations. Moreover, most of the previous neuroimaging studies in MDD have taken a univariate approach, which has important consequences in terms of the clinical applicability of the obtained results. For example, univariate approaches neglect the highly interconnected nature of the brain and, consequently, the statistical dependency of the given units of analysis (e.g. voxels or regions-of-interest) (14). Moreover, even if two groups (e.g. patients with depression and healthy controls [HC]) differ at a statistically significant level with respect to a target variable (e.g. hippocampal volume), there is typically substantial overlap of the two distributions, hindering reliable differentiation of depressed from nondepressed individuals.

To address these limitations, investigators have begun to apply multivariate statistical methods to the analysis of neuroimaging data (15; 16). By focusing on patterns of brain changes that are distributed across multiple regions, these methods allow for the generation

of statistical models with high diagnostic or predictive power. In this context, a recent meta-analysis showed that patients with schizophrenia can be accurately differentiated from healthy volunteers in 80% of the cases using only neuroimaging-based diagnostic models (17). Moreover, these methods may facilitate the development of neuroimaging tools to distinguish among different psychiatric disorders (18–21) or to predict clinical outcomes (22–24). Indeed, multiple proof-of-concept studies have successfully used multivariate statistical methods to guide the diagnosis of depression based on structural MRI (sMRI) data (19; 21; 25–27), resting-state functional MRI (rsfMRI) data (26; 28–34), and task-based functional MRI (fMRI) data (35–39). The sensitivity and the specificity reported in these studies both range from 70% to 90%. This variable diagnostic performance may be due to methodological differences among these studies with respect to the neuroimaging data modality, preprocessing protocol, classification algorithm, or the cross-validation procedure used. In addition, these studies differ with respect to demographic and clinical characteristics of depressed patients. Differences in performance and study heterogeneity make it difficult to evaluate the potential of neuroimaging to identify diagnostic biomarkers for depression. Here, we report the results of a meta-analysis conducted on studies that used multivariate statistical methods to differentiate patients with depression from healthy controls. This meta-analytic approach allows us to quantify the ability of multivariate methods to identify depression-related patterns in neuroimaging data. In this way, we investigate the neurobiological construct validity of the current clinical definition of MDD.

Methods

Search and study selection strategy

We searched the electronic PubMed database from 1st January 1950 up to 31st June 2015 (see supplementary information for details). Subsequently, we screened studies according to the following criteria: To be included in the meta-analysis, a paper needed to report results of a neuroimaging-based, supervised, multivariate two-group classification model separating MDD patients from HC. Studies were included if the following measures of classification performance were available or if data allowed for the calculation of the following parameters: true positives (TP), true negatives (TN), false positives (FP), false negatives (FN). In cases in which insufficient data were reported, authors were asked to provide additional information regarding their published reports. The results of the literature search are presented in a flow-chart following the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) guidelines (40) (see Supplementary Info, Figure S1).

Data extraction

The main outcome was the diagnostic accuracy of the multivariate diagnostic models when applied to patients with MDD and HC as indicated by sensitivity (i.e. = TP / (TP+FN)) and specificity (i.e. = TN / (TN+FP)). Additional information was extracted from the selected studies as follows: names of the authors, year of publication, demographic characteristics of HC and patient groups (group size, age, gender, medication status, symptoms as measured by the Hamilton Depression Scale (41) or the Beck Depression Inventory (42), neuroimaging modality (volumetric measures derived of T1w MRI images 'sMRI', task-based functional MRI 'fMRI', resting-state fMRI 'rsfMRI', positron emission tomography 'PET', single photon emission computed tomography 'SPECT', diffusion tensor imaging 'DTI', scanner type, image resolution), characteristics of the neuroimaging preprocessing, configuration of the classification algorithm, and type of the cross-validation procedure (e.g. leave-one-out, k-fold cross-validation). To ensure accuracy of data extraction, two authors separately performed extraction and disagreements were resolved in a consensus conference.

Data analysis

In the present analysis we implemented the a random-effects, bivariate meta-analytical model as introduced by Reitsma et al. (43). Results of the meta-analysis are presented in forest plots separately for sensitivity and specificity. Summary estimates for sensitivity and specificity are provided separately for sMRI, for task-based fMRI studies, for rsfMRI studies, for DTI studies and for all studies combined. The robustness of the results and the effects of potentially confounding variables (e.g. age, gender ratio, year of publication) were investigated by adding moderator variables to the bivariate regression model. Furthermore, we tested for differences between studies in the clinical variables using univariate analysis-of-variance (ANOVA). Publication bias was assessed by creating funnel plots by plotting log

diagnostic odds ratios (logDOR) for all studies against $\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$ with n_1 and n_2 representing the sample sizes of the patient and the HC group, respectively. This measure is proportional

to the inverted square root of the effective sample size (ESS): $\frac{1}{\sqrt{ESS}}$. In case of a publication bias, the distribution of studies in the funnel plot is asymmetrical. A statistical test

for funnel plot asymmetry is provided by a regression of logDOR with $\frac{1}{\sqrt{ESS}}$ weighted by ESS (44). As an exploratory analysis, we generated a multivariate regression model using the elastic net algorithm to predict logDOR of individual studies based on $n=23$ clinical and methodological variables (see supplementary information for details). All computations were performed using the *R* statistical programming language version 3.3.1 (45) with the packages *mada* (46) and *glmnet* (47).

Results

Meta-analysis

The initial literature search identified 641 studies of interest. After screening all studies and applying the inclusion criteria, 608 studies were excluded (see Supplementary Information, Figure S1 for a flow-chart of the literature search). The final sample consisted of 33 studies with of a total of 912 patients (mean age: 34.27 years) and 894 HC (mean age: 32.81 years). From those studies, k=14 samples used structural MRI(19–21; 25–27; 48–54), k=9 samples used rsfMRI(26; 29; 31; 33; 54–58), k=9 samples used fMRI(35–37; 39; 59–63), and k=6 samples used DTI(26; 64–67) to build predictive models (see Supplementary Information, Table S1 for an overview of the characteristics of the studies; please note that some studies provide more than one sample). There were no studies available using SPECT methodology. One study reported 85% classification accuracy using (18)FDG-PET but was excluded from further analysis due to the small number of available studies(68).

Meta-analysis of all studies indicated a sensitivity of 76.66% (95%-CI: 71.95 to 80.80%) and a specificity of 77.7% (95%-CI: 73.7 to 81.35%). Visual inspection of funnel plots and regression test for funnel plot asymmetry ($p=0.69$) did not indicate the presence of a publication bias (see Supplementary Information, Figure S2). Moreover, there was no relationship between size of the investigated samples and sensitivity of specificity ($p>0.1$, see supplementary information Figure S4). Different neuroimaging modalities (sMRI, fMRI, DTI, rsfMRI) were compared using a moderator analysis. Resting-state MRI studies showed higher sensitivity ($p=0.007$) and specificity ($p=0.017$) compared to sMRI studies. There were no significant differences compared to DTI or fMRI studies (all $p>0.05$). DTI studies showed a higher sensitivity ($p=0.017$) and specificity ($p=0.006$) than sMRI studies, but not than fMRI studies ($p>0.05$, see Figure 3 A).

Subanalysis for every neuroimaging modality showed the following results (see Table 1, Figure 1 & 2). For the subsample of sMRI studies, there was a sensitivity of 69.85% (95%-CI: 61.81 to 76.83%, Figure 1) and a specificity of 71.13% (95%-CI: 65.41 to 76.25%, see Figure 2). For the subsample of task-related fMRI studies, there was a sensitivity of 74.06% (95%-CI: 67.17 to 79.94%, see Figure 1) and a specificity of 77.20% (95%-CI: 69.92 to 83.15%, see Figure 2). For the subsample of rsfMRI studies, there was a sensitivity of 85.39% (95%-CI: 74.75 to 92.02%, see Figure 1) and a specificity of 82.59% (95%-CI: 74.64 to 88.43%, see Figure 2). For the subsample of DTI studies, there was sensitivity of 88.16% (95%-CI: 74.18 to 95.07%, see Figure 1) and a specificity of 91.51% (95%-CI: 97.15 to 77.32%, see Figure 2). Visual inspection of funnel plots and regression tests for funnel plot asymmetry did

not indicate presence of publication bias in the meta-analysis of studies using sMRI ($p=0.97$), DTI ($p=0.68$), fMRI ($p=0.64$) or rsfMRI ($p=0.25$).

There was no significant effect of HAMD score on sensitivity or specificity ($p>0.80$, Figure 3 C). There was no effect of participants' age on sensitivity ($p=0.112$) or specificity ($p=0.476$, see Figure 3 B) in the whole sample including all neuroimaging modalities. Similarly, there was no effect of participants' age in the fMRI, or sMRI studies. There was a significant effect of age on sensitivity in the DTI studies ($p=0.014$) and in the rsfMRI studies ($p=0.015$) but not on specificity ($p>0.05$). Gender ratio of patients and of healthy controls was not related to sensitivity ($p=0.414$, $p=0.302$, respectively) or specificity ($p=0.582$, $p=0.776$, respectively).

There were heterogeneous methodological approaches in the studies included in the present meta-analysis. When comparing diagnostic accuracies between different cross-validation schemes, there was a higher sensitivity in studies employing 2-fold CV as compared to leave-one-out and leave-one-subject-per-group-out CV ($p=0.035$, $p=0.020$, respectively), but no differences in specificity (see supplementary methods Figure S5). Because of the heterogeneous methodological approaches of the studies included in the present meta-analysis, we could not make a statistically valid comparison to test the effects of different classification algorithms on classification accuracy. Thus, we provide a descriptive overview of classification performance associated with different algorithms (see Supplementary Information, Figure S2).

As an exploratory analysis, we tested whether model performance (logDOR) could be predicted on the basis of clinical and methodological variables of the individual studies. Our results indicate that predicted logDOR correlated with true logDOR with $r=0.44$ ($p=0.002$). The $n=5$ most important variables in this meta-learning model (as measured by the absolute value of their coefficient averaged across outer-CV folds) were "depression severity: severe", "feature selection: filter", "patients (age)" (all associated with higher logDOR) and "data: sMRI", and "feature selection: none" (all associated with lower logDOR; see supplementary analysis for further details).

Discussion

We present meta-analyses of a total of $k=33$ studies with of a total of $n=912$ patients diagnosed with MDD and $n=894$ HC participants. Across all studies, neuroimaging-based diagnostic models were able to differentiate patients from HCs with 77% sensitivity and 78% specificity. These results were robust with respect to potential confounding variables such as age of patients and controls, gender ratio, and year of publication. There was no evidence for

a publication bias. Resting-state fMRI studies (sensitivity of 85%, specificity of 83%) and DTI studies (sensitivity of 88%, specificity of 92%) outperformed sMRI (70% sensitivity, 71% specificity) and task-based fMRI studies (74% sensitivity, 77% specificity).

Different neuroimaging modalities

Our results suggest superior classification accuracy of diagnostic models based on rsfMRI or DTI data, compared to structural or task-based fMRI data. It is noteworthy that in a previous analysis, we found rsfMRI to outperform other neuroimaging modalities in differentiating patients with schizophrenia from healthy controls (17). We should note, however, that a limited number of studies were available using these neuroimaging modalities, so the results need to be interpreted with caution. If this pattern can be confirmed in future analyses, it suggests that rsfMRI and DTI data are the most informative neuroimaging metrics when classifying patients with psychiatric diagnoses versus HCs. On one hand, there might be factors driving this effect that are related to technical details of the neuroimaging methodology. For example, DTI and rsfMRI use scan sequences that typically take longer time to acquire than do structural MRI sequences and, therefore, might be more susceptible to motion artifacts (73–75). If motion is related to psychiatric diagnosis, then these artifacts might in turn be informative for psychiatric classification and could be picked up by the multivariate classification algorithm. The lower performance of classifiers based on task-based fMRI data compared to DTI and rsfMRI data might be caused by the lower test/re-test reliability of this method (72), the dependency on cognitive performance on this task, habituation while performing the task or variable degree of validity of the employed paradigms for the pathology of MDD. Depending on the preprocessing and the feature selection procedures employed in the task-based fMRI studies, these effects might add noise to the recorded data which, in turn, might reduce the discriminative power of extracted measures for the subsequent classification. Alternatively, rsfMRI and DTI may capture brain alterations that are more predictive in the context of classifying MDD. It is noteworthy that while both modalities are often used to investigate brain connectivity, rsfMRI is a functional measure and DTI is structural. This inherent difference suggests that these modalities capture complementary aspects of the neuropathology of MDD and, thus, that they could be combined in a multimodal classification model to improve performance. To date, there is only one study that compared uni- with multimodal classification approaches for MDD (26). In that study, multimodal classification (70% accuracy) was outperformed by unimodal classification based on DTI (77%), rsfMRI (77%), and T2 images (77%). Of note, Patel et al. (2015) assessed a sample of subjects with late-life depression and thus these results may not generalize to individual subjects with first depressive episodes that usually occur at age 30 (73). Moreover, there is evidence from studies of other psychiatric disorders such as

schizophrenia indicating that multimodal classification improves accuracy compared to unimodal approaches(74; 75).

Different classification algorithms & cross-validation schemes

The vast majority of studies in the present analysis used a support-vector machine (SVM) algorithm to classify patients (~60%). Looking at neuroimaging modalities separately, SVM was the most frequently used algorithm for DTI studies (~83%), fMRI studies (57%), rsfMRI studies (75%) and sMRI studies (~76%). Some studies used a gaussian-process classifier (19; 36), neural networks (30), random forests (50), k-means (50), random trees (50), or decision trees (26). Only two studies systematically investigated different classification algorithms within the same sample (19; 26). Redlich et al. (19) reported higher accuracy when classifying patients with depression or bipolar disorder using a SVM classifier than using a gaussian-process algorithm. Patel et al. (26) found that a decision tree algorithm (75%) outperformed linear SVMs (70%) and RBF-SVMs (68%). Interestingly, to date there are no systematic investigations of different algorithms in neuroimaging-based classification in psychiatry. It is noteworthy that, choice of classification algorithm did not appear to affect performance in the classification of individuals diagnosed with schizophrenia (17). However, it needs to be noted that in the current meta-analysis all studies were of limited sample size so that potential differences between classification algorithms might not have manifested. Moreover, some algorithms require more extensive training samples and might not have been employed due to the limited amount of available training data. Another important factor in the context of our analysis is the embedding of feature selection, classifier optimization and the estimation of the models' generalizability in a CV scheme. We should note that in three papers that were included in the present meta-analysis, a feature selection procedure was implemented outside of the cross-validation(20; 31; 64). However, it is critical to avoid information leakage between the training and the test samples to avoid overfitting and biased estimates of classification accuracy. Moreover, even in the case of correct embedding, different cross-validation schemes might lead to different results. In our analysis 2-fold CV was associated with higher diagnostic accuracy than were 10-fold or LOOCV.

Limitations of the current meta-analysis: effect of clinical symptoms and antidepressant medication

One study suggest that the degree of functional and structural brain abnormalities found in depression is related to the severity of clinical symptomatology (76). In effect, neuroimaging-based classification models should perform better in more severely ill subjects. Mwangi et al.

(76) report a correlation between scores on the Beck's Depression Inventory II (BDI-II) and the Spielberger State-Trait Anxiety Inventory (STAI) with individual SVM decision weights. In the present univariate analysis we found no effect of clinical symptoms as measured by HAMD. It is possible that the clinical and methodological heterogeneity present in our meta-analysis obfuscated a potential relation between accuracy and clinical symptoms. On the other hand, using a multivariate meta-learning model we found some evidence that depression severity as measured by the HAMD scale is an important predictor of classification accuracy. There are other clinical variables besides severity, that may influence brain anomalies in patients with depression and that may affect the accuracy of neuroimaging-based classification. These variables include age of onset or illness duration, and comorbidities such as anxiety, obsessive symptoms or substance abuse. Unfortunately, few studies assessed in the current analysis reported this information. Thus effects of these variables could not be investigated in the present meta-analysis.

A potential confounding factor in the context of our analysis is antidepressant medication. Multiple studies reported changes in brain structure (77) and function (82–84) following chronic antidepressant treatment. If such effects are present in neuroimaging-based classification experiments, the brain patterns identified might be associated with drug-effects rather than with effects specific to the pathology of depression. In our recent analysis in schizophrenia, we demonstrated that antipsychotic medication represents such potential bias (17). Because few studies in the present analysis reported treatment status, it was not possible to assess potential impact of this factor.

Future challenges for neuroimaging-based classification of depression

It is noteworthy that a substantial proportion of subjects included in the current meta-analysis (~25%) were not classified correctly. Multiple factors might drive misclassification using neuroimaging-based models. For example the pattern of brain changes associated with depression might have limited discriminative power. Alternatively, there might be one or more subgroups within individuals diagnosed with MDD that showed specific patterns of brain changes that are not shared by the majority of patients with depression. To explicitly test this hypothesis, a more detailed investigation of potential moderator variables on the basis of individual-subjects data is required. Moreover, future studies that focus on unsupervised classification methods would be better suited to identify such subgroups. This approach to classification might account for heterogeneity and improve diagnostic accuracy. Finally, the performance of neuroimaging-based diagnostic models is limited by the reliability of the diagnostic labels. For example, the recent investigation of the test-retest reliability of the diagnostic categories of the DSM V, indicated that MDD was diagnosed with limited accuracy (81). Similarly, MDD and bipolar disorder might frequently be confused (82). In effect,

misclassification in the initial psychiatric assessment might have contributed to reductions in classification performance.

An important consideration in the context of neuroimaging-based disease classification is the differentiation between diagnoses. Rather than distinguishing patients from HCs, a substantial part of clinical practice involves laborious and error-prone differential diagnostic processes to distinguish different patient groups from each other rather than from healthy controls. To date, few studies have investigated the potential of neuroimaging-based diagnostic models to differentiate among diagnostic groups. For example, Redlich et al. (19) studied two independent samples in which they were able to differentiate depressed from bipolar patients with 79.3% and 65.5% accuracy based on sMRI data, whereas Sacchet et al. report a lower classification accuracy of 59.5% (20). Similarly in our recent work we could demonstrate that patients with schizophrenia can be separated from depressed patients with 76% accuracy based on structural MRI data (18). However, Serpa et al. (21) report only 54% accuracy when differentiating psychotic bipolar patients from psychotic depressed patients, suggesting that these patient groups are harder to separate using brain-based features. In summary, differential-diagnostics represent an interesting potential application of neuroimaging-based models in clinical practice and a way to validate the current diagnostic categories in psychiatry.

Another important challenge for the application of neuroimaging-based diagnostics involves the generalizability of diagnostic models across different sites and populations. Redlich et al. (19) demonstrated that neuroimaging-based classifiers can be trained on data acquired at one site and then be applied to data from a different site. Similarly, Koutsouleris et al. (83) have also demonstrated the feasibility of such cross-site neuroimaging based classification for patients with schizophrenia. However, it needs to be noted that all studies included in the present meta-analysis were of small or modest sample size and that recent analyses suggest that larger samples are required for reliable estimates(84). A large-scale investigation of the generalizability of neuroimaging-based models (e.g. in the form of an “individual patient data meta-analysis” or “mega-analysis”) is still missing and the clinical and methodological factors that influence generalization are not clear.

We should note that while the present analyses support the hypothesis that multivariate methods are able to identify biological signatures of MDD in neuroimaging data, the current accuracy of around 75 % does not allow direct clinical application of these models. Moreover, neuroimaging-based diagnostic models must be evaluated critically with respect to cost efficiency. For example, self-rated screening questionnaires like the 9-item Patient Health

Questionnaire (PHQ9) provide an estimated sensitivity of 77% and a specificity of 85% in identifying MDD(85). Moreover, clinical questionnaires can be administered at substantially lower costs compared to neuroimaging investigations. Therefore, the main potential of neuroimaging-based diagnostic models might be to predict response to treatment interventions or to predict the course of the disorder. Generally subjects receiving pharmacological or psychotherapeutic interventions show large heterogeneity with respect to improvement or side-effects (86). Patel et al. (26) showed that response to treatment with a selective serotonin reuptake inhibitor (SSRI) could be predicted with up to 89% accuracy using neuroimaging. Relatedly, Fu et al. (59) used brain activation from a fMRI-Scan prior to treatment initiation to predict partial response to antidepressant treatment with 75% and full response with 62% accuracy. In another study, Siegle et al. (87) found that brain activation in response to negative words predicts response to cognitive-behavioural therapy with 75% and remission with 70% of accuracy. Using DTI data, Korgaonkar et al. (66) report the prediction of treatment response in major depression with 74% accuracy. Relatedly, Lythe et al. (88) report that neuroimaging-based models allow the prediction of recurrence risk of medication-free patients with MDD with 75 % accuracy. In summary, neuroimaging-based classification represents a promising approach for classification of subjects with depression. Moreover, this approach might be of benefit to other endeavors, such as the prediction of disease course or treatment outcome. Current limitations include the generalizability of the models across research centers and the identification of methodological and clinical variables that moderate classification success.

Acknowledgements

We would like to thank the authors of the included studies for providing additional information.

Funding and Disclosure

All authors report no biomedical financial interests or potential conflicts of interest.

JK is supported by funds from the Friedrich-Baur Stiftung as well as the Förderung Forschung und Lehre (881/856).

References

1. Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, *et al.* (2011): Cross-national epidemiology of DSM-IV major depressive episode. *BMC Med.* 9: 90.
2. Albert PR, Benkelfat C (2013): The neurobiology of depression--revisiting the serotonin hypothesis. II. Genetic, epigenetic and clinical studies. *Philos Trans R Soc Lond B Biol Sci.* 368: 20120535.
3. Sacher J, Neumann J, Fünfstück T, Soliman A, Villringer A, Schroeter ML (2012): Mapping the depressed brain: a meta-analysis of structural and functional alterations in major depressive disorder. *J Affect Disord.* 140: 142–148.
4. Sexton CE, Mackay CE, Ebmeier KP (2009): A systematic review of diffusion tensor imaging studies in affective disorders. *Biol Psychiatry.* 66: 814–823.
5. Schmaal L, Veltman DJ, van Erp TGM, Sämann PG, Frodl T, Jahanshad N, *et al.* (2016): Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. *Mol Psychiatry.* 21: 806–812.
6. Diener C, Kuehner C, Brusniak W, Ubl B, Wessa M, Flor H (2012): A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression. *NeuroImage.* 61: 677–685.
7. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA (2015): Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity. *JAMA Psychiatry.* . doi: 10.1001/jamapsychiatry.2015.0071.
8. Kühn S, Gallinat J (2011): Resting-State Brain Activity in Schizophrenia and Major Depression: A Quantitative Meta-Analysis. *Schizophr Bull.* . doi: 10.1093/schbul/sbr151.
9. Gryglewski G, Lanzenberger R, Kranz GS, Cumming P (2014): Meta-analysis of molecular imaging of serotonin transporters in major depression. *J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab.* 34: 1096–1103.
10. Kambeitz JP, Howes OD (2015): The serotonin transporter in depression: Meta-analysis of in vivo and post mortem findings and implications for understanding and treating depression. *J Affect Disord.* 186: 358–366.
11. Fried EI, Kievit RA (2016): The volumes of subcortical regions in depressed and healthy individuals are strikingly similar: a reinterpretation of the results by Schmaal *et al.* *Mol Psychiatry.* 21: 724–725.
12. Borgwardt S, Radua J, Mechelli A, Fusar-Poli P (2012): Why are psychiatric imaging methods clinically unreliable? Conclusions and practical guidelines for authors, editors and reviewers. *Behav Brain Funct BBF.* 8: 46.
13. Kapur S, Phillips AG, Insel TR (2012): Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Mol Psychiatry.* 17: 1174–1179.

14. Davatzikos C (2004): Why voxel-based morphometric analysis should be used with great caution when characterizing group differences. *NeuroImage*. 23: 17–20.
15. Klöppel S, Abdulkadir A, Jack CR Jr, Koutsouleris N, Mourão-Miranda J, Vemuri P (2012): Diagnostic neuroimaging across diseases. *NeuroImage*. 61: 457–463.
16. Wolfers T, Buitelaar JK, Beckmann CF, Franke B, Marquand AF (2015): From estimating activation locality to predicting disorder: A review of pattern recognition for neuroimaging-based psychiatric diagnostics. *Neurosci Biobehav Rev*. 57: 328–349.
17. Kambeitz J, Kambeitz-Illankovic L, Leucht S, Wood S, Davatzikos C, Malchow B, *et al.* (2015): Detecting Neuroimaging Biomarkers for Schizophrenia: A Meta-Analysis of Multivariate Pattern Recognition Studies. *Neuropsychopharmacology*. 40: 1742–1751.
18. Koutsouleris N, Meisenzahl EM, Borgwardt S, Riecher-Rössler A, Frodl T, Kambeitz J, *et al.* (2015): Individualized differential diagnosis of schizophrenia and mood disorders using neuroanatomical biomarkers. *Brain J Neurol*. . doi: 10.1093/brain/awv111.
19. Redlich R, Almeida JJR, Grotegerd D, Opel N, Kugel H, Heindel W, *et al.* (2014): Brain morphometric biomarkers distinguishing unipolar and bipolar depression: a voxel-based morphometry-pattern classification approach. *JAMA Psychiatry*. 71: 1222–1230.
20. Sacchet MD, Livermore EE, Iglesias JE, Glover GH, Gotlib IH (2015): Subcortical volumes differentiate Major Depressive Disorder, Bipolar Disorder, and remitted Major Depressive Disorder. *J Psychiatr Res*. 68: 91–98.
21. Serpa MH, Ou Y, Schaufelberger MS, Doshi J, Ferreira LK, Machado-Vieira R, *et al.* (2014): Neuroanatomical classification in a population-based sample of psychotic major depression and bipolar I disorder with 1 year of diagnostic stability. *BioMed Res Int*. 2014: 706157.
22. Kambeitz-Illankovic L, Meisenzahl EM, Cabral C, von Saldern S, Kambeitz J, Falkai P, *et al.* (2015): Prediction of outcome in the psychosis prodrome using neuroanatomical pattern classification. *Schizophr Res*. . doi: 10.1016/j.schres.2015.03.005.
23. Koutsouleris N, Meisenzahl EM, Davatzikos C, Bottlender R, Frodl T, Scheuerecker J, *et al.* (2009): Use of neuroanatomical pattern classification to identify subjects in at-risk mental states of psychosis and predict disease transition. *Arch Gen Psychiatry*. 66: 700–712.
24. Mourao-Miranda J, Reinders AATS, Rocha-Rego V, Lappin J, Rondina J, Morgan C, *et al.* (2012): Individualized prediction of illness course at the first psychotic episode: a support vector machine MRI study. *Psychol Med*. 42: 1037–1047.
25. Mwangi B, Ebmeier KP, Matthews K, Steele JD (2012): Multi-centre diagnostic classification of individual structural neuroimaging scans from patients with major depressive disorder. *Brain J Neurol*. 135: 1508–1521.
26. Patel MJ, Andreescu C, Price JC, Edelman KL, Reynolds CF, Aizenstein HJ (2015): Machine learning approaches for integrating clinical and imaging features in late-life depression classification and response prediction. *Int J Geriatr Psychiatry*. . doi: 10.1002/gps.4262.

27. Wu M-J, Wu HE, Mwangi B, Sanches M, Selvaraj S, Zunta-Soares GB, Soares JC (2015): Prediction of pediatric unipolar depression using multiple neuromorphometric measurements: A pattern classification approach. *J Psychiatr Res.* 62: 84–91.
28. Cao L, Guo S, Xue Z, Hu Y, Liu H, Mwansisya TE, *et al.* (2014): Aberrant functional connectivity for diagnosis of major depressive disorder: A discriminant analysis. *Psychiatry Clin Neurosci.* 68: 110–119.
29. Craddock RC, Holtzheimer PE, Hu XP, Mayberg HS (2009): Disease state prediction from resting state functional connectivity. *Magn Reson Med Off J Soc Magn Reson Med Soc Magn Reson Med.* 62: 1619–1628.
30. Guo H, Cheng C, Cao X, Xiang J, Chen J, Zhang K (2014): Resting-state functional connectivity abnormalities in first-onset unmedicated depression. *Neural Regen Res.* 9: 153–163.
31. Lord A, Horn D, Breakspear M, Walter M (2012): Changes in community structure of resting state functional connectivity in unipolar depression. *PLoS One.* 7: e41282.
32. Ma Q, Zeng L-L, Shen H, Liu L, Hu D (2013): Altered cerebellar-cerebral resting-state functional connectivity reliably identifies major depressive disorder. *Brain Res.* 1495: 86–94.
33. Wei M, Qin J, Yan R, Li H, Yao Z, Lu Q (2013): Identifying major depressive disorder using Hurst exponent of resting-state brain networks. *Psychiatry Res.* 214: 306–312.
34. Zeng L-L, Shen H, Liu L, Wang L, Li B, Fang P, *et al.* (2012): Identifying major depression using whole-brain functional connectivity: a multivariate pattern analysis. *Brain J Neurol.* 135: 1498–1507.
35. Habes I, Krall SC, Johnston SJ, Yuen KSL, Healy D, Goebel R, *et al.* (2013): Pattern classification of valence in depression. *NeuroImage Clin.* 2: 675–683.
36. Hahn T, Marquand AF, Ehliis A-C, Dresler T, Kittel-Schneider S, Jarczok TA, *et al.* (2011): Integrating neurobiological markers of depression. *Arch Gen Psychiatry.* 68: 361–368.
37. Marquand AF, Mourão-Miranda J, Brammer MJ, Cleare AJ, Fu CHY (2008): Neuroanatomy of verbal working memory as a diagnostic biomarker for depression. *Neuroreport.* 19: 1507–1511.
38. Nouretdinov I, Costafreda SG, Gammerman A, Chervonenkis A, Vovk V, Vapnik V, Fu CHY (2011): Machine learning classification with confidence: application of transductive conformal predictors to MRI-based diagnostic and prognostic markers in depression. *NeuroImage.* 56: 809–813.
39. Rosa MJ, Portugal L, Hahn T, Fallgatter AJ, Garrido MI, Shawe-Taylor J, Mourao-Miranda J (2015): Sparse network-based models for patient classification using fMRI. *Neuroimage.* 105: 493–506.
40. Moher D, Liberati A, Tetzlaff J, Altman DG (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 339. doi: 10.1136/bmj.b2535.

41. Hamilton M (1960): A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 23: 56–62.
42. Beck AT, Steer RA, Ball R, Ranieri W (1996): Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *J Pers Assess*. 67: 588–597.
43. Reitsma JB, Glas AS, Rutjes AWS, Scholten RJPM, Bossuyt PM, Zwinderman AH (2005): Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol*. 58: 982–990.
44. Deeks JJ, Macaskill P, Irwig L (2005): The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol*. 58: 882–893.
45. R Core Team (2013): *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing. Retrieved from <http://www.R-project.org/>.
46. Doebler P (2012): Meta-Analysis of Diagnostic Accuracy with mada. . Retrieved May 18, 2013, from <http://cran.gis-lab.info/web/packages/mada/vignettes/mada.pdf>.
47. Friedman J, Hastie T, Tibshirani R (2010): Regularization Paths for Generalized Linear Models via Coordinate Descent. *J Stat Softw*. 33: 1–22.
48. Gong Q, Wu Q, Scarpazza C, Lui S, Jia Z, Marquand A, *et al.* (2011): Prognostic prediction of therapeutic response in depression using high-field MR imaging. *NeuroImage*. 55: 1497–1503.
49. Liu F, Guo W, Yu D, Gao Q, Gao K, Xue Z, *et al.* (2012): Classification of different therapeutic responses of major depressive disorder with multivariate pattern analysis method based on structural MR scans. *PLoS One*. 7: e40968.
50. Kipli K, Kouzani AZ (2014): Degree of contribution (DoC) feature selection algorithm for structural brain MRI volumetric features in depression detection. *Int J Comput Assist Radiol Surg*. . doi: 10.1007/s11548-014-1130-9.
51. Rondina JM, Hahn T, de Oliveira L, Marquand AF, Dresler T, Leitner T, *et al.* (2014): SCORS-A Method Based on Stability for Feature Selection and Mapping in Neuroimaging. *IEEE Trans Med Imaging*. 33: 85–98.
52. Johnston BA, Steele JD, Tolomeo S, Christmas D, Matthews K (2015): Structural MRI-Based Predictions in Patients with Treatment-Refractory Depression (TRD). *PLoS One*. 10: e0132958.
53. Wade BSC, Joshi SH, Pirnia T, Leaver AM, Woods RP, Thompson PM, *et al.* (2015): Random Forest Classification of Depression Status Based On Subcortical Brain Morphometry Following Electroconvulsive Therapy. *Proc IEEE Int Symp Biomed Imaging Nano Macro IEEE Int Symp Biomed Imaging*. 2015: 92–96.
54. Jie N-F, Zhu M-H, Ma X-Y, Osuch EA, Wammes M, Théberge J, *et al.* (2015): Discriminating Bipolar Disorder From Major Depression Based on SVM-FoBa: Efficient Feature Selection With Multimodal Brain Imaging Data. *IEEE Trans Auton Ment Dev*. 7: 320–331.

55. Guo H, Cao X, Liu Z, Li H, Chen J, Zhang K (2012): Machine learning classifier using abnormal brain network topological metrics in major depressive disorder. *Neuroreport*. 23: 1006–1011.
56. Guo S, Yu Y, Zhang J, Feng J (2013): A reversal coarse-grained analysis with application to an altered functional circuit in depression. *Brain Behav*. 3: 637–648.
57. Lois G, Wessa M (2016): Differential association of default mode network connectivity and rumination in healthy individuals and remitted MDD patients. *Soc Cogn Affect Neurosci*. . doi: 10.1093/scan/nsw085.
58. Qin J, Shen H, Zeng L-L, Jiang W, Liu L, Hu D (2015): Predicting clinical responses in major depression using intrinsic functional connectivity. *Neuroreport*. 26: 675–680.
59. Fu CHY, Mourao-Miranda J, Costafreda SG, Khanna A, Marquand AF, Williams SCR, Brammer MJ (2008): Pattern classification of sad facial processing: toward the development of neurobiological markers in depression. *Biol Psychiatry*. 63: 656–662.
60. Zhang X, Yaseen ZS, Galynker II, Hirsch J, Winston A (2011): Can depression be diagnosed by response to mother's face? A personalized attachment-based paradigm for diagnostic fMRI. *PLoS One*. 6: e27253.
61. Yang W, Chen Q, Liu P, Cheng H, Cui Q, Wei D, *et al.* (2016): Abnormal brain activation during directed forgetting of negative memory in depressed patients. *J Affect Disord*. 190: 880–888.
62. Sato JR, Moll J, Green S, Deakin JFW, Thomaz CE, Zahn R (2015): Machine learning algorithm accurately detects fMRI signature of vulnerability to major depression. *Psychiatry Res*. 233: 289–291.
63. Shimizu Y, Yoshimoto J, Toki S, Takamura M, Yoshimura S, Okamoto Y, *et al.* (2015): Toward Probabilistic Diagnosis and Understanding of Depression Based on Functional MRI Data Analysis with Logistic Group LASSO. *PLoS ONE*. 10. doi: 10.1371/journal.pone.0123524.
64. Qin J, Wei M, Liu H, Chen J, Yan R, Yao Z, Lu Q (2015): 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*. 180: 129–137.
65. Fang P, Zeng L-L, Shen H, Wang L, Li B, Liu L, Hu D (2012): Increased cortical-limbic anatomical network connectivity in major depression revealed by diffusion tensor imaging. *PLoS One*. 7: e45972.
66. Korgaonkar MS, Williams LM, Song YJ, Usherwood T, Grieve SM (2014): Diffusion tensor imaging predictors of treatment outcomes in major depressive disorder. *Br J Psychiatry J Ment Sci*. 205: 321–328.
67. Sacchet MD, Prasad G, Foland-Ross LC, Thompson PM, Gotlib IH (2015): Support vector machine classification of major depressive disorder using diffusion-weighted neuroimaging and graph theory. *Front Psychiatry*. 6: 21.
68. Nugent AC, Neumeister A, Goldman D, Herscovitch P, Charney DS, Drevets WC (2008): Serotonin transporter genotype and depressive phenotype determination by

discriminant analysis of glucose metabolism under acute tryptophan depletion. *NeuroImage*. 43: 764–774.

69. Van Dijk KRA, Sabuncu MR, Buckner RL (2012): The influence of head motion on intrinsic functional connectivity MRI. *NeuroImage*. 59: 431–438.

70. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE (2012): Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*. 59: 2142–2154.

71. Satterthwaite TD, Wolf DH, Loughhead J, Ruparel K, Elliott MA, Hakonarson H, *et al.* (2012): Impact of in-scanner head motion on multiple measures of functional connectivity: relevance for studies of neurodevelopment in youth. *NeuroImage*. 60: 623–632.

72. Cao H, Plichta MM, Schäfer A, Haddad L, Grimm O, Schneider M, *et al.* (2014): Test-retest reliability of fMRI-based graph theoretical properties during working memory, emotion processing, and resting state. *NeuroImage*. 84: 888–900.

73. Eaton WW, Anthony JC, Gallo J, Cai G, Tien A, Romanoski A, *et al.* (1997): Natural history of Diagnostic Interview Schedule/DSM-IV major depression. The Baltimore Epidemiologic Catchment Area follow-up. *Arch Gen Psychiatry*. 54: 993–999.

74. Cabral C, Kambeitz-Ilankovic L, Kambeitz J, Calhoun VD, Dwyer DB, von Saldern S, *et al.* (2016): Classifying Schizophrenia Using Multimodal Multivariate Pattern Recognition Analysis: Evaluating the Impact of Individual Clinical Profiles on the Neurodiagnostic Performance. *Schizophr Bull*. 42 Suppl 1: S110-117.

75. Sui J, Castro E, He H, Bridwell D, Du Y, Pearlson GD, *et al.* (2014): Combination of FMRI-SMRI-EEG data improves discrimination of schizophrenia patients by ensemble feature selection. *Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf*. 2014: 3889–3892.

76. Mwangi B, Matthews K, Steele JD (2012): Prediction of illness severity in patients with major depression using structural MR brain scans. *J Magn Reson Imaging JMRI*. 35: 64–71.

77. Jung J, Kang J, Won E, Nam K, Lee M-S, Tae WS, Ham B-J (2014): Impact of lingual gyrus volume on antidepressant response and neurocognitive functions in Major Depressive Disorder: a voxel-based morphometry study. *J Affect Disord*. 169: 179–187.

78. Abler B, Grön G, Hartmann A, Metzger C, Walter M (2012): Modulation of frontostriatal interaction aligns with reduced primary reward processing under serotonergic drugs. *J Neurosci Off J Soc Neurosci*. 32: 1329–1335.

79. Metzger CD, Wieggers M, Walter M, Abler B, Graf H (2015): Local and Global Resting State Activity in the Noradrenergic and Dopaminergic Pathway Modulated by Reboxetine and Amisulpride in Healthy Subjects. *Int J Neuropsychopharmacol Off Sci J Coll Int Neuropsychopharmacol CINP*. 19. doi: 10.1093/ijnp/pyv080.

80. Posner J, Hellerstein DJ, Gat I, Mechling A, Klahr K, Wang Z, *et al.* (2013): Antidepressants normalize the default mode network in patients with dysthymia. *JAMA Psychiatry*. 70: 373–382.

81. Regier DA, Narrow WE, Clarke DE, Kraemer HC, Kuramoto SJ, Kuhl EA, Kupfer DJ (2013): DSM-5 Field Trials in the United States and Canada, Part II: Test-Retest Reliability of Selected Categorical Diagnoses. *Am J Psychiatry*. 170: 59–70.
82. Oiesvold T, Nivison M, Hansen V, Skre I, Ostensen L, Sørgaard KW (2013): Diagnosing comorbidity in psychiatric hospital: challenging the validity of administrative registers. *BMC Psychiatry*. 13: 13.
83. Koutsouleris N, Davatzikos C, Borgwardt S, Gaser C, Bottlender R, Frodl T, *et al.* (2014): Accelerated brain aging in schizophrenia and beyond: a neuroanatomical marker of psychiatric disorders. *Schizophr Bull*. 40: 1140–1153.
84. Schnack HG, Kahn RS (2016): Detecting Neuroimaging Biomarkers for Psychiatric Disorders: Sample Size Matters. *Front Psychiatry*. 7: 50.
85. Manea L, Gilbody S, McMillan D (2015): A diagnostic meta-analysis of the Patient Health Questionnaire-9 (PHQ-9) algorithm scoring method as a screen for depression. *Gen Hosp Psychiatry*. 37: 67–75.
86. Cipriani A, Purgato M, Furukawa TA, Trespidi C, Imperadore G, Signoretti A, *et al.* (2012): Citalopram versus other anti-depressive agents for depression. *Cochrane Database Syst Rev*. 7: CD006534.
87. Siegle GJ, Thompson WK, Collier A, Berman SR, Feldmiller J, Thase ME, Friedman ES (2012): Toward clinically useful neuroimaging in depression treatment: prognostic utility of subgenual cingulate activity for determining depression outcome in cognitive therapy across studies, scanners, and patient characteristics. *Arch Gen Psychiatry*. 69: 913–924.
88. Lythe KE, Moll J, Gethin JA, Workman CI, Green S, Lambon Ralph MA, *et al.* (2015): Self-blame-Selective Hyperconnectivity Between Anterior Temporal and Subgenual Cortices and Prediction of Recurrent Depressive Episodes. *JAMA Psychiatry*. 72: 1119–1126.

Figure/Table legends

Figure 1: Forest plot of sensitivities & specificities. Summary estimates for sensitivity are computed using the approach described by Reitsma et al. (2005).

Figure 2: SROC curve of the Reitsma model with the summary sensitivity and false positive rate indicated in black as well as color-coded the sensitivity and false positive rate of the individual studies of different imaging modalities.

Figure 3: Results from the moderator analysis: (A) effect of age, (B) differences in sensitivity and specificity between imaging modalities, and (C) clinical symptoms as measured by HAMD.

data	n of controls	n of patients	sensitivity	specificity	positive LR	negative LR	diagnostic OR
sMRI	482	450	69.85 (61.81 to 76.83)	71.13 (65.41 to 76.25)	2.44 (1.85 to 3.14)	0.428 (0.312 to 0.566)	5.93 (3.31 to 9.87)
fMRI	179	183	74.06 (67.17 to 79.94)	77.2 (69.92 to 83.15)	3.29 (2.41 to 4.45)	0.339 (0.256 to 0.436)	10.00 (5.77 to 16.2)
rsfMRI	237	243	85.39 (74.75 to 92.02)	82.59 (74.64 to 88.43)	5.03 (3.07 to 7.76)	0.186 (0.0925 to 0.326)	31.90 (9.79 to 78.2)
DTI	162	135	88.16 (74.18 to 95.07)	91.51 (77.32 to 97.15)	12.30 (3.42 to 32.8)	0.145 (0.0513 to 0.32)	133.00 (11.2 to 573)
all combined	1060	1011	76.66 (71.95 to 80.8)	77.76 (73.7 to 81.35)	3.47 (2.79 to 4.26)	0.302 (0.24 to 0.374)	11.70 (7.57 to 17.4)

Table 1: Results from bivariate meta-analyses applying the approach by Reitsma et al. (2005). Positive LR, negative LR and DOR are estimated via MCMC (Zwindermann & Bossuyt, 2008).

