Maximum Credibility Voting (MCV) An Integrative Approach for Accurate Diagnosis of Major Depressive Disorder from Clinically Readily Available Data

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Abstract-Diagnosis of Major Depressive Disorder (MDD) is currently a lengthy procedure, due to the low diagnostic accuracy of clinically readily available biomarkers. We integrate predictions from multiple datasets based on a credibility parameter defined on the probabilistic distributions of individual sparse prediction models. We demonstrate by means of structural and resting-state functional Magnetic Resonance Imaging and blood markers obtained from 62 treatment naive MDD patients (age 40.63±9.28, 36 female, HRSD 20.03±4.94) and 66 controls without mental disease history (age 35.52±12.91, 30 female), that our method called Maximum Credibility Voting (MCV) significantly increases diagnostic accuracy from about 65% average classification accuracy of individual biomarker models to 80% (accuracy after integration of the models). Classification results from different combinations of the available datasets validate the method's stability with respect to redundant or contradictory predictions. By definition, MCV is applicable to any desired data and compatible with missing values, ensuring continued improvement of diagnostic accuracy and patient comfort as new data acquisition methods and markers emerge.

I. INTRODUCTION

Due to a lack of profound knowledge of functional and physiological characteristics, the diagnosis of Major Depressive Disorder (MDD) is currently based on lengthy and tedious evaluations of behavioral symptoms [1]. The complexity in expression, as well as progression of these symptoms, further impede diagnostic procedures. However, reliable diagnosis and connection of the symptoms to physiology is a prerequisite for effective psychological and pharmacological interventions. Hence, with the number of MDD patients surging worldwide, identification of accurate and distinctive fingerprints of the disease is becoming increasingly urgent [2]. Advances in neuroimaging and data analysis techniques have triggered an intensive search for MDD-relevant biomarkers, continuously revealing statistically significant differences between depression patients and healthy controls [2] and encouraging diagnosis of MDD through machine learning algorithms [3]. Despite significant progress, however, accurate clinically translatable biomarkers for MDD are yet to be defined[4], [2], [5], one pervasive limitation being the heterogeneity inherent in MDD studies. As a result, individual biomarkers generally exhibit low specificity and sensitivity and are prone to confounding factors.

Integrative evaluation methods using multiple biomarkers have thus been suggested to improve prediction. Hahn et al. [6] trained Gaussian process (GP) classifiers of brain activity during three separate tasks involving emotional and reward processing and integrated their predictions using a decision tree algorithm. This method resulted in a classification accuracy of 83% (sensitivity, 80%; specificity, 87%), an improvement in accuracy of 11% compared with the single best of all GP classifiers, suggesting that several neurological pathways contribute to a more robust classification. A similar effect was demonstrated with multiplex protein assays, where over 90% prediction accuracy was achieved [7], [8] by mathematically integrating nine blood protein markers as well as physical measures into a single MDD score, again suggesting the consideration of multiple biological pathways as robust source of tissue-based MDD biomarkers with trait and state characteristics [2]. Considering the multiple facets of MDD symptoms and development, this seems a reasonable if not necessary approach. While both of the aforementioned studies are very promising, an obstacle for clinical application is that they are both highly specific with respect to the acquired biomarkers, as well as data evaluation.

We propose a novel, more flexible method, which allows for integration of any biomarker acquired by any modality. The idea is to simplify the process of deciding which of the available biomarkers delivers the most reliable diagnosis for a certain subject. In the studies described above, this is done by creating a decision tree and mathematical formula, respectively, both of which are tailored specifically for the available biomarkers. In a previous study [9] we reported that probabilistic classification algorithms can provide an estimation of the prediction reliability based on the overlap of the odds ratio distributions for target and control group. Here, we make this idea explicit and introduce a prediction credibility measure C(z), defined on these odds ratio distributions, which expresses the chance that a certain odds ratio predicts the correct diagnosis. Essentially, this measure can be seen as local prediction accuracy. This credibility measure can be estimated for any probabilistic model, enabling ranking of multiple predictions according to their diagnostic reliability. The most reliable prediction is considered diagnostically valid. Commonly, it is believed that the higher the absolute value of the odds ratio, the higher the chance of correct prediction. However, this is only true if the distributions are to a certain extent well separated and even then the problem of prediction reliability for small odds ratios, where the distributions overlap, still remains. We demonstrate that in contrast to other simple integration methods applied to the odds ratios (majority of votes, sum, maximum, and mean of odds ratio), our method called Maximum Credibility Voting (MCV), consistently improves prediction accuracy. It is further superior to common approaches such as support vector machine (SVM) and regression tree with respect to its formulation. It is formulated such that the addition of biomarkers remains optional and its application to data with missing values (i. e. measurements) is possible without modification of the algorithm. The only requirement is the estimation of the credibility measure for the model of the new data.

We demonstrate the aforementioned benefits of MCV for clinical MDD diagnosis by means of anatomical MRI data, resting state fMRI data, and the methylation rate at several CpG islands in the promotor region of the brain derived neurotrophic factor (BDNF) gene. We further demonstrate how the results of MCV can be used to stratify subjects based on which data yields the most reliable diagnosis and which MDD symptoms they exhibit. In contrast to task-based fMRI data acquisition, structural MRI and rsfMRI scans can be rapidly acquired and processed. Instructions are simple and prognostic procedures can be kept short and uncomplicated, making them suitable for a wide range of subjects (i. e. subjects with difficulties adhering to task paradigms). Further, identified discriminative brain regions can be directly related to their physiological cause, namely, substance loss or increase in brain tissue in the case of structural data and loss or increase of spontaneous neural activity in the case of rsfMRI. The same is true for the methylation rate, which inhibits gene transcription and in turn inhibits neurogenesis in cortex [10]. Unlike protein identification, determination of the methylation rate at several sites can be accomplished in a single measurement.

The only requirement for classification models of the data we wish to integrate is that they are of probabilistic nature. In this study, we chose Elastic Net and sparse logistic regression with a least absolute shrinkage and selection operator (LASSO). These models limit the number of effective variables by penalizing the sum of the absolute weights or the sum of squared weights and setting small weights to zero depending on a given threshold. As a result, they return a model based on features with the most discriminative relevance only (compare with SVM, which is inherently based on all input features, so that there is a risk of noise or nothing at all). In addition, we have previously shown that these algorithms can successfully handle a number of features that are several times larger than the number of training instances [9]. For this reason, we opted for whole brain analysis rather than targeted brain area analysis, with the intent to construct an unbiased classification model and to reveal new brain areas as MDD indicators. The same holds for the application of these algorithms to the methylation data.

II. MATERIALS AND METHODS

This study was approved by Research Ethics Committee of the Okinawa Institute of Science and Technology and the Research Ethics Committee of Hiroshima University (permission nr.172). All methods were performed in accordance with the relevant guidelines and regulations.

A. Subjects

Sixty-two MDD patients (age 40.63 ± 9.28 , 30 female), free of substance-related disorders other than alcohol and any co-morbidity were recruited by the Psychiatry Department of Hiroshima University. They were diagnosed by senior psychiatrists according to DSM-IV[1] criteria, interviews and information from medical records. Diagnosis was reconfirmed by experienced psychiatrists and psychologists at the time of participation in the study, using the Japanese version of the Mini-International Neuropsychiatric Interview (M.I.N.I [11]), which has been shown to have good to excellent interrater and test-retest reliability [12]. All patients had been treated less than 14 days at the time of participation in the study. Beck Depression Inventory (BDI) scores for this group ranged from 11 to 53 (average 30.52±9.08) and Patient Health Questionnaire (PHQ9) scores from 6 to 26 (average 17.71±4.5). About half of the patients had experienced a previous depression period. Age of depression onset was 38.22 ± 1.07 . The length of the episode at time of the study varied considerably (160.98±209.54 days). Depression severity was evaluated using the Hamilton Rating Scale for Depression (HRSD17 20.03±4.94). In addition the scores for following self-reported measures were recorded: Snaith-Hamilton Pleasure Scale (SHAPS), State Trait Anxiety Inventory (STAI), Child Abuse Trauma Scale (CATS), Life Event Scale (LES).

As control group, 66 persons (age 35.52 ± 12.91 , 36 female) free of mental or neurological disease history were recruited by advertisements in local newspapers. All healthy controls (HC) underwent the same self-assessments and examinations administered to the MDD group (except for MDD-specific HRSD). BDI scores were between 0 and 24 (average 6.74 ± 5.88) and PHQ9 ranged from 0 to 18 (average 3.36 ± 3.76). 61 MDD subjects (out of 62) had values ≥ 14 (standard cutoff for MDD at Hiroshima University), while 57 controls (out of 66) had scores under 14. For PHQ9 scores with a cutoff value of 10, 60 patients had scores ≥ 10 and 61 controls under 10. Subjects of both groups completed the Japanese version of the National Adult Reading Test [13] for an estimate of their IQ (108.37 \pm 9.81 for the MDD group and 113.32 \pm 8.03 for controls, Table I).

Two-sample t-test was used for continuous variables, χ square test for binary variables. For estimation of the classification models, sex and age matched subsets of these subjects were used (see appendix for comparative evaluation of the demographic and clinical characteristics of these subsets). Nomenclature: BDI II = Beck's Depression Inventory II, PHQ9 = 9 Question Patient Health Questionnaire, SHAPS = Snaith-Hamilton Pleasure Scale, STAI = State Trait Anxiety Inventory, CATS = Child Abuse and Trauma Scale, LES = Life Event Stress, HRSD17 = 17 Question Hamilton Rating Scale of Depression

Written informed consent was obtained from all participants (approved by the Research Ethics Committee of the Okinawa Institute of Science and Technology and the Research Ethics Committee of Hiroshima University).

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF ALL SUBJECTS INCLUDED IN TH	HI
STUDY.	

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	MDD	Control	p-value
Number of subjects	62	66	-
Sex (male/female)	32/30	30/36	0.49
Age (years)	40.63 ± 9.28	35.52 ± 12.91	0.04* ^a
IQ	108.37 ± 9.81	113.32 ± 8.03	0.6
Alcohol dependent subjects	5	0	0.02*
BDI II ^b	30.52 ± 9.08	6.74 ± 5.88	2.03e-09***
PHQ 9	17.71 ± 4.50	3.36 ± 3.76	9e-14***
SHAPS	37.26 ± 5.46	23.62 ± 6.13	2.34e-09***
STAI	56.48 ± 7.76	40.5 ± 8.82	1.45e-05***
CATS	34.75 ± 23.20	24.89 ± 14.30	0.56
LES	-6.57 ± 6.39	-0.71 ± 3.90	0.006**
HRSD	20.03 ± 4.94	-	-
Age of Depression Onset (years)	38.22 ± 1.07	-	-
Number of Previous Episodes	0.61 ± 0.94	-	-
Length of Current Episode (days)	160.98 ± 209.54	-	-
Lexapro single agent	52	-	-
Lexapro combination	2	-	-
Other single agent	2	-	-
No Treatment	6	-	-

^a Asterisks denote significant differences: *p<0.05, **p<0.01,***p<0.001.

^b Nomenclature: BDI II = Beck's Depression Inventory II, PHQ9 = 9 Question Patient Health Questionnaire, SHAPS = Snaith-Hamilton Pleasure Scale, STAI = State Trait Anxiety Inventory, CATS = Child Abuse and Trauma Scale, LES = Life Event Stress, HRSD17 = 17 Question Hamilton Rating Scale of Depression

B. Data

Anatomical and resting state functional MRI data were collected from all participants. Blood samples could only be obtained for a subgroup.

MRI Data: Anatomical T1 images were acquired on a 3T GE Signa HDx scanner (IRP FSPGR, TR = 6.32 ms, FA=20, voxel size 1x1x1mm, matrix size 256 x 256 x 180) and processed using VBM8 (Christian Gaser, University of Jena, Department of Psychiatry), yielding voxel wise white matter (WM) and gray matter (GM) density maps.

For acquisition of resting state functional MRI (rsfMRI) data, subjects were asked to close their eyes and relax. Images were obtained over 5 min, resulting in 145 images (2D EP/GR, TR=2000ms, no gaps, interleaved, matrix size 64 x 64 x 32, voxel size 4x4x4mm). Debriefing routinely conducted after the scans revealed that two subjects had fallen asleep during the measurement. Their data were thus excluded from analysis. Measurements during which patients had moved more than 3mm or 3 degrees translationally or rotationally, respectively, were also excluded (exclusion of the whole time series). The difference in motion between MDD and HC subjects of which

data was used to estimate classification models was not significant (p=0.68, average framewise displacement for controls 0.08 ± 0.10 mm and 0.07 ± 0.05 mm for MDD subjects, see Appendix).

Images were realigned, normalized and smoothed (FWHM = 8mm) using SPM8 (Wellcome Trust Centre for Neuroimaging, UCL, London). Motion was regressed out using the standard six-head motion parameters. Time series were band pass filtered (0.009-0.1Hz) and detrended using the Resting-State fMRI Data Analysis Toolkit (REST [14]). Using the band pass filtered rsfMRI measurements, functional connectivity between regions of interest (ROIs) was evaluated as correlation coefficients between the average time series of BOLD fMRI signals of ROIs. The ROIs consist of 90 brain regions across 14 intrinsic connectivity networks that were derived by means of Independent Component Analysis [15]. These networks comprise (number of ROIs in parentheses): Anterior Salience (7), Auditory (3), Basal Ganglia (5), Dorsal Default Mode (9), Language (7), Left Executive Control (6), Precuneus (4), Posterior Salience (12), Right Executive Control (6), Ventral Default Mode (10), Visuospatial (11), Primary Visual (2), Higher Visual (2), and Sensorimotor (6) network. Nifti templates of the ROIs are publicly available [16]. We discarded correlations if the probability that there is an actual relationship between the time series, was small (p¿0.01) for all healthy subjects. This ensures that connections passed to the classification algorithms are functionally meaningful in terms of synchronization. The threshold of 0.01 was used in order to retain connections for which there is substantial evidence against the null hypothesis (i. e. that the found correlation is coincidence), while leaving a margin for weaker correlations that might be of importance to establish group differences. This resulted in 108 connections.

While functional connectivity identifies spatial patterns of synchronous low-frequency oscillations on a network level, it does not reveal information on localized dysfunctions of specific brain regions, which ultimately contribute to network abnormalities. Such local brain activity can be assessed by evaluating low-frequency oscillations themselves. We have done this by calculating the Amplitude of Low frequency fluctuation (ALFF), which accounts for the summed amplitude in the low frequency range (0.009-0.1Hz), and Regional Homogeneity (ReHo), which accounts for signal homogeneity between neighbouring voxels. We also assessed fractional ALFF (fALFF), which evaluates the ratio of a low frequency amplitude (0.009-0.1Hz) with respect to the amplitude of the whole frequency spectrum. As a results we have an absolute measure of low frequency fluctuations (ALFF) and a relative measure (fALFF). While fALFF is robuster to physiological noise, ALFF shows higher test-retest reliability in gray matter regions and thus more sensitive for differences between groups [17]. However, we decided to evaluate both measures due to their different characteristics. All three local parameters were assessed using REST[14].

Bloodmarkers: Genomic DNA was extracted from the acquired blood samples and the methylation rate at 32 CpG islands at promoters of the BDNF exon1 gene was assessed using a MassArrayH system (SEQUENOM). The majority of these sites have previously been shown to be related to depression [18] (see appendix for details).

For each acquired diagnostic feature, data were age- and sexmatched with respect to patient and control group. The number of subjects in each group was matched in order to avoid sample size bias during model estimation. This resulted in 60 subjects per group for the anatomical data, 42 subjects for per group for the resting state data and 33 subjects per group for the BDNF methylation data (See Appendix for demographic and clinical comparison of the groups used for each feature).

Data Availability Statement: Due to potentially identifying information, data for this study are restricted by the Ethical Committee for Epidemiology of Hiroshima University, Japan. Interested, qualified researchers may request the data by contacting Dr. Shoji Karatsu (kasumikenkyu@office.hiroshimau.ac.jp)

C. Classification

Datawise Classification: The sole requirement for Maximum Credibility Voting is for the applied models to be probabilistic, i. e. the models provide odds ratio distributions for control and target (i. e. MDD patient) group. As previously mentioned, we chose algorithms that are effective in handling a large number of features relative to the number of subjects [9]. In this way, we can make use of all information in the datasets and achieve classification without bias introduced by prior assumptions.

We applied Elastic net and logistic regression with Least Absolute Shrinkage and Selection Operator (sLASSO) regularization to the brain area-wise mean of WM, GM, rsfMRI ALFF and ReHo maps. We also applied both methods to FC and BDNF methylation. The whole volume data of WM, GM, ALFF and ReHo were also subjected to group LASSO (gLASSO) regression, where the sum of weights for voxels located in the same brain area (defined in the anatomical labeling atlas AAL [19]) is constrained, resulting in brain areawise reduction of discriminative voxels [9]. These sparse algorithms return only features with the greatest diagnostic relevance, clearly identifying MDD correlates.

Validity of models and their regularization parameters were assessed using 10-fold nested cross-validation, repeated 10 times, each time shuffling training and test data.

Model evaluation was based on standard parameter accuracy (percentage of correctly diagnosed subjects), specificity (the percentage of healthy controls, correctly identified as such) and sensitivity (percentage of patients correctly identified as such).

Integrated Classification - Maximum Credibility Voting (MCV): Probabilistic classifiers yield negative and positive log odds ratios $z = \ln(p/(1-p))$, where p is the predictive probability that the subject belongs to the target group (here, the MDD group). These log odds ratios (usually) assume different distributions for control and target groups. The overlap of these two distributions gives information on the reliability of a prediction with a certain odds ratio. We fit the normalized log odds ratio distributions for HCs and patients in the training data using the Weibull distribution function (Fig. 1):

$$W_{\lambda k}(z) = \frac{k}{\lambda} \left(\frac{z+1}{\lambda}\right)^{k-1} e^{-\left(\frac{z+1}{\lambda}\right)^k},\tag{1}$$

z > 0, where k > 0 allows for a skewed shape of the distribution and $\lambda > 0$ determines the width of the distribution. These parameters were fitted using maximum likelihood estimation. Since the Weibull function exists strictly only for positive values, log odds ratios were shifted by 1 before fitting and were shifted back thereafter.

In the following, we denote the Weibull distribution fitted for log odds ratios of HCs and MDD patients as W_{-} and W_{+} , respectively. The values of W_{-} and W_{+} at a certain log odds ratio allow estimation of how many false positive or negatives in comparison to true positives or negatives we can expect. In other words, they give an estimate on how high the chance is for a prediction with a specific log odds ratio to be correct. We define the credibility function C as:

$$C(z) = \begin{cases} W_{-}/(W_{-} + W_{+}) \text{ for } z < 0\\ W_{+}/(W_{-} + W_{+}) \text{ for } z > 0, \end{cases}$$
(2)

the ratio of true (negative or positive) predictions within all (negative or positive) predicted outcomes (Fig. 1). For the sake of completion, we define the C(z) = C(1) for z > 1 and C(z) = C(-1) for z < -1 (i.e. predictions with log odds ratios outside the normalised range are assigned the respective credibility at the far ends of the distributions).

We use this credibility measure to estimate diagnosis reliability for predictions obtained from each dataset. The prediction with the highest credibility is chosen as the final diagnosis. We refer to this method as *Maximum Credibility Voting (MCV)*:

$$MCV(z_1, ..., z_N) = I(z_j > 0), \text{ with } j = \operatorname*{argmax}_{i=1:N} C(z_i),$$
 (3)



Fig. 1. The credibility C(z) (Eq. 2) of each log odds ratio is defined through the ratio of the Weibull distributions fitted to the log odds ratio distributions of healthy controls (W_+) and MDD patients (W_-) , respectively (Eq. 1). It reflects the portion of true predictions among all predictions with certain odds ratio. Here, the low credibility of small negative odd ratios compared to the high credibility for large positive log odds ratios, is a result of false negatives toward the end of the spectrum.

 z_i the normalized log odds ratios obtained from N models yielded by different data obtained from the same subject and z_j the odds ratio with the highest credibility value $(C(z_i)$ the credibility function as defined in Eq. 2). For $MCV(z_1, ..., z_N) = 1$, the subject's diagnosis is MDD and for $MCV(z_1, ..., z_N) = 0$ healthy. Intuitively, this procedure is straight forward. Out of several predictions, we pick the one we can trust the most (Fig. 2). We remark that MCV itself does not require training data per se, but is a method that can be applied as is. However, the more training data are available for each of the underlying classification models, the more accurate their credibility functions (due to the increased number of data points (i.e. odds ratios) outlining the probability distributions, Fig. 2, left column), resulting in MCV being more effective in its prediction improvement.

We validated MCV using 10-fold cross validation, where prediction credibility functions for each model were estimated based on the log odds ratio distributions obtained in each cross validation of the training data. In this way, test and training data are kept independent throughout the model estimation procedure, as well as in the following MCV procedure.

We compared MCV to other model integration methods, where the number of negative or positive predictions (most votes), sum, maximum and mean of log odds ratio, respectively, determine diagnosis. Further, comparisons to the performance of support vector machine (SVM) and classification tree are made. As opposed to the arithmetic approaches, SVM and classification tree cannot be applied to data with missing values.

III. RESULTS

A. Diagnostic Accuracy for Each Diagnostic Feature

For clarity, we only consider one model per data modality and restrict the MCV results to the models that achieved the highest classification accuracy in each data modality. Models with accuracy lower than 60% are disregarded. Further, only features selected in more than 80% of all cross validated models are presented and considered of diagnostic relevance. A performance summary for all models and their diagnostic features can be found in the appendix.

Anatomical MRI: For the white matter and gray matter density volumes, only white matter classification using group LASSO yielded an accuracy over 60% ($63\pm2\%$ accuracy, $58\pm3\%$ specificity, $68\pm4\%$ sensitivity). Left and right post central cortex, left frontal superior cortex and right middle temporal cortex were assigned negative



Fig. 2. Maximum Credibility Voting (MCV): Diagnosis is based on the log odds ratios z_i of multiple classification models derived from different types of data (here, WM, ALFF, ReHo, FC and BDNF related data) and determined by the prediction (odds ratio) z_j with the highest credibility value $C_j(z_j)$ (Eq. 2). The credibility functions C_j are derived from the odds ratio distributions of the respective classification models. In the depicted case, WM decides with nearly 80% credibility, that the subject is a healthy control.

weights, indicating that these areas are denser in white matter in healthy controls than in depression patients. Left middle temporal cortex was assigned positive weight.

Resting State fMRI: Mean brain area ALFF subjected to Elastic Net, showed the best classification among the resting state data with an accuracy of $68\pm1\%$ (specificity $67\pm2\%$, sensitivity $69\pm1\%$). Left and right posterior cingulate cortex (PCC) and left thalamus thereby showed negative weights indicating that the amplitude in these areas is lower in MDD patients than healthy controls.

L1 and Elastic Net applied to the mean ReHo values in brain areas showed similar performance of 66% accuracy, 65% specificity and 67% sensitivity, but with slightly smaller variance for the model estimated with Elastic Net. Both models assigned negative weights to left PCC, medial orbitofrontal cortex (OFC). Elastic Net also showed negative weight for the left amygdala. Positive weight was assigned to the left cerebellum pars8 in both models and additionally to the right cerebellum pars 8 in the Elastic Net.

For the FC data L1 LASSO yielded the best classification with $65\pm4\%$ accuracy, $65\pm5\%$ specificity and $66\pm6\%$ sensitivity. Two connections with negative weights were selected as diagnostic: the connection between right parahippocampus and right retrosplenial cortex including a part of the posterior cingulate (network 13, areas 08 and 05) and the connection between PCC/Precuneus and medial prefrontal/anterior cingulate/orbitofrontal area (network 3, areas 04 and 01). While the first connection is part of the ventral default mode network (DMN), the other is part of the dorsal DMN.

BDNF Exon1 Methylation: Elastic Net yielded $78\pm3\%$ accuracy ($84\pm5\%$ specificity, $73\pm2\%$ sensitivity) and assigned negative weights to 12 (out of 32) sites, positive weights to 11 sites. CpG1, CpG18, CpG24, CpG52, CpG61, CpG63, CpG77 with negative weights were in agreement with the results given in Fuchikami et al., 2011[18]. The contributing islands, CpG19.20.21, CpG28, CpG32 showed reversed relation to the results in that study; however, the difference in CpG28, Cpg32 methylation between the two investigated subject groups was not significant. CpG25.26.27, CpG29.30.31 methylation, both without significant group differences and CpG33.34

methylation with significant group difference were not measured in Fuchikami et al., 2011. Indication of a role in MDD diagnosis opposite to the one found in their study was also true for CpG5, CpG15, CpG36, CpG37, CpG48 and CpG78, which were assigned positive weights in our model, but were more highly methylated in healthy controls than in MDD subjects in their study. In our study, methylation differences in these sites exist, but were not significant. CpG8.9, CpG14 also countered the relation given in their study, but in both their and our study, group differences were not significant. CpG17, CpG50.51, CpG74.75, CpG22 agreed with Fuchikami et al., 2011, but here again, significant group differences could not be found.

To summarize, none of the methylation sites that were assigned positive weights showed significant group differences. All sites with significant methylation differences between healthy and MDD subjects were negatively weighted and selected in over 98% of all crossvalidated models. Hence, the contribution of these sites with positive weights to the diagnostic power lie in the combination with the other selected methylation sites. Mean methylation rates were generally lower in our study than in Fuchikami et al., 2011, which may be attributed to the greater number of subjects (HC/MDD = 33/33 to 18/20).

B. Maximum Credibility Voting (MCV)

For demonstration of MCV, we chose the highest performing model for each diagnostic data: the group LASSO model for white matter, the Elastic Net model applied to mean brain areas values of ALFF and ReHo, L1 for FC and the Elastic Net model for the BDNF methylation data.

To evaluate MCV for different data combinations, appropriate subsets of the available data were used. Differences between results were considered significant at p<0.05. We also give the F-scores in order to account for the imbalances in cohort sizes in the test data.

All individual models were evaluated repeating ten 10-fold nested cross validations, each time shuffling the subjects. As a result, we obtain ten odds ratios for each subject and dataset available for the subject. Equally, we have ten different odds ratio distributions for controls and MDD subjects, in which the test subjects are not included. We use these to construct the credibility functions and evaluate MCV prediction accuracy.

MCV(All), Application to Dataset with no Missing Data: Within all subjects, structural MRI, resting state MRI and methylation data were available for 23 healthy controls (age 41.22 ± 11.94 , 7 female) and 20 MDD patients (age 35.1 ± 6.03 , 10 female). For these subjects, the average BDI2 and PHQ9 scores were 8.78 ± 7.00 and 4.30 ± 4.07 for the HC group and 29.60 ± 10.7 and 18.70 ± 4.53 for the MDD group. Detailed demographic and clinical characteristics are given in Table II. Figure 3 shows the data sets acquired for each subject.

The average accuracy when diagnosing this group of subjects based on each biological data modality alone was $66.22\pm6.53\%$. Application of MCV significantly improved accuracy to $80\pm3\%$ (F-score $77\pm4\%$), with a specificity of $87\pm3\%$ and sensitivity of $73\pm7\%$. This is an average increase in accuracy of 14% compared to the accuracies delivered by each individual data model alone (Table III, MCV(WM, rsfMRI, BDNFexon1)).

Note that MCV performance relies solely on the accuracy of the credibility functions, which are constructed based on training data provided for the different classification models, i. e., the number of subjects to which MCV is applied does not influence MCV performance. For the same reason, overfitting is not applicable.

Comparing MCV results with those of SVM, Decision Tree, maximum number of votes, sum, mean and maximum absolute value of the odds ratios, we find significant superiority of MCV over all other approaches (p<0.001 for all comparisons, Table III, Fig. 4(b)). For voting arithmetic methods (Most Votes, Sum, Mean and Maximum Absolute Value of the odds ratios), specificity was



Fig. 3. Available Data for Each Subject: structural MRI data (strMRI), resting state fMRI data (rsfMRI) and BDNFexon1 methylation data were evaluated for 60, 42 and 33 subjects, respectively, for each experimental group. For 23 controls and 20 MDD patients strMRI, rsfMRI and methylation data were available. For all the others, only one or two of the biomarkers could be acquired.

TABLE II DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF SUBJECTS FOR WHICH ALL DATA SETS WERE AVAILABLE.

5E1	SETS WERE AVAILABLE.					
	MDD	Control	p-value			
Number of subjects	20	23				
Sex (male/female)	10/10	16/7	0.20			
Age (years)	35.1 ± 6.03	41.22 ± 11.94	0.04^{*a}			
IQ	109.47 ± 9.45	111.00 ± 9.23	0.59			
Alcohol Dependent Subjects	0	0	1			
BDI II ^b	29.6 ± 10.70	8.78 ± 6.99	2.03e-09***			
PHQ 9	18.7 ± 4.53	4.30 ± 4.07	9.00e-14***			
SHAPS	36.65 ± 4.16	24.04 ± 6.31	2.34e-09***			
STAI	55.8 ± 6.04	43.35 ± 9.81	1.45e-05***			
CATS	35.25 ± 21.33	31.70 ± 18.71	0.56			
LES	-5.5 ± 7.08	-0.52 ± 3.93	0.006**			
HRSD17	19.5 ± 4.49	-	-			
Age of Depression Onset (years)	30.5 ± 7.17	-	-			
Number of Previous Episodes	0.75 ± 0.44	-	-			
Length of Current Episode (days)	118.65 ± 85.74	-	-			
Lexapro single agent	16	-	-			
Lexapro combination	0	-	-			
Other single agent	2	-	-			
No Treatment	2	-	-			

^a Asterisks denote significant differences: *p<0.05, **p<0.01,***p<0.001.

^b Nomenclature: BDĬ II = Beck's Depression Inventory II, PHQ9 = 9 Question Patient Health Questionnaire, SHAPS = Snaith-Hamilton Pleasure Scale, STAI = State Trait Anxiety Inventory, CATS = Child Abuse and Trauma Scale, LES = Life Event Stress, HRSD17 = 17 Question Hamilton Rating Scale of Depression

higher than that of MCV, but could not achieve comparable accuracy due to low sensitivity.

Adding the predictions from the different models to MCV one by one (Table IV) shows the stepwise increase in accuracy. Naturally, the accuracy significantly increases with addition of models that have higher accuracy to begin with. However, the importance lies in the fact that per construction, the accuracy should never significantly decrease when adding new predictions. We can see this in the decrease in accuracy when adding FC, which is not significant (p=0.81), but shows the same credibility as in the previous step. This confirms that MCV is robust to unreliable and redundant predictions, so that we always end up with a diagnosis about which we can be more

TABLE III MCV over all available diagnostic datasets outperforms single data classifiers as well as the integration methods SVM, Classification Tree, Most Votes, sum, max and mean of odds ratio. p-values are given with respect to MCV accuracy

	HC/MDD=23/20	Specificity	Sensitivity	Accuracy (F-score)	p-value
		-Feeling		, , , , , , , , , , , , , , , , , , , ,	P
	ALFF	60 ± 4	73±2	66±2 (62±4)	2.5e-10***
Single	ReHo	64 ± 4	67 ± 8	65±3 (66±1)	3.3e-09***
Feature	FC	67±8	61 ± 4	64±4 (64±5)	3.0e-08***
Classification	WM	53±6	69±7	60±3 (64±6)	1.1e-10***
	BDNFexon1	80 ± 5	68 ± 4	75±3 (71±3)	0.0017**
	SVM	79±6	64±11	72±4 (68±8)	8.5e-06***
	Classification Tree	65±9	61±11	63±8 (60±9)	2.1e-04***
Integrating	Most Votes	64 ± 4	81±7	73±4 (73±5)	6.5e-04***
Methods	Sum of odds ratio	65±3	82 ± 5	74±3 (74±3)	2.8e-04***
	Max of odds ratio	69±6	75 ± 6	72±2 (71±3)	9.1e-07***
	Mean of odds ratio	65±3	82 ± 5	73±3 (74±3)	9.9e-05***
	MCV	87+3	73+7	80+3 (77+4)	-



Fig. 4. MCV classification accuracy: MCV significantly outperforms single data models, but also the more intuitive integration methods SVM, Decision Tree, most votes, sum of odds, maximum of odds and mean of odds (see also Table III).

confident, even if the accuracy has not improved. We corroborate this fact by evaluating the results for different combinations of data, namely MCV(rsfMRI), MCV(rsfMRI, WM), MCV(WM, BDNF), see appendix.

TABLE IV Stepwise MCV for data without model of values: p-values are given in comparison to the accuracy in the previous step

HC/MDD = 23/20	Specificity	Sensitivity	Accuracy (F-score)	p-value	Credibility
WM	53±6	69±7	60±3 (62±4)	-	61±2
MCV(WM, ALFF)	60 ± 4	73±4	66±4 (66±3)	0.004^{***}	73±11
MCV(WM, ALFF, ReHo)	63±3	74±3	68±3 (68±3)	0.20	75±10
MCV(WM, ALFF, ReHo, FC)	62±3	74±3	67±3 (68±3)	0.85	75±10
MCV(WM, rsfMRI, BDNFexon1)	87±3	73±7	80±3 (77±4)	1.6e-08***	84±2

The number of true negative (TN) and true positive (TP) subjects in this dataset was 20 ± 1 and 15 ± 1 , respectively. In approximately 50% of the cases, their final diagnosis was determined by BDNF methylation ($53\pm7\%$ for TN and $49\pm11\%$ for TP subjects). ALFF was the second most frequent determining factor, comprising $27\pm4\%$ of true negatives. For the true positives, this proportion was with $47\pm14\%$ nearly as high as the BDNF proportion. WM was determining for $13\pm6\%$ of the true negatives, but only for $2\pm3\%$ for true positives. For neither group was FC the diagnostic factor.

Nineteen subjects were diagnosed as true negative and 15 as true positive in over half the cross validations. For controls in this group, the most frequent diagnostic dataset was BDNF methylation (10 subjects), followed by ALFF (5 subjects), WM (3 subjects) and finally ReHo (1 subject). Depression subjects in this group were exclusively diagnosed by BDNF methylation (8 subjects) and ALFF (7 subjects).

Missing Data Compatibility: MCV can also to be applied to data with missing values. The credibility for missing values is simply set 0; therefore, it does not interfere with the Voting process. For 47 healthy controls and 53 depression patients, at least two different, but not all measurements were available. MCV significantly outperformed all other odds ratio integration methods (here, most votes, sum, max and mean of odds ratio) with at least 7% higher correct rate (see appendix for details). SVM and classification tree are inherently incompatible with datasets that comprise missing values.

IV. DISCUSSION AND CONCLUSION

The results show that MCV allows easy integration of predictions from different datasets and significantly improves classification accuracy. The diagnostic accuracy of MCV when integrating over all data given in this study ($81.56\pm2.58\%$) is on average $15.33\pm6.53\%$ more higher than the classification accuracy yielded by the individual diagnostic datasets and $6.40\pm3.76\%$ higher than the other integration methods investigated (SVM, decision tree, maximum number as Votes, sum, maximum and mean odds ratio, Table III).

In detail, MDD diagnosis is significantly improved through application of MCV to the three characteristics, ALFF, ReHO and FC obtained from rsfMRI data (see appendix). It could be further improved by integrating white matter density or information on BDNFexon1 methylation at certain sites. The addition of BDNFexon1 methylation to rsfMRI data significantly improved the specificity, while no significant improvement could be observed for the sensitivity. Looking at the reverse operation, adding rsfMRI to already obtained diagnosis from methylation data, does not improve specificity, but significantly improves sensitivity. For the integration of methylation and white matter density data, only the specificity is significantly improved. However, the sensitivity did not significantly decrease, either. In general, all examined cases showed improved or comparable specificity and sensitivity, confirming that MCV is robust with respect to redundant or little reliable predictions.

With respect to clinical application, the results suggest the following: MDD diagnosis with reasonable accuracy is provided by sLASSO regression of BDNF methylation markers (84±5% specificity, 73±2% sensitivity). Integration of rsfMRI and anatomical data can further increase the accuracy by approximately 6%, lowering the risk of false negatives by nearly 10% and the risk of false positives by 2%. If a blood test is not available, acquisition and MCV integration of rsfMRI data is advisable (The often used PHQ9, which is fast to acquire and to evaluate, has a specificity as well as sensitivity of 88%[20], however, as a self-administered questionnaire the differences in diagnostic accuracy in comparison to the accuracy acquired from biomarkers is difficult to interpret.). Here, the procedure is based on structural MRI, rsfMRI, and BDNF methylation rate data, but the extension of MCV to an arbitrary number of appropriate data is straightforward. Moreover, in contrast to SVM and decision tree, MCV is not restricted by lack of available data for a subject. Credibility for missing data is simply set to zero.

MCV differs from the introduced integration methods[7] in that it does not try to combine all predictions into a new model. It merely decides which of the predictions is the most reliable. Intuitively, that would be the prediction derived from the model with the highest accuracy, but this accuracy is based on global evaluation of the model, ie. the sum of all positive and negative predictions, regardless of their odds ratio, are weighed against the sum of the actual positive and negative labels. In contrast, MCV considers the local accuracy of these models. It quantifies the accuracy of the model for different odds ratios, expressing it as credibility function. Despite low general diagnostic power, for example, the WM model is quite accurate for certain odds-ratios, even more accurate than the other models, thus helping to boost accuracy when using MCV. Finding the data with the highest credibility thus equals identifying the data with the most pronounced MDD or HC characteristics for the subject in question. If we consider all data as part of a single mechanism, MCV points to the weakest or strongest link in the mechanism of a specific subject, respectively. Multiple subjects with the same weakest link suggest an MDD subtype. In our data, for example, ALFF and BDNFexon1 methylation were the most pronounced determining factors for true positives. In an experiment with a bigger cohort, these groups could point to two depression types that might benefit from different treatment. If the demographic

and clinical characteristics of these groups are the same, these depression types would indicate physiological subtypes of depression. If the characteristics are different, these depression types would indicate subtypes whose demographic and clinical characteristics are linked to different physiological phenomena. In the latter case, further investigation would be needed to establish if regulation of the physiological symptoms is possible and if it can be used to remedy MDD symptoms.

We exploit the fact that MCV can be used with any type of probabilistic models, by using sparse classification algorithms, which ensure that the effective variables (here, brain regions and methylation islands) are explicit, a crucial aspect for development of effective medication. Knowing details about the contributing factors allows for insight into their possible relation to depression as well as into the relation between the different data modalities, and the underlying mechanism of MDD. The discriminative white matter brain areas, for example, are responsible for somatosensory information processing (post central gyrus), cognitive (frontal superior cortex), and language related functions (middle temporal lobe), which are hypofunctional in MDD [21], [22], [23]. ALFF data identified the PCC and left thalamus (left hemisphere), as MDD discriminative, both of them exhibiting lower activation in depressed patients. Investigation of why the spontaneous activity in these areas is suppressed represents an important future direction. Low ALFF could be, for example, an indicator of the volumetric changes in PCC seen in first episode MDD subjects [24], but which were not big enough yet in our study to be captured by the anatomical data. Such investigations reveal if and maybe also how ALFF can be altered. If subtypes like indicated above exist, subtype specific treatment and prevention methods could be developed.

Similar implications can be drawn for subjects for which other data modalities are the predominant decisive factor: Left PCC and amygdala showed lower ReHO in MDD, i. e. spontaneous activation is locally badly synchronized, which may affect not the only regional functioning of this brain area, but also the connectivity with other brain areas. For both PCC, a central node of the default mode network, and left amygdala, which has significant functional connectivity with the ventral striatum, this may have a significant impact on behaviour. Increased ReHo was found in the cerebellum, which during the last years has been shown to participate in emotion regulation, inhibition of impulsive decision making, attention, and working memory [25]. This increase might be a result of the cerebellar cortical connections known to be disrupted in depression subjects [26]. However, in line with the above, whether these ReHO alterations are entirely functional or cause to subtle anatomical changes, such as speculated above, remains to be investigated.

For FC, the merit of sparse discriminative feature selection becomes especially apparent. So far, predictions are mainly based on SVM procedures [3], yielding models based on more than a hundred relevant connections [27], despite preselection procedures. Here, two connections were selected as discriminative, one that is located within the ventral DMN (vDMN) involving right PCC/RSC and parahippocampus, and one in the dorsal DMN (dDMN), concerning the PCC/Precuneus and medial prefrontal cortex(mPFC)/anterior cingulate (ACC)/orbitofrontal cortex (OFC), respectively (Appendix, Table S5). Both connections were weaker in MDD subjects. Both connections involve part of the PCC, which has been shown in our data to exhibit altered ReHO and ALFF characteristics in MDD subjects and is thus subject to future investigation on whether and how these phenomena are related. If strongly correlated, treatment of one deficiency could be sufficient to correct several of them.

The importance of BDNF in MDD is evidenced not only by its supportive role in serotonin signaling [28], [29] and in the dopaminergic system [30], [31], but also by its impact on neurogenesis, neural differentiation and cell survival, and thus on formation, stabilization and continuity of long-term memory [32]. Its effects on white matter density are obvious. Indeed, Choi et al. [33] have shown an inverse

association of BDNF DNA methylation and reduced white matter integrity in the anterior corona radiata in major depression. Here again, these WM changes might have been too subtle to detect in the MRI images of our cohort, but might already be reflected in the DNA methylation characteristics, the major mechanism for neural plasticity[34]. This is supported by the fact that for controls, WM (which is denser in controls) was more often involved in the affirmation of the diagnosis than for MDD subjects.

Finally, examining all biomarkers identified in this study (Appendix, Table S6), we can outline their relations to each other. The cerebellum indicated as distinctive in the ReHO data, targets prefrontal as well as temporal cortices through the thalamus. This is also reflected in the functional connectivity of the cerebellum with these regions [35]. While prefrontal and temporal areas were discriminative in the WM, the thalamus was distinctive in the ALFF data. Further, the medial OFC, also selective in the ReHO data, has strong connections with the hippocampus and associated areas of the cingulate and RSC (identified in the FC data), as well as with the anterior thalamus (ALFF)[36].

Considering the above, the aspects found in ALFF, ReHO, FC and WM density each seem to depict potential deficiencies in MDD within a common functional and anatomical network that connects the limbic system and cortical areas. This hypothesis is supported by Chen et al., 2016 [37], who found that the frontal-striatal-thalamic pathways are affected in MDD. A more recent study found clusters of functional connections in the above mentioned areas to lie at the core of four anxiety- and anhedonia-related subtypes of depression [38]. The well known symptom variability in MDD may result from these equally variable network deficiencies. While they cannot always be picked up by the data modality one might expect (e. g. FC), they might be reflected in mechanism-related characteristics of other data modalities (here, ALFF, ReHo, WM or BDNF methylation).

With this whole picture now illuminated, we return to the original purpose of identifying the most reliable diagnostic dataset for a subject and reiterate that in MCV, this equates to finding the dataset with the most pronounced MDD or HC characteristics for a given subject. In other words, it pinpoints which of the biological factors in the variable network is dysfunctional (in a typical way). At the same time, it is just that consideration of variability, i. e. consideration of potential MDD subtypes, that results in higher prediction accuracy. The derived effective variables are limited by the small number of subjects and need to be reconfirmed on a lager data sample. However, the proposed MCV method itself is by construction robust and flexible, so that we are confident that it will allow simple to use and accurate MDD diagnosis in clinical settings. Its transparency with respect to the "weakest link" aids the identification of MDD subtypes and consequently the development of adequate medical treatment. As cheaper and more accessible neural and physiological markers become available, this method will naturally become an increasingly useful clinical tool. Finally, we wish to underscore the fact that MCV is not restricted to MDD diagnosis alone, but is widely applicable.

V. ACKNOWLEDGMENT

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APPENDIX: SUPPORTING INFORMATION

CpGs used for classification:

CpG1, CpG4, CpG5, CpG7, CpG8.9, CpG14, CpG15, CpG17, CpG18, CpG19.20.21, CpG22, CpG23, CpG24, CpG25.26.27, CpG28, CpG29.30.31, CpG32, CpG33.34, CpG36, CpG37, CpG47, CpG48, CpG50.51, CpG52, CpG59, CpG61, CpG63, CpG72.73, CpG74.75, CpG77, CpG78, CpG79.

TABLE S1
AVERAGE FRAMEWISE TRANSLATIONAL AND ROTATIONAL DISPLACEMENT
DURING RSFMRI SCAN IN MM AND DEGREES, RESPECTIVELY.

		· · · · · · · · · · · · · · · · · · ·	
	HC	MDD	p-value
$\triangle trans_x$	0.0069 ± 0.0028	0.0061 ± 0.0032	0.21
$\triangle trans_y$	0.0381 ± 0.0466	0.0423 ± 0.0417	0.67
$\triangle trans_z$	$0.0364 {\pm} 0.0560$	$0.0255 {\pm} 0.0161$	0.22
$\triangle rot_x$	3.63e-04±2.48e-04	3.34e-04±2.13e-04	0.56
$\triangle rot_y$	1.86e-04±1.47e-04	1.65e-04±8.29e-05	0.41
$\triangle rot_z$	1.42e-04±5.45e-05	1.36e-04±6.05e-05	0.62
Framewise displacement	0.08 ± 0.10	0.07 ± 0.05	0.68

 TABLE S2

 Demographic and clinical characteristics of subjects which were used to estimated the WM and GM model.

	MDD	Control	p-value
Number of subjects	60	60	-
Sex (male/female)	29/31	32/28	0.5738
Age (years)	40.57 ± 8.99	36.95 ± 12.6657	0.0738
IQ	108.52 ± 9.7	1113.34 ± 7.4	0.0028**a
Alcohol Dependent Subjects	5	0	0.0224*
BDI2	30.15 ± 8.79	6.63 ± 6.03	1.08e-33***
PHQ9	17.65 ± 4.41	3.13 ± 3.80	2.38e-38***
SHAPS	37.12 ± 5.48	23.70 ± 6.21	1.92e-23***
STAI	56.33 ± 7.74	40.6 ± 8.88	2.97e-18***
CATS	34.69 ± 23.41	24.47 ± 14.86	0.0060**
LES	-6.64 ± 6.43	0.42 ± 3.37	2.48e-11***
HRSD17	19.95 ± 4.96	-	-
Age of Depression Onset (years)	38.06 ± 10.83	-	-
Number of Previous Episodes	0.51 ± 0.6	-	-
Length of Current Episode (days)	164.68 ± 212.01	-	-
Lexapro single agent	50	-	-
Lexapro combination	2	-	-
Other single agent	2	-	-
No Treatment	6	-	-

a asterisks denote significant group differences, *p<0.05, **p<0.01, ***p<0.001

TABLE S3								
DEMOGRAPHIC .	AND CLINICAL	CHARACTER	RISTICS	OF SUBJECTS	WHICH	WERE	USED	то
	ESTIMATED	THE ALFE.	REHO	AND FC MOD	EL.			

	MDD	Control	p-value
Number of subjects	42	42	-
Sex (male/female)	23/19	25/17	0.6592
Age (years)	36.24 ± 6.04	38.36 ± 13.22	0.3476
IQ	108.65 ± 10.84	112.39 ± 7.40	0.0686
Alcohol Dependent Subjects	4	0	0.0404*
BDI 2	30.17 ± 9.25	7.64 ± 6.35	1.21e-21***
PHQ9	17.88 ± 4.40	3.83 ± 4.08	1.60e-25***
SHAPS	37.71 ± 5.21	25.05 ± 6.11	2.73e-16***
STAI	56.02 ± 7.93	41.26 ± 8.69	3.84e-12***
CATS	37.23 ± 25.32	27.48 ± 15.90	0.0390*
LES	-6.275 ± 6.71	0.02 ± 3.58	8.44e-07***
HRSD17	19.55 ± 5.076	-	-
Age of Depression Onset (years)	32.83 ± 8.36	-	-
Number of Previous Episodes	0.56 ± 0.63	-	-
Length of Current Episode (days)	148.90 ± 195.61	-	-
Lexapro single agent	35	-	-
Lexapro combination	2	-	-
Other single agent	2	-	-
No Treatment	3	-	-

TABLE S4	
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF SUBJECTS WHICH WERE USED T	0
ESTIMATED THE METHYLATION MODEL.	

	MDD	Control	p-value
Number of subjects	33	33	-
Sex (male/female)	15/18	21/12	0.1380
Age (years)	40.36 ± 10.26	36.42 ± 12.76	0.1716
IQ	108.15 ± 9.46	111.42 ± 9.79	0.1721
Alcohol Dependent Subjects	1	0	0.3136
BDI	30.76 ± 9.76	8.18 ± 6.26	1.05e-16***
PHQ9	18.30 ± 4.86	4.18 ± 3.73	5.28e-20***
SHAPS	36.97 ± 4.44	23.33 ± 6.22	4.01e-15***
STAI	56.54 ± 6.60	42.61 ± 9.14	1.22e-09***
CATS	34.17 ± 19.56	29.15 ± 16.69	0.2767
LES	-6.07 ± 6.50	0.303 ± 4.61	2.92e-05***
HRSD17	20.36 ± 4.97	-	
Age of Depression Onset (years)	37.29 ± 11.96	-	
Number of Previous Episodes	0.52 ± 0.51	-	
Length of Current Episode (days)	162.45 ± 196.34	-	
Lexapro single agent	27	-	-
Lexapro combination	0	-	-
Other single agent	2	-	-
No Treatment	4	-	-

		TABLI	E S5		
CLASS	IFICATION ACC	URACY FOR EA	ACH INDIVIDU	AL DATA MOD	DALITY
Data	HC/MDD	Algorithm	Specificity	Sensitivity	Accuracy
		gLASSO	58±2	68 ± 4	63±2
WM	66/66	sLASSO	<60	<60	<60
		Elastic Net	<60	<60	<60
		gLASSO	<60	<60	<60
GM	66/66	sLASSO	<60	<60	<60
		Elastic Net	<60	<60	<60
		gLASSO	64±4	66±4	65 ± 2
ALFF	42/42	sLASSO	66±3	69 ± 2	68 ± 2
		Elastic Net	67 ± 2	69±1	68 ± 1
		gLASSO	<60	<60	<60
fALFF	42/42	sLASSO	<60	<60	<60
		Elastic Net	<60	<60	<60
		gLASSO	<60	<60	<60
ReHo	42/42	sLASSO	65 ± 4	67 ± 6	66 ± 3
		Elastic net	65 ± 2	67 ± 6	66 ± 2
FC	42/42	sLASSO	65±5	66 ± 6	65 ± 4
		Elastic Net	< 60	< 60	< 60

Elastic Net Each MRI dataset was subjected to group LASSO, L1 LASSO and Elastic Net. All models were evaluated based on ten times repeated 10-fold cross validation.

sLASSO

 81 ± 2

 84 ± 5

TABLE S6 DIAGNOSTIC FEATURES, INDIVIDUAL DATASETS: BRAIN AREAS AND METHYLATION SITES, WHICH HAD DISCRIMINATIVE CAPABILITY IN MORE THAN 80% OF THE CROSSVALIDATED CLASSIFICATION MODELS (AREAS AS DEFINED IN [15]). NEGATIVELY WEIGHTED FEATURES EXHIBIT LARGER VALUES IN HEALTHY CONTROLS THAN DEPRESSION SUBJECTS. POSITIVELY WEIGHTED FEATURES SHOW LARGER VALUES IN DEPRESSION SUBJECTS.

Data	Accuracy		
(HC/MDD)	(Algorithm)	Negative weights	Positive weights
WM	63±2	Post Central Gyrus L/R	Middle Temporal Cortex L
(66/66)	(gLASSO)	Frontal Superior Cortex L	
		Middle Temporal Cortex R	
ALFF	68±1	Posterior Cingulum L/R	
(42/42)	(Elastic Net)	Thalamus L	
ReHo	66±2	Posterior Cingulum L	Cerebelum8 L/R
(42/42)	(Elastic Net)	Middle Frontal Orbitalis L	
		Amygdala L	
FC	65±4	Ventral DMN 8 - Ventral DMN 5 a	
(42/42)	(sLASSO)	Dorsal DMN 4 - Dorsal DMN1 ^b	
BDNFexon1	78±3	CpG33.34	CpG8.9
(33/33)	(Elastic Net)	CpG24	CpG14
		CpG1	CpG5
		CpG63	CpG37
		CpG77	CpG48
		CpG52	CpG78
		CpG61	CpG36
		CpG19.20.21	CpG22
		CpG18	CpG74.75
		CpG25.26.27	CpG17
		CpG29.30.31	CpG15
		CpG32	
- Ventual D	O.	-	

TABLE S7
MCV FOR RSFMRI DATA: PREDICTION RATE BASED ON INDIVIDUAL DATASETS AND FOR MCV
COMBINATIONS. IF NOT INDICATED OTHERWISE P-VALUES INDICATE PERFORMANCE DIFFERENCE
WITH RESPECT TO MCV(RSFMRI)

	WIT	TH RESPECT TO	O MCV(RSFI	MRI)	
HC/MDD=42/42	Specificity	Sensitivity	Accuracy	p-value	Credibility
ALFF	67±2	69±1	68 ± 1	3.6e-05***	71±2
ReHo	65 ± 2	67±5	66 ± 2	3.1e-06***	61 ± 4
FC	65 ± 5	66 ± 6	65 ± 4	6.3e-05***	55±3
MCV(ALFF, ReHo)	65±3	77±2	71±2	2.7e-04*** wrt ALFF	73±2
				1.3e-05*** wrt ReHo	
				0.716	
MCV(ALFF, FC)	67±3	77±3	72 ± 2	1.2e-04*** wrt ALFF	72 ± 2
				1.3e-04*** wrt FC	
				0.6	
MCV(ReHo, FC)	64±3	73±7	68 ± 4	0.104 wrt ReHo	64±3
				0.096 wrt FC	
				0.007**	
MCV(rsfMRI)	66±4	79±3	73±2	-	74±2

TABLE S8
MCV FOR RSFMRI AND WM: PREDICTION RATE BASED ON INDIVIDUAL DATASETS AND FOR
MCV COMBINATIONS. IF NOT INDICATED OTHERWISE P-VALUES INDICATE PERFORMANCE
DIFFERENCE WITH RESPECT TO MCV(RSFMRI,WM)

	DIFFERENCE	WITH RESPEC	1 TO MC V (KSFMIKI, V	v (v1)	
HC/MDD=39/41	Specificity	Sensitivity	Accuracy (F-score)	p-value	Crediblity
ALFF	67±1	64±2	70±2 (69±1)	1.5e-07***	70±2
ReHo	63±3	66±5	64±2 (66±3)	2.4e-06***	61 ± 4
FC	65±6	66±6	66±4 (67±5)	0.002**	55±3
WM	52±3	70 ± 6	61±3 (65±4)	5.7e-09***	62±2
MCV(rsfMRI)	64 ± 4	79±3	71±2 (74±2)	0.033*	73±2
MCV(rsfMRI, WM)	69±4	78±3	74±2 (75±0)	-	75±2

TABLE S9
MCV FOR RSFMRI AND BDNF METHYLATION: PREDICTION RATE BASED ON INDIVIDUAL DATASETS
AND FOR MCV COMBINATIONS. IF NOT INDICATED OTHERWISE P-VALUES RATE PERFORMANCE
DIFFERENCE WITH RESPECT TO MCV(RSFMRI, BDNFEXON1)

DIFFERE	NCE WITH RE	SPECT TO MC	V(RSFMRI, BDNFEX	(ONI)	
HC/MDD=25/21	Specificity	Sensitivity	Accuracy (F-score)	p-values	Credibility
ALFF	63±4	70±2	66±2 (66±2)	5.1e-07***	71±2
ReHo	67±3	68±7	67±3 (65±4)	3.2e-06***	61 ± 4
FC	60±7	65±10	62±4 (61±6)	1.6e-07***	54±3
BDNFexon1	82±5	65±3	70±4 (70±3)	1.4e-08***	74±3
MCV(rsfMRI)	59±5	76±3	67±3 (68±2)	5.0e-06***	74±2
MCV(rsfMRI, BDNFexon1)	83±4	70±7	77±4 (74±5)	-	82±2

TABLE \$10
MCV FOR WM AND BDNF METHYLATION: PREDICTION RATE FOR INDIVIDUAL DATASETS AND FOR
MCV COMBINATIONS. IF NOT INDICATED OTHERWISE P-VALUES INDICATE PERFORMANCE DIFFERENCE
WITH RESPECT TO MCV

HC/MDD=28/31	Specificity	Sensitivity	Accuracy (F-score)	p-values	Credibility
WM	53±4	70±6	62±3 (66±4)	1.6e-12***	61±2
BDNFexon1	81±6	75±2	78±3 (78±3)	0.005**	72±4
MCV(WM, BDNFexon1)	89±5	73±5	80±4 (79±4)	-	78±3

TABLE S11
MCV VS STRAIGHT FORWARD INTEGRATED PREDICTION METHODS FOR DATA
WITH MISSING VALUES. FOR ALL SUBJECTS AT LEAST TWO DIFFERENT, BUT NOT
ALL MEASUREMENTS WERE AVAILABLE. P-VALUES INDICATE PERFORMANCE
DIFFERENCE WITH RESPECT TO MCV
HC/MDD = 47/53 Specificity Sensitivity Accuracy (E-score) p-value

HC/MDD = 47/53	Specificity	Sensitivity	Accuracy (F-score)	p-value
Most Votes	61±2	67±4	64±3 (78±3)	7.1e-10***
Sum of odds ratio	69±3	76 ± 4	72±3 (75±3)	1.9e-05***
Max of odds ratio	69 ± 2	72 ± 5	70±2 (72±3)	2.5e-07***
Mean of odds ratio	69±2	76 ± 4	73±3 (75±3)	2.8e-05***
MCV	84±4	77±5	80±3 (81±3)	-

BDNFexon1 33/33

a Ventral DMN: Area 5: Right Retrosplenial Cortex, Posterior Cingulate Cortex (BA 20, 23), Area 8: Right Parahippocampal Gyrus (BA 37,30) b Dorsal DMN: Area 1: Medial Prefrontal Cortex, Anterior Cingulate Cortex, Orbitofrontal Cortex (BA 9,10,24,32,11) Area 4: Poterior Cingulate Decempent (BA 23, 20)

Area 4 : Posterior Cingulate, Precuneus (BA 23, 30)

77±2

78±3

 74 ± 4

73±3